The 18th Annual Neuroscience Retreat

May 8th, 2026

ABSTRACTS

2026 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Electrocortical Propagation Dynamics Reflect Myelin Health in SCC DBS for Treatment Resistant Depression

Authors:
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Background:
Deep brain stimulation (DBS) of the subcallosal cingulate cortex (SCC) is a promising treatment for patients with treatment-resistant depression, yet objective biomarkers to track individualized recovery are lacking. Stimulation evoked potentials (EPs) provide a direct measure of cortical responsiveness to DBS and may reveal treatment-related changes in network communication.

Methods:
Ten patients with treatment-resistant depression underwent bilateral SCC DBS. High-density EEG was collected after 4 weeks and 24 weeks of treatment. Unilateral 2Hz SCC stimulation was delivered across all contacts. EP features were extracted from an inverse model of SCC source activity. Latency and magnitude changes were quantified longitudinally and related to white matter structural connectivity, fractional anisotropy (FA), and clinical wellness trajectories.

Results:
Across patients, EP latency significantly decreased over the course of treatment, reflecting faster electrocortical signal propagation at 24 weeks compared with 4 weeks ($p = 0.005$). EP magnitude increased over time in treatment ($p = 0.045$). Greater latency reduction was associated with slower clinical improvement, indicating that patients with later wellness onset showed the largest electrophysiological change. Latency also correlated with baseline myelin integrity: individuals with lower FA in the mid-cingulum demonstrated the largest latency improvement ($p = 0.019$).

Conclusions:
SCC DBS produced longitudinal changes in stimulation EP dynamics. EP latency emerged as a promising mechanistic biomarker of circuit engagement, sensitive to both treatment-related adaptation and myelin health.

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Diagnostic Trajectory of Anxiety and Depression in Routine Psychiatric Care

Aashree Gandhi

BACKGROUND: The longitudinal relationship between depression, anxiety, and comorbidity remains a primary challenge in clinical psychiatry. While cross-sectional studies show high co-occurrence, the directional velocity of diagnostic migration is poorly understood. This study aimed to quantify the five-year stability and transition probabilities within the internalizing spectrum.

METHODS: A retrospective longitudinal study used EHR data from adults aged 18–44 with depressive or anxiety disorder ICD-10 diagnoses. The final sample consisted of 2,255 patients followed for 60 months. Diagnoses were grouped into three states: depression only, anxiety only, and comorbid depression/anxiety. First-order Markov models estimated annual transition probabilities. Logistic regression examined predictors of diagnostic change and comorbidity emergence.

RESULTS: At baseline, 71.53% of patients were classified as depression only, 21.95% as anxiety only, and 6.52% as comorbid. Depression showed the greatest annual persistence (P = .939), as compared to anxiety (P = .156) and comorbid states (P = .000). Anxiety was less stable and more likely to transition to depression (P = .177), than depression was to anxiety (P = .051). Baseline depression was associated with lower odds of diagnostic change than anxiety (OR = 0.11, p < .001). Male patients were less likely than female patients to experience change (OR = 0.48, p = .003), and Black and Asian patients also had lower odds of change than White patients (OR < 0.44, p < .02). The 35-44 age group was associated with higher odds of comorbidity emergence (OR = 177.55, p = .002).

CONCLUSIONS: In this sample, depression appeared more stable over time than anxiety, while comorbidity appeared highly unstable. Findings suggest movement from anxiety and comorbidity toward depression, although patterns may also reflect diagnostic clarification, treatment exposure, and variation in follow-up intensity. Overall, the study supports the value of longitudinal approaches to understanding internalizing disorders in psychiatric settings.

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Anxiety and Acute Mania-Like Responses During Ventral GPe Stimulation in Patients with Obsessive-Compulsive Disorder

Authors: Abby Kiros, Martijn Figee, Andrew H. Smith

Background: Deep brain stimulation (DBS) of the anterior limb of the internal capsule (ALIC) is an effective treatment for patients with treatment resistant obsessive-compulsive disorder (OCD). However, stimulation of the most ventral ALIC nodes may trigger unwanted emotional side-effects including hypomania and anxiety. We examined behavioral and subjective responses to ventral globus pallidus externus (GPe) gray matter stimulation in participants with OCD.

Methods: We present two participants diagnosed with treatment resistant OCD who received DBS treatment using the chronically implanted Medtronic Percept system. They were asked to participate in tasks every other month during the first year of DBS, including experimental stimulation settings based on participants' tractography. In the two participants presented here, experimental stimulation included the two most ventral contacts 0 and 8, which are in the (GPe) gray matter.

Results: Participant 202 displayed high distress and anxiety in response to ventral stimulation. Observations during ventral stimulation included increased blinking, restlessness, repeatedly adjusting their body, difficulty concentrating on the task, and frequent sighing. Participant 209 exhibited manic-like and psychotic-like symptoms during ventral stimulation. 209 continued to report for several hours after ventral stimulation that they felt alert, energetic, unusually intelligent, and frequently described the stimulation as the “manic setting.” Behavioral observations included increased giddiness, rapid speech, and tremors. These acute effects were not present in other participants whose ventral stimulations were more dorsal in the ALIC.

Conclusions: These cases of acute behavioral reactions associated with ventral GPe stimulation suggest that gray matter stimulation in this region may have implications for the emergence of acute neuropsychiatric side effects and warrants further investigation.

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Investigating roles of the disease-associated DYRK1A kinase in developing cortical astrocytes

Adelajda Turku, Vicente Pedrozo, Raquelle Sloan, Shreya Nagarajan, Ralitsa Petrova, and Georgia Panagiotakos

Background. The gene encoding dual-specificity tyrosine-(Y)-phosphorylation-Regulated Kinase 1A (DYRK1A) is linked to neurodevelopmental conditions including Down syndrome and autism spectrum disorder. While DYRK1A was shown to mediate astrocyte reactivity during neuroinflammation and neurodegeneration, little is known about its roles in developing astrocytes, cells that serve essential functions during circuit development and are increasingly implicated in neurodevelopmental disorders. Our lab previously inactivated Dyrk1a from the cortical radial glial (RG) stem cell (Emx1Cre;Dyrk1aFLX), resulting in altered abundance of RG and their progeny, which include excitatory neurons and astrocytes.

Methods. To dissect astrocyte-specific roles of Dyrk1a, independent of earlier changes in RG, we inactivated Dyrk1a using a tamoxifen-inducible approach (Aldh1l1CreERT2;Dyrk1aFLX) at the peak of astrogliogenesis. We first crossed a membrane-tagged mTmGFLX reporter mouse strain into our astrocyte-specific Dyrk1a inactivation model (Aldh1l1CreERT2;Dyrk1aFLX;mTmGFLX), to investigate morphological changes in recombined GFP+ astrocytes across postnatal development. Using an alternative nuclear labeling strategy (Sun1-GFPFLX), we are also investigating astrocyte generation and transcriptomic changes on sorted GFP+ astrocyte populations upon astrocyte-specific Dyrk1a inactivation.

Results. We first analyzed morphological parameters at the beginning of cortical astrocyte morphological maturation, postnatal day (P)7, in control mice and Aldh1l1CreERT2;Dyrk1aFLX;mTmGFLX mutants. We found a qualitative reduction in the cell area coverage of recombined GFP+ astrocytes in homozygous mutants compared to control mice. We are currently collecting brains at additional timepoints, including P21, which marks the completion of astrocytic morphological maturation. In parallel, we are breeding Sun1-GFPFLX into our astrocyte-specific Dyrk1a deletion model to reliably sort pure populations of GFP-labeled astrocyte nuclei for transcriptomic analysis.

Conclusions. This study will elucidate the contributions of Dyrk1a to the developmental roles of astrocytes, shedding light on astrocyte dysfunction in the context of developmental disorders.

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Regulation of the Extracellular Matrix by Hyperglycemia May Contribute to Behavioral Dysregulation

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BACKGROUND: Diabetes is highly comorbid with neuropsychiatric disorders such as depression. Yet, little research has been focused on understanding the biological mechanisms by which these two disorders are linked. The habenulo-interpeduncular pathway stands out as a promising circuit to study diabetes-induced changes to mood-related behavior because this circuit has been shown to regulate both blood glucose and behavior. In this study we aim to investigate how diabetes affects the function of the extracellular matrix (ECM) to influence the development of neuropsychiatric disorders.

METHODS: Adult male mice were treated with either saline or streptozocin (50 mg/kg for 5 consecutive days), a pancreatic beta cell toxin that induces the development of hyperglycemia.

RESULTS: We found that hyperglycemic mice display an anhedonia-like phenotype in a two-bottle choice task. To further understand how hyperglycemia may be altering the function of the medial habenula (mHb), we conducted targeted purification of polysomal mRNA (TRAP-Seq) in cholinergic neurons of the mHb and found that several pathways involved in the regulation of the ECM are upregulated in mice with diabetes. We next stained the ECM in the mHb and interpeduncular nucleus (IPN) of hyperglycemic male mice. We found that hyperglycemia induced changes to the organization of the ECM, with a significant reduction to the total area and length of the ECM in the IPN, but not the mHb.

CONCLUSIONS: Together, these findings identify the ECM as a possible mechanism by which diabetes is able to elicit changes to the central nervous system. Understanding how diabetes interacts with the ECM to elicit changes in neuronal function will be imperative as cases of diabetes increase worldwide.

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Title: Single chromatin fiber and single cell genomic and transcriptomic profiling of the postpartum mouse brain

Authors: Aileen Harnett, Yueyan Zhu, Molly Estill, Travis Dawson, Li Shen, Schahram Akbarian

Background: Pregnancy induces significant plasticity in the maternal brain, but it also presents a vulnerable period for neurological disease. Structural brain changes in mothers are often linked to hormones like estradiol and progesterone, with studies in rodents showing how these hormones drive neuroplasticity during the transition to motherhood. Similar changes are observed across both pregnancy and adolescence, periods marked by steroid hormone fluctuations. While much is known about brain structure and hormone dynamics, less is understood about the molecular and genomic plasticity of human neurons and glial cells during these hormonally-dynamic periods. This project aims to explore how ovarian hormone withdrawal during the early postpartum period affects the epigenetic landscape. Our study will provide crucial insights into the genomic mechanisms underlying brain changes during pregnancy and postpartum, including how gene regulation may influence psychiatric risk.

Methods: We employ a hormone-simulated mouse model of pregnancy, with a ‘postpartum’ period relevant to human conditions. Following hormonal withdrawal, brain regions were harvested and nuclei isolated for long-read fiber-sequencing and short-read multiomic snRNA-seq and snATAC-seq.

Results: Fiber-seq analysis of mouse hippocampus revealed pregnancy-stage-specific chromatin changes, with gene ontology analysis of postpartum samples showing enrichment of hormone-responsive pathways. ESR1 and PGR motif analyses indicated reduced hormone motif accessibility in the postpartum period, accompanied by decreased differential transcription footprinting at the remaining accessible sites.

Conclusion:

Hormonal fluctuations during the peripartum period drive alterations in chromatin accessibility within the ventral hippocampus. These changes are likely associated with hormone-responsive gene regulation. Future work will involve mapping candidate genes identified in our mouse model to human GWAS datasets for psychiatric disorders, identifying potential risk genes for postpartum mental health conditions

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Form Follows Function: Spatially Organized Neuron-Glia Interactions Dictate Habenula Function

Alberto Corona, Masago Ishikawa, Victor Mathis, Lauren Wills, Adam Catto, Richard O'Connor, Emma Hays, Junshi Wang, Angel Prats, Molly Heyer, Philip Huang, Anne Schaefer, Paul J. Kenny

BACKGROUND: Social deprivation is highly aversive in humans and increases risk of depression and other stress-related disorders. Lateral habenula (LHb) neurons exhibit burst-firing in response to aversive stimuli, but LHb involvement in maladaptive responses to social deprivation have not been explored. Microglia are emerging as key homeostatic regulators of neural activity through their ability to sense activity-dependent ATP release. Microglia also express β2-adrenergic receptors (β2ARs) and their function is directly gated by stress-related neuromodulator norepinephrine (NE). Here, we investigated the role of microglial β2AR signaling in social isolation-induced alterations in LHb burst-firing.

METHODS: Adult male and female mice were socially isolated for >2 weeks prior to experiments. Extracellular ATP and NE transmission in LHb were monitored using genetically encoded sensors (GRABNE and GRABATP). Intrinsic activity patterns of LHb neurons were characterized using whole-cell current-clamp recordings. Microglia responses to ATP and NE were monitored via ex vivo calcium imaging in LHb slice preparations.

RESULTS: We found that: (1) Social deprivation increased LHb burst-firing and markedly altered the number and function of LHb microglia; (2) Burst-firing of LHb neurons triggered ATP release; (3) microglia sense burst-induced ATP release; (4) ATP-sensing microglia and burst-firing LHb neurons are situated in close physical proximity; (5) microglia depletion increases LHb burst-firing; (6) β2ARs are expressed by microglia but not neurons in the LHb; (7) stressors known to induce LHb burst-firing evoke NE release in LHb; (8) β2AR activation impairs microglia ATP sensing and thereby increases LHb burst-firing.

CONCLUSIONS: We conclude that microglia are critical regulators of burst firing neurons in the LHb.

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BACKGROUND: In Alzheimer's disease (AD), specific neocortical neurons are vulnerable to pathology and neurodegeneration while others remain resistant. However, the mechanisms underlying this regional vulnerability remain unclear. Spatial approaches such as highly multiplexed immunofluorescence (MxIF), combined with computational image analysis, enable investigation of cellular contributors to these differences. Astrocytes and microglia, which exhibit heterogeneous distributions and functional states across brain regions, are implicated in many AD-related pathological processes.

METHODS: We performed MxIF staining for 26 markers on postmortem human samples from the dorsolateral prefrontal cortex (DLPFC, AD-susceptible), and the primary visual cortex (V1, AD-resistant). Subjects included AD (n = 3, CDR 3), mild cognitive impairment (n = 4, CDR 0.5), and age-matched controls (n = 5, CDR 0), spanning Thal and Braak stages and including both sexes.

Images were background-subtracted, stitched into composite panels, and registered across staining rounds using nuclear alignment. Using QuPath, images were segmented for astrocytes (ALDH1L1), reactive astrocytes (GFAP), microglia (IBA1 colocalized with CD68, MHCII, or TSPO), vasculature (collagen IV), and Aβ plaques.

RESULTS: Both reactive astrocytes and microglia increased in proximity to Aβ plaques with worsening CDR specifically in V1. In contrast, juxtavascular reactive astrocytes did not increase with CDR but decreased in layer 1 of the DLPFC and increased in the white matter of V1. Given parallel trends in overall astrocytic reactivity, ongoing analyses of Aβ-laden vessels will determine whether these changes reflect localized responses to cerebral amyloid angiopathy or broader changes associated with AD progression.

CONCLUSIONS: These findings indicate region- and compartment-specific glial responses to Aβ pathology across neocortical areas of differing vulnerability. Localized glial responses near plaques in V1 may confer neuroprotection, whereas vascular-associated astrocytic changes may negatively impact blood-brain barrier integrity. Ongoing work investigating glial morphology and cell states will further define how astrocytes and microglia contribute to selective neuronal vulnerability in AD.

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Extracellular Matrix Dysregulation exacerbates Amyloid Pathology through Loss of TIMP2-Dependent MMP2 Activity

Alejandro B. Grau-Perales, Suhani Yerapathi, Ana Catarina Ferreira, Brittany M. Hemmer, Sarah M. Philippi, Jacob L. Rosenstadt, Claudia De Sanctis, John F. Crary, Joseph M. Castellano

Background: Alzheimer's disease (AD) is characterized by several hallmarks, including amyloid-β (Aβ) accumulation and neuroinflammation, processes increasingly linked to extracellular matrix (ECM) dysregulation. Tissue inhibitor of metalloproteinases-2 (TIMP2), a youth-associated blood-borne factor, regulates ECM homeostasis through modulation of matrix metalloproteinase-2 (MMP2), but its role in AD remains unknown.

Methods: We combined immunohistochemistry and quantitative image analysis in postmortem human hippocampal tissue with mechanistic studies in two amyloid mouse models (5xFAD and APP-KI-NL-F). TIMP2 loss-of-function was assessed using genetic knockout mice, and rescue experiments were performed using AAV-mediated TIMP2 overexpression. ECM composition was evaluated via chondroitin sulfate proteoglycan staining, and MMP2 localization and activity were assessed using colocalization analyses and in vivo zymography. Functional perturbations of ECM were performed using stereotaxic intrahippocampal injections of chondroitinase ABC (ChABC), alongside pharmacological inhibition of MMP2.

Results: TIMP2 levels were reduced in brains of human AD subjects and in amyloid mouse models. Ablation of TIMP2 increased plaque burden, astrogliosis, and CSPG accumulation in mice. While astrocytic MMP2 expression increased with amyloid deposition, TIMP2 deficiency impaired its localization and reduced its activity at plaques. ChABC administration reduced plaque burden and restored astrocyte–plaque interactions and MMP2 localization in a TIMP2-dependent manner. Conversely, TIMP2 overexpression reduced pathology and ECM accumulation, and improved memory performance in aged APP-KI mice. Interestingly, these biochemical effects were abolished by pharmacological MMP2 inhibition.

Conclusion: TIMP2 enables MMP2-dependent ECM remodeling at plaques, regulating astrocyte behavior proximal to amyloid pathology. Disruption of this axis drives ECM accumulation and pathological progression, highlighting ECM remodeling as a novel therapeutic target in AD.

Supported by 24AARF-1201458, R01AG061382 and R01AG072300

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Elucidating the molecular mechanisms of DDX3X in human neurons

Aleta Murphy, Cong Xiao, Jacqueline Cho, Amanda Le, Adam Tengolics, Paul Slesinger, Nan Yang

Background: Mutations in DDX3X are among the most common monogenic causes of ID/ASD, particularly in females. Patients have severe cortical defects and seizures, implicating neuronal outgrowth, migration, and synaptic formation as vulnerable neurodevelopmental processes. DDX3X codes for an RNA helicase involved in many stages of RNA metabolism, especially translation. However, the extent of its regulatory roles in human neurons remain understudied.

Methods: We used human induced pluripotent stem cell (hiPSC)-derived excitatory neurons to investigate the roles of DDX3X in a human neurodevelopmental context. We performed enhanced CLIP (eCLIP) sequencing to determine direct binding targets. We next generated a DDX3X-specific degron system using dTAGV1 to allow for temporal control of DDX3X degradation. The system models loss-of-function variants seen in DDX3X syndrome. We profiled the transcriptomic and proteomic effects of DDX3X knockdown. Additionally, ongoing electrophysiological and imaging assays will assess the cellular impact of knockdown.

Results: We find that DDX3X binds transcripts enriched for axonogenesis and synaptic function primarily at the 5'UTR. The neuronal transcriptome and proteome show alterations to synaptic signaling, morphogenesis, and post-transcriptional RNA regulation pathways. The majority of differentially expressed/abundant targets overlap with eCLIP targets, including DCX, CREBBP, and RBFOX3/NeuN, which are crucial for cortical development. Differentially abundant proteins are mainly downregulated, which suggests DDX3X plays a positive role in regulating their translation. At the functional level, multielectrode array recordings indicate that DDX3X knockdown perturbs NMDA receptor–mediated activity.

Conclusions: DDX3X regulates neuronal gene expression mainly via translation, the disruption of which leads to molecular and electrophysiological abnormalities. Given the effects on neurite outgrowth-related genes, we expect imaging will reveal morphological defects. By delineating relevant targets and pathways, we hope to improve therapeutic strategies for DDX3X syndrome.

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Sex- and mutation-dependent abnormalities in cognitive function, ACh dynamics, and cholinergic innervation in a Parkinson's mouse model

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DL Benson, GW Huntley

BACKGROUND
Cognitive impairment is common in Parkinson's, with a higher risk in males. Fronto-striatal functions are affected, but mechanisms and the basis for sex differences are unclear. In mice, we tested the hypothesis that LRRK2-G2019S mutation-dependent alterations in cholinergic modulation of mPFC contribute to sex-specific differences in cognitive performance.

METHODS
WT and Lrrk2-G2019S (GS) male/female mice were crossed into a ChAT-Cre; tdTomato reporter line. An AAV-GRAB-ACh3.0 sensor was targeted to area PL; signals were recorded by fiber photometry during a continuous performance task (CPT). To suppress elevated mutation-dependent, elevated Lrrk2 kinase activity, nursing dams were fed LRRK2 inhibitor MLi-2 in-chow. Male pups exposed via lactation from P7–21 were switched to normal chow at P21 and assessed at P100.

RESULTS
Male GS mice showed reduced cholinergic innervation density in mPFC, whereas females showed increased density compared to WT. In CPT, GS males showed increased false alarms, indicating impaired response inhibition, and enhanced cue-evoked ACh responses during these trials. In contrast, GS females showed improved accuracy with no changes in false alarms or ACh dynamics relative to WT. In male GS mice, early postnatal MLi-2 treatment rescued CPT performance, ACh signaling dynamics, and cholinergic innervation at P100.

CONCLUSIONS
The GS mutation produces sex-specific differences in mPFC cholinergic innervation, likely contributing to impaired response inhibition and abnormal ACh dynamics in males, but preserved function in females. Early postnatal LRRK2 inhibition rescues these deficits in males, implicating disrupted mPFC circuit development. Our data suggest that sex-specific vulnerability of mPFC cholinergic circuitry to elevated LRRK2 kinase activity contributes to risk for early cognitive impairment in Parkinson's.

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NEUROBIOLOGICAL UNDERPINNINGS OF CANNABIDIOL'S ACTION IN ATTENUATING OPIOID RELAPSE

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Introduction: Opioid use disorder is a chronic relapsing disorder characterized by cycling periods of compulsive drug use, abstinence, and relapse. Cannabidiol (CBD), a non-intoxicating cannabinoid, is under investigation as an anti-relapse treatment. CBD attenuates cue-induced heroin-seeking and attenuates craving and anxiety induced by drug-associated cues in abstinent individuals with heroin use disorder. The exact mechanisms by which CBD exerts its anti-relapse effects are poorly understood. The objective of the current study was to assess the effects of CBD administration on heroin-seeking in conjunction with transcriptomic profiling in the basolateral amygdala (BLA), a brain region highly implicated in drug craving and relapse.

Methods: Long Evans rats intravenously self-administered heroin over 15 days followed by 14 days of forced abstinence. Rats were acutely injected with either vehicle or CBD (5 or 10 mg/kg, i.p) 24 hours prior to a drug-seeking session. BLA tissue was dissected, and bulk RNA sequencing was performed.

Results: Both doses of CBD attenuated heroin-seeking. CBD also reversed the BLA transcriptional signature associated with heroin-seeking, particularly within glial-related pathways and microglial processes. Notably, CBD normalized expression of genes that regulate microglial function, and these genes showed strong correlations with heroin-seeking behavior.

Conclusions: These findings suggest that CBD reduces cue-induced drug-seeking by normalizing heroin-disrupted BLA pathways, particularly those related to microglial function.

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Title: The MS4A Locus in Alzheimer's Disease: Functional Roles of MS4A4A and MS4A6A in Myeloid Biology

Authors: Alexandra Münch, Grace Peppler, Michael Sewell, Anastasia Efthymiou, Maria João Duarte Gaspar, Edoardo Marcora, Anne Schaefer, Alison Goate

Background: Genome-wide association studies increasingly implicate myeloid cells in Alzheimer's disease (AD) pathogenesis, highlighting microglia as promising therapeutic targets. The MS4A locus is strongly associated with AD risk and cerebrospinal fluid levels of soluble TREM2, a biomarker of microglial activity linked to slower cognitive decline. This locus encodes a family of structurally related transmembrane proteins predominantly expressed in immune cells. We previously identified a candidate causal variant, rs636317, whose risk allele is predicted to disrupt CTCF binding and is associated with increased expression of MS4A4A and MS4A6A. However, the functional roles of these MS4A proteins remain poorly defined.

Methods: Using CRISPR-edited iPSC-derived microglia (iMGL) we directly test the hypothesis that the rs636317 mediates its effect by modulating MS4A4A and MS4A6A expression via differential CTCF binding. Given predicted interactions between MS4A proteins and other immune receptors implicated in AD, such as TREM2, we perform omics and targeted functional assays in MS4A4A/MS4A6A knockout iMGLs. In parallel, we generated myeloid-specific conditional knockout mouse lines for orthologs Ms4a4a and/or Ms4a6d crossed with the 5XFAD model to study gene-mediated effects on amyloid pathology.

Results: As predicted, we observe decreased CTCF binding and increased MS4A4A and MS4A6A expression in iMGLs homozygous for the risk allele. Knockout of MS4A4A/MS4A6A alters TREM2 shedding and signaling, and impacts lysosomal mass and phagocytosis. In vivo, loss of Ms4a4a reduces plaque burden, whereas loss of Ms4a6d modulates pathways linked to TREM2 signaling and antigen presentation, including increased MHC-II expression.

Conclusions: Reduced MS4A4A and MS4A6A expression may promote protective microglial responses via TREM2 signaling, mitigating amyloid pathology and cognitive decline.

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A single nucleus meta-atlas of ALS and FTLD-TDP reveals cell type specific cryptic splicing and alternative polyadenylation

Authors: Alice Giani, Brooke Friedman, Irika Sinha, Yi Zeng, Sam Bryce-Smith, Anna-Leigh Brown, Veronique Belzil, Tammaryn Lashley, Aaron Gitler, Pietro Fratta, Towfique Raj, Jack Humphrey

Background: TDP-43 pathology is a defining feature of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP). Mislocalization and aggregation of TDP-43 disrupt RNA metabolism, resulting in cryptic splicing and the more recently described cryptic alternative polyadenylation (APA). Although these RNA processing defects are implicated in neuronal dysfunction, their full spectrum, cell type specificity, variability across disease subgroups, and contributions to neurodegeneration remain poorly defined.

Methods: We harmonized a snRNA-seq meta-atlas of the human prefrontal and motor cortices, integrating over 1.3 million nuclei from 251 brain samples spanning 138 ALS, FTLD-TDP, and non-neurological control donors. This meta-atlas resolves seven major cortical cell types subdivided into 34 subtypes, providing a high-resolution map of TDP-43-affected cell populations.

Results: Using curated reference sets of cryptic events, we detected significant cryptic splicing in established TDP-43 targets including STMN2 and KALRN, and more recently recognized targets as ARHGAP32. Layer 2/3 and layer 5 excitatory neurons exhibited the highest cryptic splicing burden, highlighting selective neuronal vulnerability. Additionally, recently reported cryptic APA events in STMN2, ARHGAP32, ELK1, and additional targets concentrated predominantly in excitatory neurons, consistent with their susceptibility to TDP-43 loss-of-function. Beyond cryptic events, disease-associated APA shifts were further identified in TARDBP itself, reflecting a broader 3' RNA landscape remodeling in TDP-43 proteinopathy. Notably, disease-associated APA alterations were also detected in oligodendrocytes, astrocytes, and vascular cell populations, underscoring that TDP-43-associated RNA dysregulation extends beyond neurons.

Conclusions: These findings reveal cell type specific vulnerabilities to TDP-43 pathology and provide a comprehensive framework for further investigating the molecular mechanisms of neurodegeneration across the ALS–FTLD-TDP spectrum.

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The Role of Alzheimer's Disease Risk Allele APOE4 in Oligodendrocyte Development and Function

Alison Salinas

Background: Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by memory impairment due to degeneration of brain regions. Apolipoprotein E4 (APOE4) confers the strongest genetic risk factor for late-onset AD, though its mechanism remains unclear. Human brain imaging reveals hypomyelination in young, cognitively normal APOE4 carriers, suggesting that myelin dysfunction is an early feature of AD. Myelin is generated by oligodendrocytes derived from oligodendrocyte precursor cells (OPCs), and APOE is highly expressed during a period of oligodendrocyte development, but its role in this process is unknown. I hypothesize that APOE4 disrupts oligodendrocyte development, contributing to hypomyelination and disease vulnerability in the adult brain.

Methods: To investigate how APOE4 alters oligodendrocyte development, I used human APOE knock-in (KI) mice to conduct immunohistochemistry staining using stage-specific and cell type-specific markers across postnatal timepoints. I am also generating transgenic mice that label OPCs to investigate their ability to differentiate into mature oligodendrocytes.

Results: I found that APOE4 KI mice exhibited no differences in oligodendroglia populations at birth, but by one week demonstrated decreased numbers of OPCs and immature oligodendrocytes compared to APOE3 KI mice. This reduction was independent of hippocampal volume and not due to altered OPC proliferation. During the juvenile period, APOE4 KI mice exhibited increased numbers of mature oligodendrocytes and a reduced proportion of OPCs.

Conclusions: My results demonstrate that APOE4 differentially alters oligodendrocyte development at distinct stages, with early delays in maturation followed by compensatory increased differentiation later in development. Future studies will define how APOE4 alters additional stages of oligodendrocyte development, identify underlying molecular mechanisms, and uncover the impact on myelination. This research will yield innovative insights into early APOE4-driven AD susceptibility, guiding the design of therapeutics to prevent cognitive decline in APOE4 carriers.

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Submit your abstract here:

Abrogating astrocyte calcium activity in the basolateral amygdala increases risky decision- making

Alyshia Davis, Manasa Kumar, Jacqueline-Marie Ferland

BACKGROUND: Decision making is a critical cognitive process that involves choosing a course of action based on potential outcomes. Impairments in decision making are common in psychopathologies including substance use disorders and have been linked to treatment drop-out. Determining mechanisms involved in risky decision making is essential to identify novel targets for addiction treatment. Astrocytes are abundant glial cells with diverse functions relating to regulation of synaptic transmission and support of the blood-brain-barrier which are regulated by fluctuations in calcium activity. To investigate the role astrocytes play in cost/benefit decision-making, astrocytic function was attenuated by blocking calcium signaling dynamics in the basolateral amygdala (BLA), a region important for the development of choice biases. Decision-making was then assessed using a translational rodent analogue of the human Iowa Gambling Task, the rat gambling task (rGT).

METHODS: Adult male Long-Evans rats were infused with a calcium extruder (pZac2.1-GfaABC1D-mCHerry-hPMCA2w/b) or mCherry-control into the BLA. After recovery, rats began training on the rGT. In the task, animals chose between four options associated with different amounts of sucrose pellets (1-4 sugar pellets), length of penalty time-out (5-40s), and probability of winning a reward over punishment (0.9-0.4). Impulsivity and motivation were also recorded. Following behavior, rats were perfused and identification of placement was completed using immunohistochemistry.

RESULTS: Reducing astrocytic calcium signaling in the BLA increased risky decision making on the rGT. These effects were unique to decision-making as impulsivity and motivation were unaffected.

CONCLUSIONS: The current findings are the first of their kind demonstrating that BLA astrocytes play a causal role in decision making. Ongoing replication studies are underway to determine whether this effect is distinct in males and the impact of astrocyte modulation on the BLA transcriptomic landscape.

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Submit your abstract here:

The kidney-brain axis: how renal signals affect neuronal ensembles and cognition

Andrea Muñoz Zamora, 1 Ignacio Beccacece,1 Verónica Burstein,1 Rahul Sabnis, 1 and Michel Enamorado1

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External environmental cues are known to influence cognitive and neural processes. In contrast, how physiological signals from the body shape neuronal function and mental health remains poorly understood. Here, we investigated how a life-threatening immune challenge, bacterial sepsis, affects distinct neuronal populations and their impact on behavior and cognition. Clinically, sepsis affects 1.7 million individuals annually in the U.S. and is associated with long-term cognitive impairments characteristic of post-sepsis syndrome (PSS). Using a murine model of bacterial sepsis, we recapitulated key features of PSS, including persistent anxiety-like behavior and impaired short-term memory. Notably, these behavioral alterations correlated with sustained bacterial infection in the kidney, implicating this organ as a potential driver of long-term neurological sequelae. Using an automated brain-wide c-Fos detection pipeline, we mapped infection-associated changes in neural activity over time and identified altered activation in hippocampal, hypothalamic and amygdalar regions, as well as disrupted brain-wide functional connectivity. Next, we used the IEG-labeling techniques to identify neuronal ensembles activated during sepsis and found that these ensembles are re-engaged upon secondary challenge, suggesting the formation of a persistent neuronal trace. Finally, we observed that region-specific changes in neuronal activity correlate with distinct patterns of renal immune infiltration, supporting a functional link between peripheral immune responses and brain activity. Taken together, these findings implicate a kidney-brain axis in PSS pathogenesis and suggest that renal immune signaling can modulate neuronal ensemble activity.

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Submit your abstract here:

APOE4 Impairs Oligodendrocyte Lineage Progression via Dysregulated BMP Signaling

Anna Bright, Joel Blanchard

BACKGROUND: APOE4, the strongest genetic risk factor for Alzheimer's disease (AD), profoundly affects glial functions. Emerging evidence from our lab and others implicates oligodendroglial cells (OLCs) and myelin loss as early contributors to disease. Studies in postmortem mouse and human brains show that APOE4 carriers have reduced OLC numbers and myelin volume; however, inherent limitations of these approaches have prevented exploration of mechanisms underlying these deficits.

METHODS: We developed a protocol to generate iPSC-derived cortical organoids that produce OLCs. In this system, we can track OLC development, maturation, and myelination in vitro in isogenic APOE3 and APOE4 cell lines.

RESULTS: At 20 weeks, APOE4 myelinating organoids recapitulate the decreased myelin coverage and OLC number observed in mouse and human brains. Single-nucleus RNA sequencing revealed that the reduced abundance of OLCs in APOE4 organoids is accompanied by an enriched population of neural progenitor cells (NPCs), the cell type developmentally upstream of OLCs. APOE4 NPCs exhibit suppression of pathways critical for OLC fate acquisition and show dysregulated BMP signaling, a pathway that impedes OLC development and maturation. The transition from NPCs to OLC progenitors is developmentally patterned around week 2 of organoid differentiation. At this time point, APOE4 cultures exhibit reduced expression of OLIG2, the earliest marker of OLC commitment, and increased expression of ID3, a key downstream effector of BMP signaling. Increasing BMP signaling with recombinant BMP4 in APOE3 cultures reduces OLIG2 expression and blocks myelination in vitro. In contrast, pharmacological inhibition of BMP signaling in APOE4 cultures decreases ID3 transcription, rescues OLIG2 expression, and increases myelination.

CONCLUSIONS: Together, these findings demonstrate that APOE4 disrupts OLC lineage progression through aberrant BMP signaling, suggesting that this risk factor may developmentally prime the brain for dysmyelination that contributes to AD.

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Examining the association between striatal dopaminergic markers and white matter integrity in older adults

Anna Marin, Ryan Wales, Cody Ruais, Jasmin Richard, Trey Hedden

Introduction: Multi-modal imaging methods enable the examination of how neurobiological processes related to aging, AD, and other co-occurring neurodegenerative diseases interact in-vivo. This study examines whether alterations in dopaminergic function constitute an independent cascade from alterations in white matter microstructure, amyloid, and tau accumulation. This investigation is important to understand how we frame neurobiological aging-cascades in relation to the pathological cascade of AD and other neurodegenerative diseases in cross-sectional studies of brain aging.

Methods: 86 older adults (age: mean 72.3, range 60-82; 16 cognitively impaired) completed 3 PET/MR sessions over an average period of three months. 18F-Fallypride, 18F-Florbetaben, and 18F-PI-2620 were used to measure striatal D2/3 receptor density, amyloid and tau burden, respectively. T1 sequences were used to measure white matter hypo-intensities. The Parkinson's Progressive Markers Initiative (PPMI) dataset was separately examined to expand our analyses within a PD cohort and evaluate the potential role of alpha-synuclein pathology, measured using the Amprion CSF α-synuclein Seed Amplification Assay.

Results: A regression analysis showed that D2/3 receptor density in the caudate was predicted by white matter hypo-intensity volume, even after controlling for chronological age. Amyloid and tau accumulation were not associated with dopamine receptor density. These results were replicated in the PPMI PD cohort when examining DAT availability. Preliminary results showed that individuals with increased white matter pathology displayed lower levels of misfolded alpha-synuclein in the CSF.

Conclusions: These findings demonstrate that changes in dopamine function are not directly associated with AD neuropathology but are linked to increased white matter lesions. Preliminary findings from the PPMI dataset suggest that alpha-synuclein may also play a role. Future work will examine plasma-based markers of alpha-synuclein in the Mount Sinai cohort.

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Transcription factor regulation of microglial state and its relation to Alzheimer's disease risk

Anna Podlesny-Drabiniok, Jeanne Kim, Lotte Bezemer, Edoardo Marcora, Alison Goate

Background
Alzheimer's disease (AD) genetic risk variants are enriched in non-coding regulatory elements active in myeloid cells, particularly microglia. Single-cell transcriptomic studies have identified disease- and lipid-associated microglial (DLAM) states characterized by enhanced lysosomal function and lipid metabolism; however, the transcriptional mechanisms governing these state transitions remain incompletely defined. Several transcription factors (TFs) prioritized by gene regulatory network analyses—including MEF2C, BHLHE40/41, and NR1H2/3—reside within AD GWAS loci, suggesting they may link genetic risk to microglial functional states.

Methods
We integrated human AD GWAS, myeloid eQTL, and single-cell transcriptomic datasets to prioritize TFs associated with microglial activation states. Using isogenic human and mouse models we genetically or transiently perturbed MEF2C, BHLHE40/41, and NR1H2/3 and assessed transcriptomic, epigenomic, and functional outcomes. Fine-mapping and chromatin interaction analyses linked AD risk variants to TF-regulated regulatory elements and target genes.

Results
Loss of MEF2C or BHLHE40/41 consistently shifted microglia toward DLAM states, marked by activation of lysosomal and lipid-processing programs, suppression of homeostatic signatures, and expansion of DLAM populations. Functionally, deficient microglia exhibited increased lysosomal activity, enhanced cholesterol efflux, and lipid droplet accumulation. In contrast, loss of NR1H2/3 attenuated DLAM programs, reduced APOE secretion, and impaired cholesterol clearance, indicating opposing regulatory roles. Fine-mapping identified high-confidence AD risk variants within TF-regulated epigenomic regions linked to lysosomal, lipid-associated, and antigen presentation pathways. In co-culture models, MEF2C- or BHLHE40/41-deficient microglia reduced toxic Aβ42/40 ratios and attenuated reactive astrocyte responses.

Conclusions
These findings identify MEF2C, BHLHE40/41, and NR1H2/3 as genetically informed regulators of microglial state transitions that couple AD risk to functional neuroinflammatory responses, highlighting transcriptional

control of microglial states as a potential therapeutic axis in AD.

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Effects of chronic stress on social motivation

Ansel Shirasu-Hiza, Rachel L. Fisher-Foye, Teagan Daly, Romain Durand-de Cuttoli, Scott J. Russo

BACKGROUND: The paucity of therapeutics for social deficits reflects our limited understanding of the underlying neurobiological mechanisms. Human research links empathy and motivation to the anterior cingulate cortex (ACC). Additionally, the ACC is a target region in deep brain stimulation for treatment-resistant depression. Our lab found differences in ACC activity during social interaction between stressed and control mice. We seek to understand if the ACC plays a role in social reward and motivation and how this changes with stress. We hypothesize that mice susceptible to chronic stress will exhibit decreased social motivation, correlated with changes in ACC activity, after social defeat.

METHODS: We used a chronic social defeat stress paradigm, exposing experimental mice (C57BL/6 strain) to aggressive mice (CD-1 strain), and the Social Interaction test to categorize mice as “resilient” or “susceptible” to stress (spending more or less time near a CD-1 mouse, respectively). Using the Resident Intruder and Social Self-Administration tasks, we quantified social motivation. Before beginning, the male mice received fiber photometry implants and virally encoded reporters of neuronal activity.

RESULTS: Susceptible mice exhibited a trend of increased social avoidance and decreased social interaction duration compared to unstressed control mice. Resilient and control mice also tended to lever press more frequently for a social reward than susceptible mice. We are currently analyzing the fiber photometry data collected during the Resident Intruder and Social Self-Administration tasks.

CONCLUSION: Generally, these results confirm those from previous studies. The novel aspect is the real-time tracking of neuronal activity in the ACC during behavioral assays. We will identify patterns around lever pressing, social interaction, and social avoidance. This will clarify in which phase of social pursuit (approach, consumption, avoidance) the ACC is involved.

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Role of Plexin Receptors in Coupling Neuronal Activity to Glioblastoma Progression through Neuron-Tumor Interactions

April Li, Sangjo Kang, Hongyan Zou, Roland Friedel

Glioblastoma (GBM), the most common and lethal primary brain malignancy, is characterized by extensive infiltration and dynamic interactions with the neural microenvironment. Recent studies have demonstrated that GBM cells integrate into neural circuits and exploit neuronal activity to promote tumor growth and invasion; however, the underlying molecular mechanisms remain incompletely defined.

Axon guidance ligands of the Semaphorin family have been identified as regulators of activity-dependent infiltration and network hyperexcitability. The cognate Plexin receptors, particularly Plexin-B2 (PB2), expressed on GBM cells and tumor-associated macrophages (TAMs), and Plexin-D1 (PD1), which is enriched at the invasive front, are potential mediators of this process. Using a patient-derived GBM cell line with combined PB2 and PD1 KO deletions, we observed microtube overgrowth and membrane instability. In intracranial GBM transplant models, PB2/PD1 double KO (dKO) GBM tumors exhibit markedly reduced tumor size and decreased invasion across the corpus callosum. RNA-seq analysis revealed downregulation of synaptogenic programs, along with defects in dendritic spine morphology and function, suggesting disrupted GBM integration into neural networks.

To further characterize these changes, I am applying monosynaptic rabies virus tracing to compare neuron–tumor connectivity between control and dKO tumors. Synaptic organization is assessed by immunofluorescence imaging of synaptic markers. Tumor–astrocyte coupling is evaluated through gap junction analysis using Connexin43 staining and live brain slice imaging with the astrocyte-permeable dye SR101. Finally, I employ a chemogenetic DREADD approach using systemic J60 to remotely activate neurons contralateral to the tumor, enabling sustained modulation of neuronal activity. This approach assesses Plexin's role in activity-dependent tumor growth and invasion in tumor-intrinsic and TAM-mediated contexts. These studies will test whether Plexin signaling couples neuronal activity to GBM progression by regulating synaptic integration and microenvironmental interactions.

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Submit your abstract here:

Title: NPS Landscape of an MCI Population vs. Controls

Authors: Arianna LaBarbiera, Rachel Fremont

Mild cognitive impairment (MCI) is an intermediate stage between normal cognition and dementia, yet the neuropsychiatric symptoms (NPS) that frequently accompany it have received little attention. Current research suggests that more than half of individuals with MCI experience NPS, with symptom severity escalating alongside cognitive decline. However, the full profile of NPS in MCI, including which symptoms predominate, how they co-occur, and how they compare to those observed in cognitively healthy individuals, remains incompletely characterized. To address this gap, the present study uses data from the National Alzheimer's Coordinating Center (NACC) to examine NPS prevalence, burden, and co-occurrence patterns in individuals with MCI relative to healthy controls.

Methods: We obtained deidentified data from NACC including the Uniform Data Set (UDS), Neuropathology Data Set (NP), and data from the FTLD and LBD modules. Analyses were restricted to first-visit data. Participants were classified into four cohorts based on Cognitive Status at UDS Visit ratings. Using NPI-Q data from MCI (n = 12,466) and normal cognition (n = 22,863) groups, we assessed NPS prevalence and burden, and applied chi-square tests with false discovery rate (FDR) correction to evaluate between-group differences.

Results: On average, all NPS assessed by the NPI-Q (e.g. depression, irritability, anxiety, nighttime behaviors, apathy, agitation) were significantly more prevalent in individuals with MCI compared to healthy controls, with greater symptom severity across all domains. Co-occurrence of NPS with depression was also greater in the MCI population.

Conclusions: These findings indicate that patterns of NPS in MCI are distinct from those in cognitively healthy individuals in both prevalence and severity. A more complete characterization of NPS in MCI has implications for identifying these symptoms as early markers of progressive cognitive impairment and for developing more targeted treatments in this population.

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Submit your abstract here:

Differential Pre-Frontal Cortex Engagement During Cue-Reactivity in Individuals with Alcohol and Opioid Use Disorders: An fNIRS Study

Armaan S. Dullat[1], Riaz B. Shaik[1], William Miao[1], Siddhartha Peri[4], Karmiella S. Ferster[1], Nikhil Tondehal[1], Yasmin L. Hurd[1], Iliyan Ivanov[1], Muhammad A. Parvaz[123]

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Background: Drug cue-reactivity reflects neural processes that predict relapse in substance use disorders. Prefrontal cortical regions play a key role in attention and regulatory control of drug-related cues. Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique with clinical translational potential. fNIRS was used to characterize cortical engagement during cue-reactivity in alcohol use disorder (AUD), opioid use disorder (OUD), and healthy control (HC) groups.

Methods: Participants (25 AUD, 12 OUD, 11 HC) completed a picture-viewing task with drug-related and neutral images while wearing a 48-channel OBELAB fNIRS headset. Within-group differences in hemodynamic responses between drug and neutral conditions were assessed using paired t-tests. The drug–neutral contrast was compared between groups using independent-samples t-tests, with p-values corrected using FDR.

Results: AUD showed marginally greater drug cue-related engagement of the right orbitofrontal cortex ($p = .075$). Between-group comparisons revealed OUD exhibited higher engagement of the left ($p = .013$) and lower engagement of the right ($p = .05$) frontopolar cortex relative to HC. AUD showed marginally lower engagement of the right dorsolateral prefrontal cortex ($p = .057$) compared to HC.

Conclusions: Both OUD and AUD demonstrated relative hypoactivation of the right prefrontal cortex during cue-reactivity compared to HC. OUD also showed hyperactivation of the left frontopolar cortex. These findings highlight substance-specific patterns of prefrontal engagement. This proof-of-concept study supports the utility of fNIRS in identifying addiction-general and substance-specific markers of cue-reactivity.

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Title:
Opposing Impacts of Autophagy Receptor p62/SQSTM1 on Proteostasis and Transcription in a Huntington's Disease Model

Authors: Ayris Izmirli *, Cong Xiao*, You-Kyung Lee*, Shiyi Pan, Junmin Peng, and Zhenyu Yue

Abstract:
Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by striatal degeneration and accumulation of mutant huntingtin (mHTT) aggregates. Autophagy plays a critical role in the clearance of toxic aggregated proteins including mHTT. p62/SQSTM1 acts as an autophagy receptor that binds protein aggregates, mediating their degradation through selective autophagy. But how p62 exactly regulates the sub-cellular distribution and clearance of mHTT aggregates in HD remains unclear.

Here, we investigate HD mouse model Q175 lacking p62/SQSTM1 and identify the dual role of p62/SQSTM1 in the pathogenesis of HD: promoting proteostasis while exacerbating transcriptional toxicity. In Q175+/- model, expression of mHTT is largely associated with nuclear aggregates and induced widespread deregulation of transcription. However, deletion of p62 results in exclusion of nuclear mHTT and a partial rescue of striatal marker genes in the Q175+/-; p62KO HD mice. Interestingly, the lack of p62 exacerbates pathological hallmarks, including enhanced cytosolic accumulation of mHTT and ubiquitin-positive aggregates, accompanied by increased astrocyte activation and striatal atrophy. These results reveal a compartment-specific redistribution of mHTT aggregates upon p62 loss, uncoupling transcriptional regulation from cytosolic proteostasis. Together, these findings highlight cytosolic aggregate clearance as a key determinant of neurodegeneration in HD.

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Submit your abstract here:

Treatment Perceptions and Outcomes: Results from Patient Audio and Self-Report in the PREDiCTOR Study

Bailey Todtfeld, Theodore Servedio, Maya Valenzano, Nazly Suarez 1 Adam Davidson, Joseph T. Colonel , Heather Thibeau, Rachel Jespersen, Yulia Landa, Baihan Lin, Guillermo Cecchi, Cheryl M. Corcoran, René S. Kahn, Shalaila S. Haas

Background: Self-report measures of therapeutic alliance (TA), such as the Working Alliance Inventory and its derivatives, provide quantitative indicators of patient-clinician relationships and have been linked to treatment disengagement as well as changes in patient symptoms and functioning. However, unstructured patient speech about mental health care experiences offers an additional, qualitative source for understanding patient perceptions of providers.

Methods: In the PREDiCTOR Study, participants provide open-ended speech samples through the neuropsychiatry app mindLAMP and semi-structured interviews. Speech and quantitative TA data from the Session Alliance Inventory (SAI), administered after each session, were reviewed. Speech samples were qualitatively coded to group positive, neutral, or negative sentiments regarding one's care. Analyses were conducted for the subset of participants with both SAI and audio data (n = 36).

Results: A Kruskal–Wallis test showed no significant difference in total SAI scores across sentiment groups; however, pairwise comparisons revealed a significant difference between the positive and neutral groups for the bond dimension of the SAI ($W=4.73$; $p=0.002$). Speech-derived sentiment and SAI data were also analyzed in relation to adverse outcomes (emergency department visits, hospitalization, treatment disengagement). A chi-square test showed a significant difference between sentiment group and adverse outcomes ($\chi 2=7.39$; $p=0.025$), but no significant differences between SAI scores and adverse outcomes.

Conclusions: These findings suggest that attitudes toward care expressed in speech may not align with self-reported TA and that speech-elicited sentiments may better predict patient outcomes. Future analyses will incorporate speech data from semi-structured six-month check-ins to evaluate sentiment concordance over time.

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Aberrant state transitions on brain energy landscape reveal clinically relevant system entrapment in Major Depressive Disorder

B. Ülgen Kilic, Jenna Jubeir, Priti Balchandani, James W. Murrough, Laurel S. Morris, Yael Jacob

BACKGROUND: It's unknown how rs-fMRI spatio-temporal activation patterns differ in MDD and how DTI-based connectivity constrains these dynamics, underscoring the need to link large-scale brain activity with structural connectivity to explain depression's pathophysiology.

METHODS: We used rs-fMRI from HCs (n=38) and MDDs (n=38) to cluster recurrent brain states, quantifying fractional occupancy, dwell time, and transition probabilities; applied network control theory to DTI-derived connectomes (HC=27, MDD=26) to estimate transition energies; and fit linear models linking these dynamics to clinical symptoms.

RESULTS: 4 brain states were identified. Greater dwell time in State 3 was inversely associated with MASQ-anhedonia scores (HCs r^2=0.421, p=3.8e-5; MDD r^2=0.261, p=0.042), indicating lower anhedonia with more time in this state. In MDD participants, fractional occupancy of State 3 correlated positively with depression severity (r^2=0.268, p=0.008) and anhedonia (r^2=0.284, p=0.008), relationships absent in healthy controls (all Bonferroni corrected). MDD participants also showed reduced transition probability from State 4 to 1 (t=2.590, p=0.011), and within the MDD group higher State 4 to 1 transition probability predicted lower symptom severity across multiple domains: QIDS depression (r^2=0.285, p=0.017), RRS-Depression (r^2=0.298, p=0.017), RRS-Brooding (r^2=0.265, p=0.024), MASQ-Anxiety (r^2=0.287, p=0.017), MASQ-Anhedonia (r^2=0.313, p=0.017), and MASQ-General Distress (r^2=0.410, p=0.003; all FDR corrected). Finally, network control analysis showed that in MDD, more frequent State 3 to 2 transitions were associated with higher energetic cost (r^2=0.152, p=0.040), suggesting that structural connectivity imposes greater energetic demands on these maladaptive state transitions.

CONCLUSION: Our work (in-press for publication in Nature Communications) provides a mechanistic explanation for how depression may arise from maladaptive brain-state trajectories within an energetically imbalanced neural landscape.

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Submit your abstract here:

Loss of the Histone Serotonylation Reader MLL5 Drives ODLURO Syndrome Phenotypes

Benjamin Weekley, Jennifer Chan, Ian Maze

Background

Monoamine neurotransmitters regulate neurodevelopment and dysregulation of 5-HT is often implicated in autism spectrum disorders (ASD). We recently identified histone H3-serotonylation at glutamine 5 (H3Q5ser) and found it stabilizes H3K4me3 to form H3K4me3Q5ser, a mark driving permissive mRNA transcription. During mouse neurodevelopment, H3K4me3Q5ser exhibits dynamic changes, including shifts between narrow and broad domains enriched at neuronal specific genes. A screen of histone 'reader' domains identified the PHD finger of KMT2E (MLL5) as preferentially binding H3K4me3Q5ser, which we hypothesize drives chromatin alterations. Notably, KMT2E mutations are linked to ASD and cause ODLURO syndrome.

Methods

We generated Kmt2e HET/KO mice and performed behavioral assays and electrophysiology of adult mice, and transcriptomic/epigenomic profiling of P14 mice cerebellum/neurons. To investigate molecular mechanisms, we conducted immunoprecipitation–mass spectrometry (IP-MS) using FLAG-tagged MLL5 in human cells, since MLL5 itself is catalytically inactive. As a follow up, assessed histone PTM changes in vivo and ex vivo in WT/HET/KO mice.

Results

Kmt2e knockout mice exhibited altered anxiety-like behavior, impaired motor coordination, sensory abnormalities, and increased seizure susceptibility. RNA-seq revealed widespread gene expression changes in the P14 cerebellum, particularly in neurodevelopmental and synaptic pathways. Electrophysiological recordings showed reduced cerebellar granule neuron activity (mEPSCs and mIPSCs) in heterozygous and knockout animals. IP-MS identified strong interactions between MLL5 and a major histone deacetylase complex (NCOR/HDAC3). Consistent with this, Kmt2e knockout cerebella displayed increased histone acetylation, suggesting loss of chromatin repression.

Conclusions

These findings support a model that MLL5 functions as a reader of H3K4me3Q5ser, recruiting repressive chromatin machinery and modulating gene expression during neurodevelopment. Disruption of this pathway leads to epigenomic and transcriptional dysregulation driving neurodevelopmental deficits. Ongoing studies

are testing whether utilizing drugs to reverse histone acetylation gains in neurons can rescue this.

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Neuroeconomically dissociable decision-making computations are altered by SHANK3 haploinsufficiency

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BACKGROUND: Autism spectrum disorders are characterized by intellectual impairments, altered social communication, repetitive behaviors, and/or restricted interests, yet their impact on decision-making information processing remains difficult to define. Phelan McDermid Syndrome is a rare ASD caused by a hemizygous deletion in the SHANK3 gene characterized by profound intellectual impairment. Rodent studies modeling SHANK3 deletions fail to capture robust changes in cognition, often relying on full, homozygous knockouts to detect behavioral effects. However, this limits the translational potential of animal models, as homozygous SHANK3 deletions are often nonviable in humans.

METHODS: Our laboratory characterized complex decision-making behavior of mice by leveraging a neuroeconomic foraging paradigm that has been translated for use across species. In two studies, we tested C57BL/6J mice (N=48/N=16) (SHANK3+/+ vs SHANK3+/-, male/female) daily for months across a changing economic landscape in which mice had a limited time-budget to forage for their primary source of food by navigating a maze weighing opportunities to earn rewards of varying costs (delays cued by the pitch of a tone) and subjective value (unique flavors located in distinct spatial contexts).

RESULTS: We discovered robust decision-making deficits in SHANK3+/- mice, specifically in their ability to develop economic strategies learning how to deliberate between competing options. These mice displayed impairments when making cost-informed choices that were independent of other learning or motivational processes (e.g., spatial memory, expression of subjective flavor preferences, willingness to wait for rewards, or the ability to flexibly update decision policies).

CONCLUSION: Fitting our data to a drift-diffusion-model revealed impairments in dissociable computations when accumulating evidence during deliberation separate from strong decision biases that fail to adapt over time.

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Playing Unfair: Computational Mechanisms of Social Decision-Making in Borderline Personality Disorder

Blair R. K. Shevlin, Cameron Le Roux, Olivia Berin, Daniela Schiller, Harold W. Koenigsberg, Xiaosi Gu

BACKGROUND

Borderline Personality Disorder (BPD) is characterized by profound deficits in emotion regulation and interpersonal functioning. Economic decision-making paradigms, such as the Ultimatum Game (UG), offer a principled framework for probing sensitivity to social fairness; however, the computational mechanisms underlying UG decisions in BPD remain poorly understood.

METHODS

102 participants – including individuals with BPD (n = 31), healthy controls (HC; n = 39), anxiety/avoidant personality (ANX; n = 32) – completed a modified UG featuring Controllable and Uncontrollable offer blocks. Mixed-effects models assessed acceptance rates, response times, and perceived control. A Drift Diffusion Model (DDM) integrated with an inequality aversion utility function was fitted to individual choice and reaction-time data via hierarchical Bayesian MCMC estimation in JAGS.

RESULTS

Behaviorally, BPD participants strategically leveraged rejections to escalate subsequent offers ($b = 0.022$, $p = .032$) and reported greater perceived control in the Controllable block than HC ($b = 5.76$, $p = .029$). Computationally, BPD exhibited significantly higher drift rates ($b = 0.126$, $p < .001$), reflecting greater sensitivity to offer utility when accept/reject decisions. Most strikingly, BPD showed markedly reduced inequality aversion relative to HC ($b = -0.422$, $p < .001$) – the largest reduction across groups – alongside elevated control parameters ($b = 1.79$, $p < .001$) and shortened non-decision times ($b = -0.121$, $p = .004$).

CONCLUSIONS

BPD is computationally characterized by diminished sensitivity to unfair social outcomes and amplified perceived agency in interpersonal economic interactions. These findings suggest altered social valuation and impulsivity at a mechanistic level, with potential implications for targeted treatments of interpersonal dysfunction in BPD.

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Submit your abstract here:

Leveraging long-read RNA-seq to define TDP-43-associated isoform changes across neurodegenerative disease

Brooke Friedman, Matthew Keuss, Alice Giani, Irika Sinha, Michael Ward, Pietro Fratta, Towfique Raj, Jack Humphrey

Background: TDP-43 dysfunction disrupts essential cellular processes and produces mis-spliced isoforms in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD). Although emerging evidence suggests TDP-43 may be a viable therapeutic target, the mechanism by which TDP-43 pathology exacerbates neurodegeneration remains unclear. We propose that the full landscape of TDP-43's effects on splicing and polyadenylation has not been revealed, due to the reliance on short-read RNA-seq. Here, we performed long-read RNA-seq, which captures full-length mRNA isoforms, to quantify novel isoform changes associated with TDP-43 dysfunction in vitro and examined these events in post-mortem human brain tissue from ALS, FTD, and AD patients.

Methods: We profiled iPS-derived cortical neurons (n = 6 control, n = 5 CRISPRi knockdown of TDP-43) using long-read RNA-seq (Oxford Nanopore) and short-read RNA-seq (Illumina). Using these isoforms, we quantified their expression in bulk RNA-seq in frontal cortex samples from the Risk and Modifying Factors of Frontotemporal Dementia (RiMod-FTD) consortium (n = 20 FTLD-TDP cases, n = 16 controls), and performed differential transcript usage. Significant isoforms were externally validated using published bulk RNA-seq from sorted TDP-43 positive (n = 7) and negative (n = 7) nuclei from the frontal cortices of ALS-FTD cases.

Results: Hybrid isoform assembly and quantification identified 13,347 novel isoforms, of which 437 were upregulated in TDP-43 knockdown, including 146 previously reported as cryptic exon and/or alternative polyadenylation events. Of these 437 novel isoforms, 205 isoforms were replicated in FTLD-TDP brains, and 129 were further validated in TDP-43-negative nuclei from ALS-FTD brains, including STMN2 and UNC13A.

Conclusions: Our isoform-centric approach provides a robust framework to define TDP-43–dependent isoforms and prioritize candidates for downstream mechanistic and therapeutic investigation.

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Submit your abstract here:

Title: Npas4 Regulates the Balance Between Hippocampal Memory Stability and Flexible Updating

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Abstract

Background: The ability to update memories in response to environmental changes is critical for adaptive behavior. Many studies have shown that the hippocampus encodes spatial maps, but it is unclear how it coordinates stably storing of memory while updating that memory with new information.

Methods: We investigated the role of the immediate early gene Npas4 (related to inhibitory synaptic plasticity) in dorsal CA1 (dCA1) during a spatial memory updating paradigm with the CRISPR-mediated deletion of Npas4 gene. Mice learn the spatial locations of 2 reward ports. During the updating phase, the previous ports are no longer rewarded so mice need to find 2 new reward ports. Also, we performed longitudinal in vivo calcium imaging with Miniscope to track neural dynamics over weeks.

Results: We found that Npas4 deletion in dCA1 impairs memory precision during training but facilitates memory updating. In vivo calcium imaging with Miniscope suggested that during memory updating, the spatial map of the dCA1 remapped more prominently in the neurons that were newly active during the updating, possibly supporting flexible memory updating. However, the spatial tuning of neurons that were previously active during training (overlap neurons) showed minimal remapping, possibly supporting the stability of the spatial map.

Conclusions: These findings suggest that distinct ensembles in dCA1 may have differential roles in supporting memory stability and flexibility and Npas4 is a key molecular regulator of this process.

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Validation of a Two-Stage Questionnaire and Actigraphy Screening for iRBD in a Multicenter Case-Control Cohort

Caleb A. Massimi, Giorgio Ricciardiello Mejia, Andre Metzger, Kang Hyun Ryu, Eva Grzegorczyk, Boris Gilyadov, Eliana Jacobs, Claudia Kunney, Ankit Parekh, Emmanuel Mignot, Fanny Elahi, Joseph Winer, Kathleen Poston, Andreas Brink-Kjær, Emmanuel H. During

Introduction
REM sleep behavior disorder (iRBD) is a prodromal marker of synucleinopathies, yet cases remain undiagnosed because questionnaire performance and access to video-polysomnography (vPSG) are limited. We evaluated a 2-stage screening strategy combining a 4-item questionnaire on dream enactment, hyposmia, constipation, and orthostatic symptoms, followed by home wrist actigraphy.

Methods
Participants aged 40–80 without neurodegenerative disease were recruited from Mount Sinai and Stanford cohorts. iRBD cases were vPSG-confirmed. The cohort included 396 participants (99 cases, 297 controls; mean age 64 ± 11; 55% male). Of these, 289 completed the questionnaire, 236 completed 2-week wrist actigraphy, and 129 (75 cases, 54 controls) completed both. The algorithm used four movement features: mean motor activity, activity index, immobile bouts, and twitch activity. Models were trained using nested cross-validation with XGBoost.

Results
The dream enactment question achieved an AUC of 0.85, improving to 0.86 with the full questionnaire. In the questionnaire dataset (95 cases, 194 controls), dream enactment showed 78% sensitivity and 92% specificity, while the 4-item model achieved 78% sensitivity and 91% specificity. Actigraphy achieved an AUC of 0.88, with 82% sensitivity and 84% specificity. At 1.5% population prevalence, adjusted positive predictive value was 10% for the questionnaire and 6% for actigraphy. Among participants completing both assessments, the 2-stage protocol achieved 68% sensitivity and 100% specificity using dream enactment preselection, and 73% sensitivity and 100% specificity using the full questionnaire.

Conclusion
A 2-stage protocol combining questionnaire and actigraphy demonstrated excellent specificity, good sensitivity, and generalizability. This low-cost, scalable approach warrants further validation.

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Title: Revealing the neural basis of functional neuroimaging activations in frontal cortex

Authors: Elorette, C; Fujimoto, A; Stoll, FM; Fujimoto, SH; Fleysher, L; Russ, BE; Rudebeck, PH

It remains unclear how functional magnetic resonance imaging (fMRI) signals correlate with underlying neural activity. Because prior investigations have focused on occipital and temporal regions, the relationship between these measures in prefrontal cortex (PFC) is unknown.

We trained three female rhesus macaques (Macaca mulatta) to perform two tasks known to cause fMRI activations within PFC. Task 1 was a probabilistic associative learning task with either novel (requiring learning) or familiar stimuli. In Task 2, monkeys viewed different categories of images, including monkey faces and objects. We used the fMRI signals in these tasks to generate regions of interest (ROIs) to target for neural recordings.

In Task 1, we observed an ROI in ventrolateral PFC (vlPFC) selective for reward in the novel learning context. In Task 2, we observed an ROI in orbitofrontal cortex (OFC) selective for faces. We simultaneously recorded single neuron activity within both fMRI-defined ROIs while animals performed both tasks. We calculated the proportion of single neurons within each ROI whose encoding matched the fMRI results. 41% (150/369) of neurons in vlPFC were selective for reward during novel stimulus-association learning, while 32% (73/226) of visually-responsive neurons in OFC were selective for faces. However, we observed a large overlap in encoding across PFC areas. 41% (120/296) of OFC neurons were selective for reward during novel stimulus-association learning, while 28% (65/229) of visually-responsive vlPFC neurons were selective for faces.

Notably, our results differ from previous reports in temporal cortex and suggest a weaker relationship between fMRI signals and the activity of single neurons in PFC. Our findings indicate that encoding at the single neuron level within PFC is more distributed.

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Submit your abstract here:

The Role of Oligodendrocytes and Bone Morphogenetic Protein Signaling in the Development of the Neural Stem Cell Niche

Charles Mangan, Kavya Harish, Michelle Lu, Allison Bond

Background: Quiescent neural stem cells (NSCs) in the adult hippocampus give rise to new neurons, contributing to neuroplasticity through neurogenesis. Adult NSC quiescence is maintained by signals like bone morphogenetic proteins (BMPs) in a microenvironment called the neurogenic niche. During early postnatal development, hippocampal NSCs transition from actively proliferating to quiescence, allowing for long-term NSC maintenance; however, the mechanisms that regulate this transition are poorly understood. We hypothesize that the development of the niche orchestrates the NSC transition to quiescence.

Methods: Publicly available single-cell RNA-sequencing data and RNA-scope with immunohistochemistry was used to identify the cellular source of BMP ligands in the hippocampus and the developmental timeline of oligodendrocyte differentiation. Then a tamoxifen-inducible Pdgfra-CreER mouse line was used to delete Bmp4 from the oligodendrocyte lineage during early postnatal development and immunohistochemistry was used to assess the effects on NSCs' transition to quiescence.

Results: We found that BMP ligand expression was cell type-specific, and that immature oligodendrocytes specifically expressed Bmp4 in the hippocampus during development and in adulthood. We also found that oligodendrocyte precursor cells differentiated into immature oligodendrocytes beginning at postnatal day 7, coinciding precisely with NSCs' transition to quiescence. Finally, Bmp4 knockout in the oligodendrocyte lineage during early postnatal development disrupted the formation and organization of NSCs in the subgranular zone.

Conclusions: Our results suggest that immature oligodendrocytes are a source of BMP signaling in the developing hippocampus, helping establish the adult quiescent NSC pool and supporting a new role for oligodendrocytes in the NSC niche. These insights demonstrate the importance of niche development in establishing the adult NSC pool and expand our understanding of how adult regenerative capacity is established during development.

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Submit your abstract here:

Age-associated protein CCL11 regulates microglial state through receptor CCR3 in the context of aging and Alzheimer's disease pathology

Charlotte Stiplosek, Ralphyn Pallikunnath, Brittany Hemmer, Kevin Spehar, Vinaya Sahasrabuddhe, Anne Schaefer, Joseph M. Castellano

Background: Aging is the strongest factor for Alzheimer's disease, and prior studies established that specific age-accumulating blood-borne factors drive cognitive dysfunction in healthy mice. One such factor, chemokine CCL11, enters brain from blood where it may interact with CCR3 on microglia and neuron cell surfaces, leading to dysfunction. Individuals at high risk for AD harboring CCL11 mutations have lower levels of plasma CCL11 and significantly delayed AD onset compared to non-carriers. We tested the hypothesis that plasma CCL11 drives AD pathology in APP-knockin mice through changes in CCL11-CCR3 signaling on microglia.

Methods: To evaluate how age-associated plasma factors affect early AD pathology, we intravenously administered aged mouse plasma into young APP-KINL-G-F mice to evaluate exacerbation of AD pathology. ELISA was used to evaluate CCL11 differences across age and in the differing models (WT vs. APP-KI). To assess sufficiency of CCL11 as a systemic factor driving AD pathology, we treated early-pathology APP-KI mice for several months and performed confocal imaging analyses for various relevant markers of neurogenesis, amyloid load, and microglial activation.

Results: We found that aged plasma significantly drives amyloid pathology and that systemic CCL11 treatments were sufficient to impair adult neurogenesis, exacerbate amyloid plaque load, and resulted in increased numbers of microglia expressing phagolysosomal-associated marker (CD68). After confirming microglial expression of CCL11's canonical receptor CCR3 by flow cytometry, we confirmed that CCL11 activates primary microglia, arguing that CCL11 directly affects microglial state in vitro.

Conclusions: Our results argue that CCL11 is sufficient to exacerbate features of AD pathology, including changes in microglial state and amyloid load, perhaps pointing to a novel axis linking aging with AD.

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Submit your abstract here:

Title: Study the Link of KDM6B-mediated Lipid Metabolism and Immunosuppression in GBM

Author: Chenye Shen

Abstract:Glioblastoma (GBM), the most aggressive primary brain tumor, is characterized by rapid growth, diffuse invasion, and profound immunosuppression, rendering current immunotherapies largely ineffective. Tumor hypoxia and necrosis further contribute to poor patient outcomes. KDM6B, an oxygen-sensitive demethylase for the histone H3K27me3 repressive marker, has been implicated in cancer cell survival, proliferation, and invasion. However, its role in tumor-associated macrophages (TAMs) remains unclear. Here, we combined in vitro hypoxia/reoxygenation models using bone marrow–derived macrophages (BMDM) exposed to GBM-conditioned media and myelin debris with in vivo GBM models (CT2A, GL261, and PDGFB-overexpressed GBM models). KDM6B activity was inhibited using the inhibitor GSK-J4 or genetic knockout approaches. We found that lipid-laden TAMs expressing the immunosuppressive marker CD206 are enriched in hypoxic regions of GBM. Notably, KDM6B inhibition significantly reduced the accumulation of these foamy TAMs and shifted the tumor microenvironment toward an immune-activated state, as evidenced by increased infiltration of cytotoxic $CD8^+$ T cells. Together, our findings uncover a mechanistic link between KDM6B-mediated epigenetic regulation, hypoxia/reoxygenation dynamics, and lipid metabolic reprogramming in TAMs. Targeting KDM6B disrupts the formation of immunosuppressive, lipid-laden TAMs and promotes anti-tumor immunity, highlighting a novel epigenetic-metabolic axis with therapeutic potential in GBM.

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Submit your abstract here:

Identifying Plasma Neurodegenerative Proteomic Signatures Associated with Opioid Exposure in Humans and a Translational Rodent Model

Chinonso Nwakama, Anna Torten Rabinowitz, Maria Savoia, Nikolaos Karvelas, Kion Winston, Alexandra Chisholm, Hanish Kodali, Joseph Landry, Chloe Lopez-Lee, Fanny Elahi, Yasmin L. Hurd

Background-Literature spanning both clinical and preclinical domains has linked opioid use to neurodegenerative disease-like (NDL) alterations such as hyperphosphorylated tau (p-tau), DNA damage, and cognitive impairments. Previous work by the Hurd lab, studying postmortem brains from heroin users and corresponding rodent models, revealed that heroin exposure enhanced the chromatin accessibility and expression of the neurodegenerative disease-associated kinase, Fyn, and led to the phosphorylation of tau. However, reliance solely on postmortem tissue limits our understanding of opioid use-associated NDL progression. Novel, sensitive fluid (e.g., blood) neurodegenerative biomarkers have emerged, enabling a more comprehensive characterization of NDL alterations through the “liquid biopsy” of living opioid users.

Methods-In a small pilot study, we employed NULISAseq, an ultrasensitive assay, to quantify over 130 neurodegenerative disease-related proteins in the plasma of current human opioid users. We compared these profiles with those from non-dementia and dementia patients and identified overlapping targets that were detected by both the NULISAseq platform and our previous RNA sequencing datasets from the postmortem brains of heroin users. Using ELISAs, we then quantified the protein abundance of these targets in the plasma of rats that self-administered heroin.

Results-We observed elevated levels of p-tau181 and p-tau231 in the plasma of opioid users compared to non-dementia subjects. In rodent plasma, we detected changes in protein abundance after heroin exposure that mirrored our human pilot study.

Conclusions-Applying this approach to opioid use disorder may offer a novel opportunity to identify clinically relevant biomarkers in living individuals and investigate mechanistic targets in preclinical models to better inform disease progression and develop new treatments.

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Submit your abstract here:

Stress reshapes gene regulation by estrogen receptor alpha in a sex-dependent manner.

Christabel A. Mclain, Clementine Blaschke, Ashley Cunningham, Molly Estill, Leanne Holt, Veronika Kondev, Giselle Rojas, Eric J. Nestler.

Sex differences are evident in both the prevalence and underlying mechanisms of stress-related psychiatric disorders. Women experience these disorders at higher rates than men, and fluctuations in ovarian hormones are associated with changes in symptomatic prevalence and severity. These differences are mirrored in animal models, in which females exhibit greater stress susceptibility than males, and behavioral responses vary across the estrous cycle. Despite this, our understanding of the molecular mechanisms driving sex- and hormone-dependent differences in stress responses remains limited. Estrogen regulates transcriptional programs in the brain through its nuclear receptors; however, the role of estrogen's genomic pathway in shaping stress responses is poorly understood. To address this gap, we used CUT&RUN to investigate the role of estrogen receptor alpha (ERα) in stress-responsive brain regions in both males and females. We mapped genome-wide ERα binding sites in the nucleus accumbens and ventral hippocampus at baseline and following chronic stress exposure. Our analyses reveal region-, sex-, and estrous-stage-specific ERα binding patterns and demonstrate that chronic stress markedly alters ERα regulatory activity. Finally, by integrating our CUT&RUN data with existing RNA-sequencing datasets, we identify gene networks and biological processes that are differentially regulated by ERα and transcriptionally altered after chronic stress. These findings provide a mechanistic framework for understanding how estrogen's genomic signaling contributes to sex- and hormone-dependent stress vulnerability and may inform the development of more precise, sex-specific therapeutic strategies for stress-related psychiatric disorders.

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Submit your abstract here:

Boosting feedforward inhibition through circuit editing decreases seizures in experimental TLE

Christopher Adam, Claudia Garcia Jou, Kafui Dzirasa, Tristan Shuman

BACKGROUND: Temporal lobe epilepsy (TLE) is a debilitating disorder characterized by spontaneous, reoccurring seizures and pervasive learning and memory deficits. In TLE, there are stereotyped patterns of cell loss and circuit reorganization in the hippocampal formation. Unpublished work from the lab specifically demonstrated a loss of medial entorhinal cortex (MEC) inputs to parvalbumin positive (PV+) interneurons in the hippocampal dentate gyrus (DG). The recently developed Long-term integration of Circuits using connexins (LinCx) system was designed to manipulate the strength of connectivity between specific neuronal subpopulations using virally expressed engineered gap junctions Cx34.7M1 and Cx35M1. LinCx constructs exclusively link to each other forming heterotypic gap junctions that preferentially pass current in the Cx34.7M1 to Cx35M1 direction which unidirectionally boosts the strength of connectivity between synaptically connected cells.

METHODS: PV-cre mice were injected with pilocarpine to induce chronic epilepsy, then implanted with an EEG electrode for continuous seizure monitoring. After a baseline recording period of at least 3 weeks, mice received LinCx viral injections (Cx34.7M1 in MEC excitatory cells and Cx35M1 in DG PV+ interneurons) or non-functional controls. Continuous EEG monitoring was resumed 6 weeks after viral injections and seizures were identified and compared across groups.

RESULTS: Mice that received LinCx showed a significant reduction in seizure frequency as measured by the number of seizures per day. When compared to baseline, seizure rates decreased by ~40% in LinCx animals while they roughly doubled in controls.

CONCLUSIONS: Increasing connectivity between excitatory cells in MEC and DG PV+ interneurons not only stops seizures from worsening over time, but actually decreases seizure frequency in mice. Because MEC-hippocampal communication is implicated in memory, future studies will assess whether this manipulation restores spatial memory deficits in TLE.

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Integrated Biofluid Proteomics Reveal Dynamic Functional Biomarkers of LRRK2-Linked Parkinson's Disease Progression

Cong Xiao1*, Takahiro Shimizu1*, Bik Tzu Huang1*, Duc Tung Vu2, Ericka Itang2, Matthias Mann2, Ozge Karayel2, and Zhenyu Yue1#

BACKGROUND: The hyperactivated leucine-rich repeat kinase 2 (LRRK2) variants are the most common genetic cause of Parkinson's disease (PD) and represent a validated therapeutic target. However, the incomplete penetration of common LRRK2 variants highlights the need for molecular biomarkers that can predict disease onset and support therapeutics development.

METHODS AND RESULTS: Here, we analyze large datasets of cerebrospinal fluid (CSF) and urinary proteomics from the Parkinson's Progression Markers Initiative (PPMI) and identify distinct lysosomal and immune protein signatures as potential biomarkers for LRRK2-linked PD (LRRK2 PD). Longitudinal analysis reveals that levels of specific lysosomal and immune proteins remain elevated in CSF during the prodromal phase but decline following clinical symptom onset. Furthermore, examination of multiple brain cell types from Lrrk2G2019S mutant show increased secretion of lysosomal proteins by microglia and astrocytes, but not neurons, supporting a glial origin and cell-intrinsic effect of mutant LRRK2 activity. Furthermore, proteomics analysis of urine from humanized LRRK2G2019S transgenic mice identify lysosome and glycosphingolipid protein signatures shared with human LRRK2 PD patients.

CONCLUSIONS: Collectively, our integrated proteomics reveals dynamic changes of functional biofluid signatures for LRRK2 PD, which enables the determination of biomarkers for early disease onset, monitoring, and biomarker guided therapeutic development. Our humanized LRRK2G2019S mice provide an unprecedented platform for biomarker refinement and translational studies.

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Dormant breast cancer cells reprogram astrocytes via secreted CLU to establish pro-survival niches in the brain

Cristina Megino-Luque, Aubrey Houser, Rachel Estrera, Alexis Wilder, Simoni Sidoli, Adrienne Boire, Serafin Morales, Esperanza Arias, Andrew Li, José Javier Bravo-Cordero

Brain metastases originating from breast cancer are linked to poor clinical outcomes, largely due to limited therapeutic options and the lack of reliable early detection strategies. This highlights the importance of understanding the earliest stages of metastatic colonization in the brain. Disseminated cancer cells (DCCs) can infiltrate the brain and persist in a dormant, non-proliferative state, remaining undetected for extended periods before reactivating and forming clinically detectable metastases. However, the biological mechanisms that enable their long-term survival and eventual reawakening remain insufficiently defined. To investigate this, we employed an integrative approach combining spatial transcriptomics, single-cell RNA sequencing, and multiplexed immunofluorescence. Our findings identify Clusterin (CLU) as a critical factor secreted by dormant DCCs that drives astrocyte reprogramming. Specifically, CLU induces astrocytes to adopt a neuroprotective phenotype that supports the sustained survival of DCCs within the brain microenvironment. Mechanistically, CLU-activated astrocytes undergo metabolic adaptations that enhance lipid clearance, thereby reducing lipid-induced stress caused by DCCs and contributing to the formation of a protective niche. Using both genetic and pharmacological strategies, we demonstrate that suppression of CLU extends survival in mouse models harboring dormant brain DCCs. In addition, intravital brain imaging reveals that CLU downregulation promotes microglial activation, facilitating the clearance of dormant tumor cells. Importantly, elevated CLU levels were detected in cerebrospinal fluid and plasma from both preclinical models and breast cancer patients, correlating with the presence of brain DCCs and the timing of metastatic relapse. Collectively, these findings uncover a previously unrecognized mechanism by which astrocytes support dormant cancer cell survival and establish CLU as a promising prognostic biomarker and therapeutic target.

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The relationship between neuromelanin-sensitive MRI and visuospatial working memory impairment in schizotypal personality disorder and schizophrenia

Dale Lippincott, Chi C. Chan, King-Wai Chu, Philip R. Szeszko, Erin A. Hazlett, Kenneth Wengler

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Background: Working memory (WM) is a hallmark cognitive deficit in schizophrenia and schizotypal personality disorder (SPD), and extensive preclinical and clinical work implicates cortical dopamine function in performance of a canonical visuospatial WM (VSWM) task. PET imaging studies have identified cortical dopaminergic hypofunction as a potential mechanism of WM deficits in schizophrenia and SPD. Here, we use neuromelanin-sensitive MRI (NM-MRI) to investigate the relationship between presynaptic dopamine function and VSWM performance across the schizophrenia spectrum.

Methods: This pilot study included 38 participants rigorously assessed with structured clinical interviews: 14 individuals with schizophrenia, 11 individuals with SPD, and 13 healthy controls. VSWM was assessed using the Dot Test. NM-MRI data were collected using an optimized acquisition protocol and voxelwise contrast maps were calculated within a substantia nigra and ventral tegmental area (SN-VTA) mask. Voxelwise analyses assessed between-group differences in NM-MRI and relationships to VSWM performance while controlling for age and sex. Correction for multiple comparisons used an extent-based permutation test. Leave-one-out (LOO) analyses were performed to estimate unbiased effect sizes.

Results: VSWM performance was impaired in schizophrenia and SPD (ANOVA: $F=3.74$, $P=0.034$) compared to healthy individuals. No differences in NM-MRI signal were observed between diagnostic groups (all $P_{corrected}>0.41$). Across all participants, better VSWM performance was associated with higher NM-MRI signal (550 voxels; $P_{corrected}=0.006$; LOO effect size $r_{partial}=-0.48$) with significant voxels predominantly located in the dorsal SN.

Conclusions: In summary, we demonstrated a relationship between NM-MRI signal and VSWM, suggesting reduced presynaptic mesocortical dopamine function as a potential mechanism of WM deficits across the schizophrenia spectrum.

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Barriers to Care: The Role of Demographics and Psychopathology in Appointment Non-Attendance

Danielle J. Obergh

BACKGROUND: Missed appointments (no-shows) undermine clinical outcomes and strain healthcare resources. Demographic variables are often studied regarding appointment adherence, although individual diagnoses and the Hierarchical Taxonomy of Psychopathology (HiTOP) framework may provide a clinically relevant understanding of no-show behavior. This study investigated the utility of individual diagnostic profiles and demographic variables as predictors of no-show behavior in outpatient psychiatric clinics.

METHODS: Electronic health record data from psychiatric clinics were analyzed (N = 119). A Negative Binomial Regression (NBR) model was employed to account for overdispersion in no-show counts. Predictors included individual diagnoses, comorbidity, age, sex, race, and education level. A sensitivity analysis was conducted by grouping diagnoses into HiTOP-informed clusters: Internalizing (N = 94) versus complex-externalizing (N = 25).

RESULTS: Individual NBR results indicated that comorbidity was associated with the highest risk of no-shows (IRR = 1.61, p = .02). Sensitivity analysis revealed that the complex-externalizing cluster was a significantly stronger predictor of no-shows compared to the internalizing cluster (IRR = 2.93, p < .001) and male sex emerged as a protective factor (IRR = 0.62, p = .032). Survival analysis revealed a retention paradox among black and multi-racial participants (HR = 0.16).

CONCLUSION: This study validates the utility of the HiTOP framework in predicting clinical behavior, demonstrating that complex-externalizing symptoms are primary drivers of no-show rates. Findings regarding sex and race highlight the necessity of intersectional approaches in psychiatric care. By shifting the focus to diagnostic profiles and demographic nuances, psychiatric services can develop more targeted, culturally responsive strategies to improve treatment retention and health equity.

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Submit your abstract here:

Investigating synaptic and neural mechanisms of Cbln2 in controlling social behavior
Darielle Lewis-Sanders, Jinye Dai

Background: Neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia (SCZ) exhibit social deficits. Genetic evidence highlights disruptions in synaptic cell-adhesion molecules, including neurexins (Nrxn), cerebellins (Cbln), and glutamate delta-type receptors (GluD), as contributors to these deficits by modulating synaptic formation and function. Cbln2, a secreted synaptic molecule, interacts with Nrxn-GluD to regulate animal behaviors associated with social interaction, emotion control, and compulsive activity.Using a conditional knockout (cKO) reporter mouse model, we confirmed robust Cbln2 expression in the hippocampal ventral subiculum (vSub) and medial prefrontal cortex (mPFC)—regions critical for social behavior and emotional processing. Our data suggest that Cbln2 regulates Ca2+-permeable AMPA glutamate receptors (CP-AMPARs), which lack the GluA2 subunit—a mechanism linked to synaptic dysfunction and social impairments. We hypothesize that Cbln2 downregulation in the vSub-mPFC neurons leads to social deficits, and this dysfunction is due to CP-AMPAR accumulation in vSub-mPFC synapses

Methods: Using Cbln2 cKO line, we inject AAV-Cre/ΔCre into the mPFC and vSub of P21-23 animals. After two weeks, animals are handled for 3 days then undergo social behavioral testing. After behavior, the brains are prepared for electrophysiology recording with 300um of horizontal vSub or coronal mPFC slices. Whole cell patch-clamp is performed to evaluate AMPA miniature EPSCs at -70, +40, and +60 mV with 50uM picrotoxin and 50uM of APV.

Results: In a three-chamber social test, Cbln2 cKO mice with AAV-Cr injected into both the mPFC and vSub had a reduced Social Index Ratio (SI). This behavioral phenotype was not seen when animals were injected in the mPFC alone.

Conclusions: Our initial findings suggest that targeted Cbln2 deletion in both regions leads to social deficits, suggesting their role in social behavior.

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AN APPROACH TO DEFINING LAWS OF MIND BASED ON PHYSICAL PROPERTIES OF MATTER THAT OUR BRAINS UTILIZE TO CONSTRUCT MIND.

Desmond Heath MD
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ABSTRACT

Our minds are constructed by our brains utilizing physical properties of matter such as pattern formation and pattern matching. The brain functions continuously. It utilizes two properties of matter to construct social mind. They are the self-tuning of a complex system to a transition between chaos and stability and Bayesian probability prediction. These two properties of matter constrain each other in a balance of mind. Close to chaos functioning inhibits the expression of Bayesian learned adaptive probabilistic predictive expectation. In the first six years of life Bayesian prediction flourishes to construct social mind in a calm and safe place originally on mother's lap. Child neglect and trauma tip the balance of mind towards close to chaos functioning that constrains Bayesian prediction distorting social mind construction. These distortion producing traumas in our “deformative years” cast a shadow throughout life in the construction of self, identity, character personality, consciousness and social mind. These distortions in childhood result in psychiatric disorders. Social mind maturation is constructed in relationships along with a genetically planned apoptosis that produces cognitive loss of parental situational anxiety that ushers in a stage of mischief making, discovering for oneself, and lifelong creativity.

KEY WORDS. Physical properties of matter. Pattern formation. Close to criticality. Bayesian learned adaptive probabilistic predictive expectation. Constraint. Balance of mind. Deformative years. Apoptosis. Learned parental situational anxiety. Mischief making. Individuation. Creativity.

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Prenatal THC Exposure Disrupts Nucleus Accumbens Gene Expression and Promotes Anxiety-Like Behavior in Offspring

Diana Municchi, Joseph Landry, James Callens, Yasmin Hurd

Background: Cannabis use during pregnancy is increasingly common, yet its effects on fetal neurodevelopment remain poorly understood. Human studies have associated maternal cannabis use with increased anxiety, hyperactivity, and elevated cortisol levels in offspring. To determine whether these outcomes are causally driven by prenatal tetrahydrocannabinol (pnTHC) exposure and to investigate the underlying mechanisms, this study examined the effects of prenatal THC exposure in rats on offspring anxiety-like behavior and the transcriptomic landscape of the nucleus accumbens (NAc).

Methods: Pregnant Long–Evans rats were exposed daily to vaporized THC and CBD (10:1 ratio) or vehicle (VEH) from approximately gestational day 5 until delivery. Offspring were cross-fostered to control dams and assessed during adolescence using the Light–Dark Test. Brains were collected 1 hour after testing, and bilateral NAc punches were processed for bulk RNA sequencing (RNA-seq).

Results: Offspring exposed to pnTHC exhibited increased anxiety-like behavior during adolescence, with no observed sex differences. RNA-seq analysis identified 2,179 differentially expressed genes (DEGs) between VEH and pnTHC groups (sexes combined). Gene Ontology analysis revealed enrichment of DEGs in pathways related to oligodendrocyte development, myelination, and synaptic organization. Notably, these pathways were also correlated with anxiety-like behavior.

Conclusions: These findings support a causal model in which prenatal THC exposure increases vulnerability to anxiety-like behavior in offspring, potentially through disruption of the transcriptional landscape of the nucleus accumbens.

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Submit your abstract here:

Small molecule screen identifies ACC as a therapeutic target to restore lipid homeostasis in APOE4 astrocytes

Dominic Haworth-Staines*, Youbin Kim*, Miranda Yang, Joel Blanchard

*These authors contributed equally.

Background: Apolipoprotein E (ApoE) plays a critical role in lipid transport in the brain, with astrocytes serving as a primary source and key regulators of lipid metabolism. The APOE4 allele, the strongest genetic risk factor for late-onset Alzheimer's disease (AD), is associated with dysregulated lipid metabolism and lipid droplet accumulation in astrocytes. These alterations impair bioenergetics and are thought to contribute to disrupted amyloid clearance. Despite strong evidence linking APOE4 to astrocyte lipid dysregulation, therapeutically actionable targets that restore lipid homeostasis remain poorly defined.

Methods: Human iPSC-derived APOE4 astrocytes were used to perform a small molecule screen targeting lipid metabolic pathways. Lipid droplets were quantified using BODIPY-cholesterol staining as a phenotypic readout. Lead compounds were validated using transcriptomic profiling and functional assays assessing lipid accumulation, mitochondrial activity, and endolysosomal function relative to isogenic APOE3 astrocytes. Effects of systemic drug treatment were further examined in a 3D multicellular human brain (miBrain) model.

Results: Inhibitors of acetyl-CoA carboxylase (ACC) emerged as top hits, significantly reducing lipid droplet accumulation in APOE4 astrocytes and miBrains. Both pharmacologic and genetic inhibition of ACC restored mitochondrial function and acetyl-CoA availability, enhancing bioenergetics of APOE4 astrocytes. Endolysosomal activity was rescued, leading to increased amyloid clearance capacity.

Conclusions: These findings identify ACC as a key regulator of astrocytic lipid homeostasis and a promising therapeutic target in APOE4-associated astrocyte dysfunction. These results highlight modulation of lipid metabolism as a viable strategy to restore cellular function and reduce AD-related pathology.

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Submit your abstract here:

The Strongest Reproducible Blood-Brain Gene Expression Concordance Signals are Not Driven by Genetics Factors

Dung Hoang, Lora Liharska, Nicole Bussola, Anina Lund, Vibhuti Patel, Brian Kopell, Noam Beckmann, Alexander Charney

Background: Blood gene expression (GE) is widely used to study brain disorders when brain tissue is not available, yet the extent to which blood GE reflects brain GE remains poorly understood. Here, we directly asked this question by characterizing GE concordance in paired blood and brain samples in a cohort of living patients undergoing deep brain stimulation surgery (Living Brain Project, LBP; n = 225 pairs). All findings were replicated in the Genotype-Tissue Expression (GTEx; n = 237 pairs).

Methods: Concordance was quantified at two levels: gene-wise (correlations across samples for each gene for the same genes in both tissues, i.e., same-gene pairs) and sample-wise (correlations across genes for each sample). Replication was assessed by correlating gene-wise correlations between LBP and GTEx. Functional and expression quantitative trait loci (eQTL) enrichment analyses were performed on the top correlated gene pairs that replicated in both LBP and GTEx, using Fisher's exact tests. For sample-wise analysis, Wilcoxon tests were used to compare GE concordance between within-individuals versus between-individuals in both datasets.

Results: Sample-wise analyses showed significantly higher blood-brain GE concordance within-individuals than between-individuals (LBP: d = 0.46; GTEx: d = 0.35). Although concordance was reproduced at the sample level, gene-wise correlations did not reproduce for all genes. Same-gene pairs did reproduce (ρ = 0.152); for these gene pairs, they were significantly depleted in brain cis-eQTL, blood cis-QTL, and blood trans-eQTL (log odds ratio ranges: 0.20-0.50), and were functionally enriched for immune-related and translational pathways.

Conclusion: Together, these findings demonstrate that blood and brain GE share a small overlapping signal that is not driven by genetic factors and is enriched for immune-related and translational pathways.

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KETOGENIC APPROACHES FOR ANTIDEPRESSANT TREATMENT

Eftychia Markopoulou, Adriana Mendez, Mariam Mahboob, Mohammad Jodeiri Farshbaf, Rachel Fisher, Hsiao-yun Lin, Yanmin Luo, Scott Russo, Jessica Ables

BACKROUND: Major depressive disorder (MDD) is associated with disrupted brain energy metabolism. Ketone bodies, which serve as alternative energy substrates, exhibit neuroprotective and anti-inflammatory properties. While ketogenic diets, exogenous ketones, and SGLT2 inhibitors elevate circulating ketones, their impact on depression-related behaviors remains unclear. This study evaluates the behavioral and metabolic effects of ketone-elevating strategies in a chronic stress model.

METHODS: Adult male mice on a C57BL6J background (n=4-7/group) underwent chronic social defeat stress to induce depression-like behaviors. Following stress exposure, animals were randomized to control or ketone-elevating interventions, including exogenous ketone administration, ketogenic diet, or SGLT2 inhibition. Body weight, blood glucose, and circulating ketone levels were monitored. Depression-like behaviors were assessed using the social interaction test, including interaction and avoidance time, as well as locomotor activity. Anhedonia was evaluated using a saccharin solution preference assay. Mice were euthanized and tissues collected for subsequent metabolic analyses.

RESULTS: All three interventions significantly increased circulating ketone levels compared with controls ($p<0.05$). Elevated ketone availability was associated with reduced anhedonia, reflected by increased saccharin solution preference, and decreased avoidance behavior in the social interaction test ($p<0.05$). Notably, mice receiving SGLT2 inhibition demonstrated increased locomotor activity relative to controls ($p<0.05$). Markers of oxidative stress, assessed by malondialdehyde (MDA) levels in brain homogenates, were significantly reduced in ketone body injected and SGLT2 inhibitor injected mice compared with controls ($p<0.05$), while circulating MDA levels were decreased in ketogenic diet–fed mice ($p<0.05$).

CONCLUSIONS: Nutritional and pharmacologic strategies that increase ketone availability were associated with improved depression-induced behavioral phenotypes and reduced oxidative stress, highlighting ketone metabolism as a potential metabolic target in depression-related disorders.

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Ketamine Increases Intrinsic Neural Timescales in Treatment Resistant Depression

Elizabeth Alcantara, Kenneth Wengler

Background. Major depressive disorder is a leading cause of disability worldwide and a third of patients develop treatment resistant depression (TRD). Ketamine is an effective treatment for TRD that modulates the excitation/inhibition balance (E/I). Intrinsic neural timescales (INT) are a resting-state fMRI (rs-fMRI) measure theoretically and experimentally linked to E/I. Here, we investigate INT alterations in TRD and changes with ketamine as a marker of E/I.

Methods. rsfMRI data from 128 TRD patients and 34 controls from the TRD-HCP were used to estimate INT maps for 188 brain regions (HCP-MMP1.0; averaged across hemispheres) using guidelines by Goldberg et al. (Imaging Neuroscience, 2024). Depression symptom severity was assessed using the HAMD. Linear regressions were used to investigate relationships between regional INT, depression severity, cognitive function, and changes with ketamine.

Results. INT were shorter throughout the brain in TRD (33 significant brain regions; pFWE = 0.0001). Additionally, shorter INT was related to worse depression severity throughout the brain (39 significant brain regions; pFWE = 0.0001). Longer INT related to increased processing speed performance (33 significant regions; pFWE = 0.0001). Depression severity decreased following ketamine treatment ($f=42.81$, $p = 8.54E-22$) and increased INT correlated with decreased depression severity throughout treatment (21 significant brain regions; $f> 3.22$, $p< 0.042$). Lastly, longer INT correlated with greater processing speed performance (all $t> 2.105$, $p< 0.037$).

Conclusions. We identified shorter INT throughout the brain in TRD with greater INT shortening relating to worse depression severity notably in regions important for emotional processing such as the accumbens, cingulate, and insula. Additionally, ketamine increased INT and related to improved depression severity in the anterior cingulate and dorsal lateral prefrontal cortex. E/I alterations offer a target mechanism underlying TRD, potentially explaining the effectiveness of ketamine.

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Submit your abstract here:

Title: Long-term fentanyl withdrawal reprograms nucleus accumbens gene networks and risk-reward decision making

Authors: E.S. Kahn, B.T. Kipp, V. Kondev, M. Estill, T. Gyles, E.P. Chen, Y.Y. Yim, E.J. Nestler

Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029

Fentanyl, a potent synthetic opioid, is a major contributor to the current overdose epidemic, yet its long-term molecular and behavioral effects remain incompletely understood. Using bulk RNA sequencing of the nucleus accumbens (NAc) in male and female mice following chronic exposure and withdrawal, we observed largely distinct transcriptional responses to fentanyl and morphine at 24 hours post-exposure at doses that elicit similar behavioral effects. However, after 30 days of withdrawal, transcriptional profiles converged dramatically, suggesting shared long-term neuroadaptive processes. Gene co-expression network analysis identified a module (c1.7), enriched for genes involved in synaptic plasticity, that is robustly upregulated in the NAc during prolonged withdrawal from both opioids. To further explore the regulatory basis of these persistent transcriptional changes, we are integrating RNA-seq with chromatin accessibility profiling from assay for transposase-accessible chromatin sequencing (ATAC-seq). In parallel, we characterized behavioral consequences of fentanyl exposure and withdrawal using the platform mediated avoidance (PMA) task and a battery of assays designed to assess core addiction-related behaviors, including reward sensitivity, risk-taking, and decision-making under conflict. We show that fentanyl exposure alters reward-seeking and risk-taking behaviors observed across multiple paradigms, suggesting persistent disruptions in natural reward processing and threat valuation that may underlie relapse vulnerability. Together, our findings reveal parallel molecular and behavioral adaptations to fentanyl withdrawal and suggest potential epigenetic mechanisms regulating long-term plasticity in opioid addiction.

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Prenatal Maternal C-Reactive Protein and Resting-State EEG Alpha Power in Early Childhood

Elizabeth Raikes, Floriana Milazzo, MPH, Marco Rizzo, PhD, Yasemin Schmitt, Rushna Tubassum, MPH, Anna-Sophie Rommel PhD

BACKGROUND: Elevated inflammatory marker levels during pregnancy have been associated with adverse behavioral and developmental outcomes in children. However, the relationship between prenatal inflammation and brain function after birth is less well understood. Neurophysiological measures, such as electroencephalography (EEG), may provide insight into early brain function and help clarify mechanisms linking prenatal inflammation to later developmental risk. In particular, prenatal exposure to elevated inflammatory markers may be associated with differences in neural activity patterns underlying early neurodevelopment.

METHODS: We included 20 mother-child dyads from the Generation C cohort with at least one High Sensitivity C-reactive protein (HS-CRP) measurement in pregnancy and child follow-up data (mean age 44.8 months±4.4, Female=55.0%). HS-CRP levels collected across pregnancy (mg/L) were averaged, log-transformed, and analyzed as a continuous exposure. Children completed a resting-state EEG. The primary outcome was absolute alpha (8–12 Hz) power measured in the central and posterior cortical regions, which serves as a neurophysiological marker of neural synchrony and reflects cortical engagement and maturation relevant to early neurodevelopment. Linear regression models estimated associations between prenatal HS-CRP and absolute alpha power, controlling for child age and sex.

RESULTS: We found no significant associations between averaged maternal CRP levels and absolute alpha power in central (β=0.30, 95% CI=-2.31, 2.92, p=0.647) and posterior (β=0.14, 95% CI=-0.82, 1.10, p=0.825) cortical areas.

CONCLUSIONS: In this preliminary sample, prenatal inflammatory markers were not associated with absolute alpha power recorded from resting-state EEG during early childhood. Given the small sample size, findings should be interpreted cautiously and require replication in larger studies.

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Submit your abstract here:

THE ROLE OF OXYTOCIN IN LONG-TERM SOCIAL MEMORY

Ella Lubbers, Huanhuan Li, Anna Schinasi, Xiaoting Wu

BACKGROUND: Social memory, the ability to recognize and remember conspecifics, is crucial for survival. Yet, its deficits remain untreated in many neuropsychiatric disorders. Mice exhibit long-term memory for their caregiving dam (dam-pup memory), but not other familiarized conspecifics. Given the neural mechanism of long-term social memory is unclear, we hypothesize that oxytocinergic projections from the paraventricular nucleus of the hypothalamus (PVH) to the dCA2 of the hippocampus mediate dam-pup memory. We further predict that the kinetics of this memory may be modulated by developmental changes and/or salient maternal behaviors like feeding.

METHODS: I established a three-chamber paradigm to probe dam-pup memory. Specificity was examined by testing for memory of cagemates and non-caregiving mothers. Mice weaned 10 days apart were compared to investigate the importance of age and mother presence. dCA2 oxytocin receptor (Oxtr) expression was quantified by immunohistochemistry at different ages and fiber photometry was used to monitor oxytocin activity during maternal interactions. The necessity and sufficiency of PVH oxytocin signaling onto dCA2 Oxtrs was assessed with chemo-/optogenetics and behavioral pharmacology. Milk feeding was inhibited to test for the necessity of this behavior.

RESULTS: Mice expressed long-term memory for a caregiving but not any familiarized dam, and the memory was modulated by mother presence. Inhibition of dCA2 Oxtrs abolished dam-pup memory. Increased activity of oxytocinergic PVH to dCA2 projecting neurons was sufficient to restore dam-pup memory in adults. Oxtr expression in the dCA2 was not upregulated during early development, but OXT activity was increased during interactions with the caregiving dam. Milk feeding inhibition prevented memory expression.

CONCLUSIONS: These results suggest PVH to dCA2 OXT signaling is necessary and sufficient for dam-pup memory, and this memory is dependent on maternal feeding.

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Submit your abstract here:

Title: Chronic Intracranial Recordings Reveal Frequency-Specific Correlates of Quality of Life in Epilepsy

Authors: Emanuel Coleman1, Ho Wing (Andy) Chan1, Madeline Stecy1, Onome Eka1, Fedor Panov1, Saadi Ghatan1, Ji Yeoun Yoo1, Anuradha Singh1, Madeline C. Fields1, Lara V. Marcuse1, Nathalie Jette1, Helen Mayberg1, James J. Young1, Ignacio Saez1

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Background:

Depressive symptoms are common in epilepsy and contribute substantially to reduced quality of life (QoL). However, the neural correlates of QoL remain unclear, partially due to difficulty in recording neural activity across the long timescales relevant for QoL fluctuations (days-to-weeks). Chronic intracranial recordings from responsive neurostimulation (RNS) systems enable longitudinal studies of limbic activity, and therefore present a unique opportunity to study the neural basis of changes in well-being.

Methods:

We analyzed local field potentials from the mesial temporal lobe (amygdala and hippocampus) in N=9 adults with epilepsy implanted with RNS. We related spectral power across frequency bands to patient-reported clinical questionnaires, including epilepsy-specific QoL (QOLIE-10) and depression scales (NDDI-E, MADRS), across long-term recordings (months to years). We used linear mixed-effects models to test for associations between band power scale scores, adjusting for seizure burden in the prior 7 days.

Results:

We found that higher mesial temporal gamma power was associated with worse QoL independent of seizure burden ($\beta=0.255$, $p=0.001$). Power in the delta and theta frequency bands showed significant seizure×power interactions ($\beta=-0.218$ to -0.169, FDR-corrected $p<0.05$), but there was no significant seizure×gamma interaction.

Conclusions:

Gamma activity in the mesial temporal lobe correlates with patient QoL independent of seizure burden, whereas low-frequency QoL associations are strongly modulated by seizures. These preliminary results suggest frequency-specific dissociation between seizure and patient-reported well-being in chronic limbic recordings, and provide a neurobiological basis for well-being fluctuation over long, pathology-relevant timescales.

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Submit your abstract here:

Title: Human oligodendrocyte development in the hippocampus

Authors: Emily K. Chapman, MD; Nadejda Tsankova, MD, PhD; Allison Bond, PhD

Background:
Oligodendrocytes are glia that produce the myelin necessary for efficient propagation of neurotransmission. The hippocampus region of the mammalian brain is crucial for learning and memory, and reduced hippocampal volume is observed in many neurodevelopmental diseases and perinatal insults such as hypoxic-ischemic encephalopathy and fetal growth restriction. While most studies focus on neurogenesis, little is known about oligodendrocyte development and their progenitors, oligodendrocyte precursor cells (OPCs), which retain the ability to generate new oligodendrocytes throughout life. Understanding the timing of oligodendrocyte development will identify windows of vulnerability when oligodendrocyte dysfunction could lead to neurodevelopmental disorders. We will characterize oligodendrocyte cell populations at fetal and postnatal stages in the human by establishing reliable markers of each stage.

Methods:
We used stage-specific markers of the oligodendrocyte lineage to perform immunofluorescence on paraffin-embedded postmortem human tissue samples. Antibody for OLIG2 marks the entire oligodendrocyte lineage, PDGRA marks OPCs, and BCAS1 marks newly formed oligodendrocytes. We performed staining on two human postnatal samples from the host institution (4 months old and 9 months old). Deparaffinization of the tissue was followed by heat-mediated antigen retrieval, permeabilization and blocking, and then primary and secondary antibody incubation.

Results:
Staining for OLIG2 and BCAS1 worked on both tissue samples, but we observed more BCAS1+ cells in the 4-month-old sample compared to the 9-month-old sample. We tested 2 different BCAS1 antibodies and found that the mouse anti-BCAS1 primary antibody stains better than rat anti-BCAS1 primary antibody. The PDGFRA antibody did not work on the samples.

Conclusion:
Immunofluorescence successfully detects developing oligodendrocytes in human hippocampus postmortem samples. Future work will extend this study to prenatal development to delineate a timeline of oligodendrocyte differentiation in the human hippocampus.

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Toward a cross-species model of social-cognitive maps

Andraka E., Durand-de Cuttoli R., Schiller D., Sweis B.M.

Prior studies have revealed that the human hippocampus and posterior medial cortex track social relationships along orthogonal dimensions of affiliation (amicable vs. antagonistic) and power (dominant vs. submissive). This information is thought to derive from an accumulation of choices made across prior social interactions and contribute to the organization of a social-cognitive map that guides behavior, which could be altered in mood, developmental, and personality disorders. Causally interrogating such pathways with temporal- and projection-specificity during social choice is challenging in humans. To this end, I adapted the food-based neuroeconomic task, “Restaurant Row”, into a social decision-making task in which mice spatially forage for social interactions rather than food rewards. In this task, socially isolated mice have 20 minutes to forage for their sole source of social contact with four conspecifics who differ in social relatedness (social identity based on familiarity and tube test-determined rank). Cost to access social interactions with each conspecific vary in the form of cued delays (auditory tones). Thus, mice must learn to optimize social decision-making strategies amidst a changing economic landscape. I recently concluded a large behavioral study which validates that mice engage this task longitudinally, respond to changes in cost, distinguish object control from mouse targets, and discriminate tone information at distinct choice points on a trial-by-trial basis. Preliminary analyses reveal social-rank based differences in cost sensitivity during deliberative decision-making. Further, we successfully recorded a dynamic range of task ultrasonic vocalizations which could indicate interaction valence and help explain choice behavior. This work sets the stage for applying cutting-edge circuit dissection tools to probe valuation algorithms influencing social choice, with the goal of advancing the understanding and development of new treatments for psychiatric disorders presenting with altered social cognition.

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Title: Characterization of Keppen Lubinsky Syndrome GIRK2 Channels and AI-Guided Drug Discover

Authors: Emma Young, Ian Glaaser, Avner Schlessinger, Paul Slesinger

Background: G protein-coupled inwardly-rectifying potassium (GIRK) channels belong to the Kir channel family and are essential for cellular excitability. Within the GIRK and Kir families there is a conserved selectivity filter which ensures preferential conduction of K^+ ions. In Keppen Lubinsky Syndrome (KLS), mutations in the selectivity filter allow the flow of Na^+ and other ions that are not normally conducted. There are four known GIRK2 mutations (L171R, G154S/C, and ΔT152) that are associated with KLS, the structures of which have not been solved. Here we sought to determine the structure of the G154C mutant GIRK2 channel.

Methods: The G154C mutant GIRK2 channel was expressed in Pichia pastoris. It was then purified with LMNG detergent followed by affinity and size exclusion chromatography. A GFP-His tag was included on the construct, which aided in affinity purification and was not cleaved for protein stability. Structural analysis was performed using cryo-EM and the data was processed to generate a 3D reconstruction of the channel using CryoSPARC.

Results: We obtained well-defined 2D classes of the G154C GIRK2 channel with a GFP-His tag. The classes show an intact tetramer channel with GFP tags present. With additional analysis and refinement we will compare the wildtype GIRK2 structure to that of the G154C mutation and characterize the structural changes that may contribute to the loss of ion selectivity in KLS.

Conclusions: We have successfully generated 2D classes of the G154C GIRK2 channel. Despite the limited resolution of these classes, the structure provides insights on the mutations effect on the selectivity filter. As well, further processing and 3D modeling could be solved and used to aid in future therapeutic design and characterizing the functional properties of KLS.

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Submit your abstract here:

Title:
Diminished Intrinsic Neural Timescales in Early Psychosis

Authors:
Erick Kim, Monalisa Munsi, Dale Lippincott, Robert Law, Guillermo Horga, Kenneth Wengler

Background:
Post-mortem studies of individuals with schizophrenia demonstrate reduced pyramidal-cell dendritic arborization, suggesting reduced cortical recurrent excitation. Biophysical modeling and chemogenetic-manipulation studies suggest that intrinsic neural timescales (INT) index recurrent excitation, and INT can be reliably measured using resting-state fMRI. Shorter INT have been observed in multiple schizophrenia cohorts. However, INT across non-affective and affective early psychosis remains unexplored.

Methods:
Resting-state fMRI data were analyzed from 121 patients with non-affective (n=93) and affective (n=28) psychosis and 57 healthy controls from the HCP-EP (NDA #2914). INT maps for 188 brain regions (HCP-MMP1.0 and FreeSurfer; averaged across hemispheres) were estimated. Linear regressions were used to investigate relationships between parcel-wise INT and diagnosis. FDR correction and permutation tests were used for multiple comparison correction.

Results:
Early psychosis patients had significantly shorter INT in 6 brain regions (1, V2, V3A, V7, 5m, and OP1; all pFDR<0.05) and exhibited widespread reductions (71/188 parcels, p<0.05; pFWE = 0.0231). Non-affective psychosis patients had significantly shorter INT in 2 brain regions (V7, 5m; all pFDR<0.05) and exhibited a widespread reduction in INT (80/188 parcels, p<0.05; pFWE = 0.0198) that was not observed in affective psychosis patients (4/188 parcels, p<0.05; pFWE = 0.32).

Conclusions:
We identified globally reduced cortical INT in early psychosis, particularly in non-affective but not affective early psychosis. These results replicate previous findings showing globally reduced cortical INT in chronic schizophrenia patients, including significant reductions of INT in the postcentral gyrus and occipital cortex, suggesting reduced recurrent excitation in these regions may serve as a neural substrate underlying non-affective psychosis.

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Submit your abstract here:

Prefrontal network synchrony and aperiodic features are associated with depression severity in epilepsy patients

Authors: Henry Asher, Katherine Belilty, Enkhjin Gansukh, Ignacio Saez

Background: Circuit-wide electrophysiological signatures of depression remain poorly defined. Here, we leverage a dataset of intractable epilepsy patients with varying degrees of comorbid depression to examine circuit-wide correlates of depression severity.

Methods: Using intracranial electrophysiology, we analyzed LFPs from frontal and temporal lobe regions during naturalistic restful phone or television viewing in 51 epilepsy patients with Beck Depression Inventory (BDI) scores. To analyze aperiodic activity, we fit Fitting-Oscillations-One-Over-F (FOOOF) models to separate periodic from aperiodic components, and used linear mixed effects models to investigate the effect of regional aperiodic features on BDI scores. To analyze synchronous oscillatory activity, we first applied clustering analyses to brain-wide periodic activity to identify electrophysiologically-defined oscillatory brain networks. We then computed the phase locking index (PLI) across canonical frequency bands (theta [4-8Hz], alpha [8-12Hz], beta [12-27Hz]) and used linear mixed effects models to investigate the effect of PLI on BDI scores.

Results: Aperiodic feature analyses revealed significant associations with BDI scores in prefrontal cortex and temporal lobe regions. Oscillatory synchrony analyses also revealed significant associations of theta-band PLI between regions in a prefrontal network.

Conclusions: Aperiodic and oscillatory features of electrophysiological activity are possible markers of depression severity in patients with epilepsy.

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Submit your abstract here:

Title: Multi-Tissue Co-expression Analysis in Amyotrophic Lateral Sclerosis

Faith Singh, Towfique Raj, Jack Humphrey

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by significant clinical heterogeneity, highlighting a need for deeper biological research. Integration of multiple molecular data types can transition ALS research from a generalized approach to personalized medicine by stratifying patients into molecular subtypes. Prior studies have begun to define biologically meaningful disease subtypes, many focused on single tissues, limiting the ability to distinguish region-specific effects from shared system-wide disease mechanisms. As such a comprehensive multi-tissue framework is needed to understand molecular processes that are coordinated across multiple CNS regions within the same disease, thereby refining patient stratification and capturing the underpinnings of ALS clinical heterogeneity.

Methods: This project uses postmortem tissue bulk RNA-seq data from 1,445 samples from the frontal and motor cortex, cerebellum, cervical and lumbar spinal cord of 406 ALS patients, sourced from the NYGC ALS consortium cohort. Applying weighted gene co-expression network analysis (WGCNA), we generated co-expression modules in each tissue, followed by downstream functional enrichment analysis. Multi-Omics Factor Analysis (MOFA) was then applied, to reveal latent factors across tissues.

Results: WGCNA identified 23-35 co-expression modules per tissue, with numerous significantly associated with cell-types, biological processes and clinical traits. For instance, a microglia enriched module was consistently detected across all tissues which was associated with shorter disease duration and immune related pathways. MOFA identified 14 latent factors, including factors shared across tissues, and distinct factors associated with sex, disease duration and C9orf72 status. Ongoing analyses are integrating these tissue-specific and shared factors with genetic data.

Conclusions: This integrated approach of multi-tissue networks provides a framework to reveal molecular signatures linked to clinical phenotypes of ALS and enhance patient outcomes through targeted interventions.

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Submit your abstract here:

Cerebellin-2 (Cbln2), a secreted synaptic molecule, interacts with presynaptic Nrxn and postsynaptic GluD to regulate animal behaviors associated with social interaction, emotion control, and compulsive activity. Cbln2 is robustly expressed in the ventral subiculum (vSub). This brain region is of interest because of its involvement in social interactions, social memory and emotional control. The vSub sends major projections to the nucleus accumbens (Nac), lateral septum (LS) and the medial prefrontal cortex (mPFC). The mPFC is implicated in the evaluation of social information, such as facial expressions or social contexts, and in regulating the emotional responses that accompany social interactions. Similarly, the LS is implicated in emotions, motivational and spatial behavior, while the Nac plays a pivotal role in the regulation of reward-seeking behaviors. This study focuses on understanding the circuitry of Cbln2 positive cells projecting from the vSub. We used retrograde viruses injected in suspected regions – LS, Nac and mPFC – to see if projections from the vSub are Cbln2 positive.

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Submit your abstract here:

Title:
EIF2B2 and EIF2B3 Alzheimer's risk variants disrupt microglial function via stress responses

Authors:
Francesca Garretti, Marcelina Ryszawiec, Emilea Okayasu, Joseph Kakkis, Brian Fulton-Howard, Edoardo Marcora, Alison Goate

Background:
Alzheimer's disease (AD) risk variants are enriched in microglial regulatory regions, implicating innate immunity in disease. Our lab has identified EIF2B3S404A as an APOE4-specific risk modifier and EIF2B2 as a myeloid-associated AD gene; however, their functional impact in human microglia is unknown. Both genes encode subunits of eIF2B, a central regulator of protein translation and the integrated stress response (ISR), suggesting a shared mechanism linking genetic risk to microglial dysfunction.

Methods:
We modeled EIF2B perturbations in THP-1 macrophages and human iPSC-derived microglia (iMGLs). Functional assays included phagocytosis (zymosan, myelin, Aβ), lysosomal activity (DQ-BSA, lysotracker), protein synthesis (ISR readouts), and inflammatory signaling (western blot, cytokine profiling). CRISPR-edited iMGLs (EIF2B3S404A, EIF2B2+/−) were analyzed in vitro and in xenotransplanted mouse models. Pharmacologic rescue was tested using the cGAS–STING inhibitor RU.521.

Results:
EIF2B3S404A impaired phagocytosis, reduced lysosomal function, and decreased lysosomal mass, indicating disrupted endolysosomal pathways. In contrast, EIF2B2 knockdown activated ISR signaling, reduced protein synthesis, and triggered cGAS–STING/type I interferon responses, enhancing inflammatory signaling and altering microglial function. Notably, cGAS–STING inhibition (RU.521) rescued inflammatory and functional defects in EIF2B2-deficient cells. These data identify divergent effects of EIF2B variants on microglial stress responses and function.

Conclusions:
EIF2B2 and EIF2B3 regulate key microglial pathways linking protein translation, stress responses, and innate immunity in AD. We propose that EIF2B dysfunction represents a convergent mechanism underlying microglial dysregulation in APOE4-associated disease. Ongoing studies in xenotransplanted mouse models

will define in vivo relevance. Histopathological analysis of human AD carriers will test these phenotypes in patients. Importantly, pharmacologic modulation of cGAS–STING represents a promising therapeutic strategy to rescue type-I interferon activation and downstream endolysosomal phenotypes.

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Submit your abstract here:

A Human miBrain Model Identifies Reduced Microglial P2RY12 as Protective in Parkinson's Disease

Georgia Gallagher, Andrea Perez-Arevalo, Alice Buonfigioli, Elena Coccia, Joel Blanchard

BACKGROUND: Parkinson's Disease (PD) affects nearly 10 million people worldwide and is characterized by α-synuclein accumulation and dopaminergic neuron loss. However, post-mortem human tissue studies increasingly implicate microglia, the brain's resident immune cells, with PD risk and progression. One such protective SNP (rs3732765, G>A) is associated with reduced expression of P2RY12, a purinergic receptor that regulates microglial chemotaxis and phagocytosis. This allele resides in a non-coding regulatory enhancer of P2RY12 rather than the protein sequence itself in humans, however, transcription factor binding sites are not conserved in rodent microglia, limiting the efficacy of transgenic rodent models.

METHODS: To model this protective allele in the context of human PD pathology, we generated isogenic iPSC lines (rs3732765G/G and rs3732765A/A) using CRISPR–Cas9 and differentiated them into microglia-like cells (iMGs). We integrated the microglia into the multi-cellular integrated Brain (miBrain), a human iPSC-derived brain tissue model that recapitulates key anatomical and physiological features of human brain tissue. Further, we traced the ability of both chemically inhibited P2RY12 and genetically reduced P2RY12 expression to rescue PD phenotypes in the miBrain using iPSC-derived α-synuclein overexpressing neurons.

RESULTS: Selective integration of rs3732765A/A iMGs into an otherwise rs3732765G/G miBrain significantly reduced Lewy body-like phosphorylated Syn (p-SYN), and improved both neuronal integrity and connectivity in α-synuclein overexpressing and healthy neurons. Pharmacological inhibition of P2RY12 in rs3732765G/G iMGs increased lysosomal activity to levels comparable to rs3732765A/A iMGs, resulting in reduced neuronal p-SYN accumulation and improved neuronal connectivity in miBrains.

CONCLUSIONS: These findings demonstrate that inhibited microglial P2RY12 function sufficiently improves neuronal network health in human brain models and highlights the miBrain as a unique tool both for modeling PD pathology, as well as accelerating therapeutic discovery.

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Submit your abstract here:

title: “Neural Correlates of Daily Affective Variability: Frontopolar Involvement in Mood and Anxiety Disorders”
authors: G. Dirupo, J. Beltràn, P.T. Neukam, J.W. Murrough, L.S. Morris
Background: Day-to-day fluctuations in affective states may reflect underlying difficulties in emotion regulation. While ecological momentary assessment (EMA) has revealed heightened emotional instability in mood and anxiety disorders, the neural structural correlates of this variability remain poorly understood.
Methods: Participants with mood and anxiety disorders (MA; n = 74) and healthy controls (HC; n = 63) completed 30 days of EMA assessing daily mood, anxiety, depression, distress, stress, sleep, and motivation. Day-to-day individual affective variability was quantified using the root mean square of successive differences (RMSSD). Structural MRI data were available for a subsample (MA: n = 21; HC: n = 13). Partial correlations examined associations between affective instability and prefrontal cortical thickness and volume, controlling for sex, age, and estimated total intracranial volume.
Results: The MA group showed greater instability in anxiety, distress and depression, whereas no group difference emerged for mood, sleep, or stress variability. External and Internal motivation instability was greater in participants with depression, but not anxiety and no difference was found in behavioral (steps, screen time, phone checks) variability between clinical groups. Neuroimaging analyses revealed a significant group × ROI interaction: in the MA group, greater distress instability was associated with thinner frontopolar cortex ($r = -0.53$, $p = 0.013$), while no such association was observed in HC ($r = +0.21$, $p = 0.50$; group difference: $Z = -2.04$, $p = 0.042$).
Conclusions: These findings suggest that affective instability is a transdiagnostic feature of mood and anxiety disorders, with specific motivational dysregulation characterizing depression. The association between affective variability and frontopolar cortical thickness in individuals with depression and anxiety points to potential neurobiological underpinnings of daily affective dysregulation, implicating prefrontal regions involved in emotion regulation and metacognition.

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Submit your abstract here:

Actigraphy-Derived REM Sleep Behavior Disorder Scores Predict Incident Parkinson's Disease: A Large-Scale Population-Based Study

Giorgio Ricciardiello Mejia, Andreas Brink-Kjaer PhD, Li Zhou PhD, Ryu Katelyn, Katarina Gunter PhD, Ankit Parekh PhD, Emmanuel During MD

BACKGROUND: Isolated REM sleep behavior disorder (RBD), causing abnormal movements and dream-enactment during sleep, is among the most specific prodromal markers of α-synucleinopathies, particularly along the “body-first” trajectory of Parkinson's disease (PD), whose prodromal phase can extend years to decades. RBD affects more than one million people in the United States and remains largely undiagnosed because polysomnography is scalability for large-scale screening. We evaluated whether an RBD model using wrist data developed by our group could predict incident PD in a population-based cohort.

METHODS: We analyzed 87,960 UK Biobank participants with valid 7-day wrist accelerometry. A previously validated RBD detection algorithm, trained in a clinical sample (42 RBD, 42 controls), was applied without retraining to derive subject-level RBD score. Participants were categorized into percentile-based strata (Low: 0–90th; Intermediate: 90–99th; High: 99–100th). Associations with PD were estimated using Cox proportional hazards models adjusted for age, sex, BMI, smoking, and alcohol.

RESULTS: Over a median follow-up of 10.2 years, 408 incident PD cases were identified. CI increased across strata (Low: 0.3% [273/79,328]; Intermediate: 1.4% [109/7,797]; High: 3.1% [26/835]), corresponding to risk ratios of 4.04 and 8.77 for the Intermediate and High groups, respectively, relative to Low risk. HR were 1.85 (95% CI 1.54–2.20; $p=1.4\times10^{-11}$) and 3.99 (95% CI 2.61–6.10; $p=1.6\times10^{-10}$). The continuous RBD score showed a dose–response association (HR per SD: 1.25; 95% CI 1.18–1.32; $p=2.5\times10^{-15}$) with good discrimination (C-index: 0.776).

CONCLUSIONS: Wearable-derived RBD scores are strongly associated with future PD risk and enable clinically meaningful stratification. These findings support actigraphy-based RBD assessment as a scalable, non-invasive approach for early identification of individuals at elevated risk of α-synucleinopathies.

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Submit your abstract here:

Characterizing the role of MS4A4A and MS4A6A in myeloid cells of the brain in Alzheimer's Disease

Grace Peppler, Alexandra Münch, Anastasia Efthymiou, Michael Sewell, Anthony Walley, Edoardo Marcora, Alison Goate

Background:

Genome-wide association studies (GWAS) increasingly implicate the brain's innate immune system in the etiology of Alzheimer's disease (AD), the most common form of dementia worldwide. While microglia have been the primary focus, border-associated macrophages (BAMs) are now recognized as critical contributors to brain function. A consistently replicated GWAS finding in late-onset AD is the association between polymorphisms in the myeloid-specific MS4A locus and reduced risk for AD. The membrane-spanning 4-domain subfamily A (MS4A) genes encode structurally related transmembrane proteins expressed in immune cells, though their precise functions remain unclear. Prior integrative work combining human genetics with myeloid transcriptomic and epigenomic data identified MS4A4A and MS4A6A as candidate modulators of AD risk, potentially through interactions with immune receptors such as TREM2.

Methods:

We generated loss-of-function genotypes for MS4A4A and MS4A6A in human induced pluripotent stem cells (hiPSCs) differentiated into microglia-like and macrophage-like cells, as well as macrophage-specific knockout mice crossed with AD models. We performed transcriptional profiling and functional assays to investigate the roles of these genes in microglia and BAMs.

Results:

Ms4a4a and Ms4a6d expression is enriched in BAMs. In iPSC-derived macrophages, knockout of MS4A4A and MS4A6A led to upregulation of genes involved in metabolism, cell motility, and oxidative stress protection. Additionally, MS4A6A knockout enhanced TREM2 signaling and increased TREM2-dependent calcium flux.

Conclusions:

Our prior functional validation of an MS4A risk variant suggests that the protective allele reduces expression of MS4A4A and MS4A6A. Together, these findings support the hypothesis that reduced expression of these genes promotes protective microglial and BAM phenotypes in AD. This protection may be mediated through enhanced TREM2 signaling, lysosomal function, and metabolic adaptation.

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Submit your abstract here:

Ephexin1 as a Sex- and Withdrawal-Dependent Regulator of Cocaine Seeking in the Nucleus Accumbens.

Yun Young Yim, Tamara Markovic, Alexa LaBanca, Zheng Xu, Matthew Rivera, Gregory Tan, Rita Futamura, Arthur Godino, Tukit Lam, Veronica Kondev, Yan Dong, and Eric J. Nestler

Background
Dysregulated signaling within reward-related brain regions drives drug-seeking behavior and relapse. While transcriptional responses to drugs of abuse are relatively well studied, our understanding of synaptic proteomic changes remains limited. Here, we aimed to identify sex- and withdrawal (WD)-dependent cocaine-induced changes in the NAc synaptic proteome to uncover candidate regulators of synaptic remodeling.

Methods
Wild-type mice received cocaine or saline for 7 days, followed by 24 hours or 30 days of forced abstinence. NAc synaptosomes were isolated and analyzed using LC-MS/MS. We then used viral manipulation of the differentially expressed protein (DEP), Ephexin1, in males and females to assess its role in baseline and reward-related behaviors, including open field, elevated plus maze, cocaine self-administration (SA), and saccharin SA. Finally, we performed whole cell patch clamp in Drd1- and Drd2-tdTomato mice to assess activity of medium spiny neurons.

Results
Proteomic analysis identified Ephexin1 as a sex- and WD-dependent target: increased in both sexes at 1WD, increased in males but decreased in females at 30WD. Ephexin1 overexpression (OE) reduced cocaine intake and seeking, while knockdown (KD) did not alter intake. Neither OE nor KD affected natural reward seeking. In males, Ephexin1 OE increased anxiety-like behavior and locomotion and reduced social interaction. In females, Ephexin1 KD did not affect locomotion or anxiety-like behavior but decreased social interaction. Electrophysiology showed that Ephexin1 OE reduced neuronal excitability without altering synaptic input.

Conclusion
These findings demonstrate that cocaine alters synaptic proteins in the NAc in sex- and WD-dependent ways. Targeting DEPs such as NGEF may help identify mechanisms and therapeutic targets for addiction.

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Submit your abstract here:

TITLE: ECT-Induced Verbal Memory Impairment is Unrelated to Antidepressant Response in Patients with Treatment-Resistant Depression

AUTHORS: Greta Kandel, Esha Talati, Marcella Corwin, Mackenzie Brown, Rachel Fremont, James W. Murrough, Sanjay Matthew, Amit Anand

BACKGROUND: Electroconvulsive therapy (ECT) remains a standard of care for treatment-resistant depression (TRD), though emerging data suggests ketamine offers comparable antidepressant efficacy. Memory impairment is a well-documented side effect of ECT, but it remains unclear whether this reflects a mechanism of therapeutic action or an independent side effect. This study compared verbal memory performance between treatment arms and examined whether memory change was associated with antidepressant response.

METHODS: Data were analyzed from 58 participants with TRD enrolled in the Mount Sinai ELEKT-D trial (ECT n=26, ketamine n=32). Antidepressant response was assessed using the MADRS and QIDS at baseline and end of treatment (EOT). Verbal memory was assessed using the Hopkins Verbal Learning Test (HVLT). Within-arm changes were evaluated using paired t-tests, between-arm differences with independent samples t-tests, and associations between memory and depression change using Pearson correlations.

RESULTS: Response rates were comparable across arms (ECT 42%, ketamine 41%). ECT was associated with a significant decline in delayed verbal recall ($p=0.011$), whereas ketamine showed no significant change ($p=0.806$). The between-arm difference in delayed recall change was significant ($p=0.029$, $d=0.58$). No significant between-arm difference was observed in HVLT total scores ($p=0.124$). Memory decline did not correlate with antidepressant response in either arm (all $r<0.19$, $p>0.35$), and ECT responders and non-responders showed similar memory impairment ($p=0.203$, $d=0.52$).

CONCLUSIONS: ECT-related memory impairment was not associated with antidepressant response, suggesting it represents an independent side effect rather than a mechanism of action. Ketamine may offer comparable efficacy with a more favorable cognitive profile, warranting investigation in larger samples.

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Submit your abstract here:

Developing a task to explore how internal states modulate hippocampal representations of context

Hailey L. Rosenblum, Denise J. Cai, Brian M. Sweis

How do internal states change environmental representations in the hippocampus to support adaptive, goal-directed behavior? Previous work suggests that internal states, such as thirst and hunger, impact hippocampal activity, which is well-known for supporting memory and spatial navigation. Motivational and attentional states also modulate hippocampal place codes. However, few studies have investigated how the hippocampus represents the same environment under multiple states (thirst, hunger) or the relationships between key environmental features relevant for different states (water, food locations; reward magnitude). Furthermore, it is unclear how transitions between states impact, for instance, reactivation of hippocampal ensembles that are context-dependent and important for memory consolidation. My thesis project will investigate how internal states shape the organizing principles of hippocampal contextual representations. We designed a task where mice navigate through four interconnected contexts associated with either food or water reward while food- or water-restricted. To probe how features of these contexts are represented across states, each context was associated with a low or high magnitude reward. We found that mice spent more time occupying contexts that corresponded to their restricted condition and that this preference scaled by reward magnitude, providing a behavioral framework for future experiments imaging hippocampus with Miniscopes. I hypothesize that the internal state (hunger vs thirst) will shift the geometry of hippocampal contextual representations. Specifically, the two contexts corresponding to the restricted condition will be more differentiated from one another, whereas those in the unrestricted condition will be more similar to each other. Furthermore, I predict that this reorganization emerges during offline periods. If observed, this would suggest that hippocampal contextual representations are internally driven and dynamic, serving as a flexible scaffold for state-dependent learning and memory.

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The ventral tegmental area and dorsal raphe nucleus control neuroeconomically distinct choice behavior
Authors: Hannah Kwa, Nusrat Jahan, Pia Davis, Alex Ramirez, Emma Andraka, Hailey Rosenblum, Samantha Pedersen, Benjamin Yakubov, Susanna Kasparov, Aisha Abid, Zainab Hussain, Romain Durand-de Cuttoli, Brian Sweis

How the brain makes choices depends on multiple decision-making systems. We interrogated how different regions and neurotransmitter systems contribute to distinct choice policies in mice tested on a neuroeconomic foraging paradigm. Mice have a limited time budget to forage for food rewards of varying costs (1-30s delays) and subjective value (unique flavors). Each trial had two stages: mice made deliberative accept vs. reject decisions in the offer zone and re-evaluative stay vs. quit decisions in the wait zone. We transfected the VTA or DRN of 44 Swiss Webster mice with adeno-associated viruses expressing hM3Dq, hM4Di, or no chemogenetic receptors driven by the synapsin promoter to bidirectionally manipulate neural activity when administered clozapine-N-oxide vs. saline. We found changes to choice policies regarding willingness to accept offers in the offer zone vs. willingness to wait out delays in the wait zone that depended on brain region and chemogenetic receptor. Inhibiting the VTA or DRN led to increased acceptance of offers in the offer zone with little to no change in wait zone choice behavior. Excitation of the VTA or DRN led to a decrease in accepting offers in the offer zone. Despite these differences, all animals retained sensitivity to offer cost. Interestingly, in the wait zone, excitation of the VTA led to more quitting, while excitation of the DRN led to higher patience to wait for a reward. These results suggest that dopamine and serotonin systems have distinguishable impacts on choice behavior, with shared influences on some but opposing influences on other computations measured across separable stages of the decision stream.

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Submit your abstract here:

Identification of Candidate Genes at Alzheimer's Disease Risk Loci Across Blood, Peripheral Myeloid, and Microglia Expression Quantitative Trait Locus Contexts.

Hao Sun, Alan Renton, Brian Fulton-Howard, Tulsi Patel, Edoardo Marcora, Alison Goate

Background: Alzheimer's disease (AD) risk variants are enriched in regulatory elements of myeloid cells, including monocytes, macrophages, and central nervous system-resident microglia. It remains unclear to what extent related myeloid contexts implicate overlapping versus distinct candidate AD genes across blood, peripheral monocyte/macrophage populations, and microglia.

Methods: We analyzed four European-ancestry Alzheimer's disease genome-wide association studies (GWAS) against 10 European-ancestry bulk and single-nucleus expression quantitative trait locus (eQTL) datasets spanning blood, peripheral monocyte/macrophage, peripheral foam-cell, and microglial contexts. We used COSI, an integrative framework combining a relaxed coloc pre-filter, OTTERS transcriptome-wide association study (TWAS) with an Alzheimer's Disease Sequencing Project European-ancestry linkage disequilibrium reference panel, SuSiE-coloc, and INTACT, to identify candidate AD genes across contexts, followed by pathway enrichment analyses.

Results: Across 40 GWAS-eQTL analyses, the relaxed coloc pre-filter retained 4,215 genes for downstream evaluation. COSI identified 1,214 candidate AD genes with INTACT posterior probability >0.8. Six genes were recovered in more than 20 of 40 analyses, including BIN1, PLEKHA1, CD2AP, PTK2B, CCDC6, and CASS4, indicating a recurrent core across related myeloid contexts. Blood datasets identified 920 candidate AD genes in the blood union. Monocyte/macrophage analyses identified 366 genes, and foam-cell analyses identified 176, with 113 shared. Bulk IsoMiGA and single-nucleus SingleBrain microglia eQTLs identified 288 candidate AD genes across the microglial union. Enrichment analysis highlighted endocytosis across all contexts and phospholipid efflux in foam-cell and monocyte/macrophage genes, while microglial genes showed enrichment for amyloid beta metabolic process.

Conclusion: Across four AD GWAS and 10 myeloid eQTL datasets, COSI distinguished a recurrent core of candidate AD genes from additional candidates supported in foam-cell and microglial contexts.

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Background:
The blood-brain barrier (BBB) preserves the neural microenvironment but also presents a major obstacle to drug delivery into the central nervous system (CNS). Current BBB-opening strategies mainly target endothelial cells, whereas astrocyte endfeet, which closely ensheath the brain microvasculature, remain largely unexplored as a therapeutic entry point.

Methods:
We investigated the role of the guidance receptor Plexin-B1 in astrocyte endfoot organization and BBB integrity using constitutive and astrocyte-specific Plexin-B1 knockout mouse models. BBB permeability was assessed with tracers of different molecular sizes and intravenously administered adeno-associated virus (AAV). Ultrastructural changes were analyzed by electron microscopy. In addition, single-cell transcriptomics and lipidomic profiling were performed to examine molecular alterations associated with Plexin-B1 deficiency.

Results:
Loss of Plexin-B1, either constitutively or selectively in astrocytes, disrupted astrocyte endfoot polarization and anchorage. Plexin-B1 deficiency impaired mitochondrial congregation, endosomal trafficking, and membrane stability at endfeet, and was associated with reduced aquaporin-4 and collagen IV levels. These alterations increased BBB permeability, permitting size-selective passage of high-molecular-mass tracers and enhancing delivery of intravenously administered AAV into the brain parenchyma. Ultrastructural analysis revealed swollen astrocyte endfeet and increased endothelial vesicular trafficking, consistent with enhanced transcytosis, while tight junctions remained intact in Plexin-B1 knockout mice. Single-cell transcriptomic analysis linked Plexin-B1 to astrocyte polarity and mitochondrial function, and lipidomic profiling demonstrated an altered lipid environment.

Conclusions:
Plexin-B1 is a critical regulator of astrocyte endfoot integrity and BBB function. These findings identify astrocyte endfeet as a mechanistically distinct and therapeutically tractable target for size-selective BBB opening to improve CNS drug delivery.

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Submit your abstract here:

Calvarial and femoral bone marrow exhibit different sensitivity to acute vesus chronic stress

Huipeng Huang; Scott Russo

Background: Previous work demonstrated that acute stress mobilized neutrophils from femoral bone marrow to the periphery, while chronic stress drives myeloid-biased hematopoiesis in long-bone marrow. However, how calvarial bone marrow responds to different phases of stress remained further elucidation. Given growing evidence that immune cells from skull are involved in various neurological diseases, defining stress-dependent responses of calvarial marrow may enhance understanding of stress-associated immune remodeling and investigate potential intervention.

Methods: 6-8 weeks old mice were subjected to chronic social defeat stress (CSDS) for 10 days, or to microdefeat as an acute stress paradigm. Mice were enthanized 1h after acute stress or after CSDS, and blood, femur and skull were collected and subjected to flow cytometry analysis followed by multidimensional scaling. Public single-cell RNA-sequencing datasets of bone marrow were integrated to compare stress-associated gene expression across compartments and cell types.

Results: Circulating neutrophils elevated dramatically after acute social defeat accompanied by a corresponding reduction in femoral marrow neutrophils. In contrast, calvarial neutrophils were unchanged after acute stress, and the overall immune composition remained similar to controls. Acute stress also altered peripheral blood composition with only modest shifts in femoral marrow composition. Conversely, calvarial marrow immune composition changed prominently after CSDS, while blood composition largely returned to baseline. Femoral bone marrow exhibited similar trends to calvarial marrow but with smaller effect sizes. Single-cell RNA-seq analysis indicated higher Adrb2 expression in calvarial neutrophils and granulocyte-monocyte progenitors (GMPs) than in femoral counterparts.

Conclusion: Skull bone marrow shows less sensitivity to acute stress but exhibits more prominent immune compositional changes after chronic stress. These results support hematopoietic compartment-specific stress responsiveness and indicate that calvarial marrow may engage distinct adrenergic-associated programs during chronic stress.

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Submit your abstract here:

Combinatorial Roles of EED and PICALM in Microglial Clearance Pathways in Alzheimer's Disease

Hyo Lee, Tulsi Patel, Sarah Neuner, Gloriia Novikova, Edoardo Marcora, Alison Goate

Background: The majority of AD risk variants lie in non-coding regions and appear to act by altering gene regulation in myeloid cells. While traditionally identified as the PICALM locus, fine-mapping revealed that the most likely causal variant in this locus may regulate the expression of both PICALM and a neighboring gene, EED. PICALM encodes an adaptor protein essential for clathrin-mediated endocytosis, and EED, a core PRC2 component, mediates both epigenetic gene silencing and cytosolic immune receptor signaling. While both genes are highly expressed in microglia, their possible joint contribution to AD risk is unknown.

Methods: Gene Regulatory Network (GRN) analysis: extracting genes that are co-expressed with either EED or PICALM from publicly available datasets. In vitro validation: siRNA-mediated knockdown in human iPSC-derived microglia and THP1-macrophages, followed by flow-cytometry, proteomics, and live-cell imaging.

Results: GRN analysis of human microglial transcriptomic datasets showed that EED and PICALM are highly co-expressed within modules enriched for phagocytosis and TREM2 signaling. We demonstrated that deficiency of either EED or PICALM in human macrophages impaired Aβ-42 uptake, lysosomal acidification and proteolytic activity. Expression of key lysosomal markers was altered by single knockdown of either EED or PICALM, with double knockdown yielding a more pronounced phenotype, suggesting an additive role of these genes in lysosomal function. Importantly, co-immunoprecipitation and proteomic analysis showed that cytoplasmic EED and PICALM may physically interact and converge on clathrin-mediated endocytosis pathways, highlighting them as a strong candidate gene pair for further investigation.

Conclusion: Our integration of GRN analysis with in vitro validation identified EED/PICALM as a gene pair that functionally converge on the endolysosomal pathway, and have important roles in microglial Aβ clearance and lysosomal functions.

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Submit your abstract here:

Neuroimmune control of sickness behavior

Ignacio Beccacece,1 Veronica Burstein,1 Andrea Muñoz Zamora,1 Rahul Sabnis,1 Michel Enamorado1,*

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Sickness behavior is a coordinated set of physiological and behavioral adaptations to infection that profoundly reshape organismal function. Although these responses are widely attributed to immune-derived signals, how dedicated peripheral neuroimmune circuits couple infected peripheral organs to the rest of organs and the brain remains unresolved. Here, we reveal a lung-brain neuroimmune circuit that actively instructs sickness behavior during respiratory infection. Pneumonia infection rapidly induces hypothermia and a conserved behavioral state characterized by suppressed locomotion, social withdrawal, and diminished exploratory drive. Mechanistically, TRPV1^{+} vagal sensory neurons innervating the lung selectively control hypothermia and behavior while sparing infection-induced weight loss. Surprisingly, this functional dissociation is independent on canonical peptidergic neurotransmitters, including CGRP and Substance P. In addition, genetic disruption of bacterial virulence programs and the use of immunodeficient mice models excluded canonical pathogen- and immune-derived signals as primary triggers of neuronal activation, suggesting an alternative host-pathogen interface that engages sensory pathways to regulate brain state. Together, these findings establish peripheral sensory neurons as organizers of infection-induced sickness behavior, redefining it as a neuronally encoded response that coordinates behavioral states and cross-organ communication.

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Title: Altered Cerebral White and Gray Matter Volumes during Aging and Vascular Disease in Great Apes
Authors: Isabel Paine, William Hopkins, Chet Sherwood, Melissa Edler, Mary Ann Raghanti, Merina Varghese, Patrick Hof
Background: Aging is a primary risk factor for cerebrovascular (CeVD) and cardiovascular diseases (CaVD), which are frequently associated with cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD). Neuronal loss, cognitive decline, and brain atrophy
are correlated but how vascular disease may exacerbate these age-related deficits is not well understood. Great apes are valuable models of aging because they have long life spans and display age-related pathologies in the brain and heart that are comparable to humans.
Methods: Ex vivo MRI scans of chimpanzee and gorilla brains were segmented using the SuperSynth tool in FreeSurfer. Volumes for cerebral grey and white matter were log-transformed and modeled as a function of log-transformed whole cerebral volume, study group, sex, and hemisphere, with subject included as a random intercept. Pairwise differences were evaluated using Tukey-adjusted comparisons.
Results: Preliminary analysis in chimpanzees shows that cerebral cortex volume is significantly decreased in the CeVD group compared to young and elderly controls. Cerebral cortex volume is also decreased in the CaVD group compared to young controls. Conversely, cerebral white matter volume was significantly increased in the CeVD group compared to both young and elderly controls. Preliminary analysis in gorillas shows no significant differences, but a decreasing trend in cerebral cortex in the CaVD group compared to young/middle-aged controls.
Conclusion: The lack of change in cerebral gray or white matter with age is consistent with studies examining whole brain volume changes with age in humans and chimpanzees. In chimpanzees, CeVD and CaVD may worsen mild cortical shrinkage that occurs with age.

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Submit your abstract here:

Cannabidiol Preemptively Upregulates Nrf2 Expression to Mitigate Tachycardia-Induced Oxidative Stress in Cue-Induced Anxiety-Like Behavior

Isabella Martinez, Katie Lynch, Yasmin Hurd

Background
Cannabidiol (CBD) is a promising therapeutic for anxiety, though its neurobiological mechanisms remain under investigation. Research by the Hurd Lab has modeled CBD's ability to decrease cue-induced anxiety in rodents, noting significant mitochondrial transcript changes in the Nucleus Accumbens Shell and the upregulation of the Nrf2 pathway. Nrf2 is a critical transcription factor that triggers antioxidant enzyme expression. While its role in brain regions associated with emotion is documented, its function in the heart, specifically regarding anxiety, remains unexplored. During the "fight or flight" response, the sympathetic nervous system rapidly increases heart rate, generating reactive oxygen species (ROS) as a byproduct. We hypothesized that Nrf2-driven proteins will be upregulated in animals exhibiting anxiety-like behaviors and that CBD treatment will increase Nrf2 and downstream antioxidant enzyme expression across all groups. It is further hypothesized that CBD's preemptive activation of the Nrf2 pathway will reduce markers of myocyte damage.

Methods
To evaluate this, qPCR was initially performed on heart tissue to observe gene expression changes. Following those results, the study has pivoted to immunofluorescence (IF) to examine the protein expression of Nrf2, SOD1, and Gpx3. Additionally, oxidative stress markers like 4-HNE will be assessed to clarify the interactions between CBD, Nrf2 activation, and myocardial protection.

Results
Initial qPCR analysis of heart tissue found no significant correlations at the transcript level. This lack of transcriptional change prompted the current shift in methodology toward protein-level analysis and immunohistochemical markers of oxidative damage.

Conclusion
By assessing these markers, this research aims to determine if CBD provides a protective mechanism against the oxidative stress generated during acute sympathetic activation.

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Submit your abstract here:

TITLE: Progression of medial entorhinal spatial coding deficits in a mouse model of temporal lobe epilepsy

BACKGROUND: Temporal lobe epilepsy (TLE) is a debilitating disorder that includes pervasive memory impairments that significantly impact patient quality of life. Using rodent models of TLE, our lab has previously shown progression of learning and memory impairments along with spatial coding deficits in the hippocampus. Whether these impairments in hippocampal spatial coding are due to only local processing deficits or can be attributed to altered spatial coding in upstream regions remains poorly understood. Indeed, hippocampal inputs from the medial entorhinal cortex (MEC) have been shown to be spatially modulated and their activity is necessary to facilitate hippocampal spatial memory and encoding. Furthermore, seizures have been shown to cause transient reorganization of MEC circuits due to cell damage.

METHODS: We used viral vector constructs for layer specific calcium indicator expression in either MECII stellate cells or MECIII excitatory neurons and performed in vivo calcium imaging with Miniscopes in freely behaving mice as they performed a battery of spatial foraging or memory tasks.

RESULTS: Our preliminary data suggests that pilocarpine induced TLE causes disruptions to the spatial coding of both MECII stellate cells and MECIII neurons. In particular, we have found reduced stability of spatial representations in MEC of epileptic mice, which emerged earliest in MECIII neurons. Thus, this region appears to be a potential site of early dysfunction in epilepsy.

CONCLUSIONS: These preliminary results suggest that CA1 spatial coding deficits may be due in part to altered inputs and implicates upstream MEC as another site of functional pathology in TLE. Together, this work uses state-of-the-art recording techniques to determine precisely where and how spatial coding breaks down in epileptic mice, revealing new insights into the cause of cognitive deficits.

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Submit your abstract here:

Quantifying Neuron-Glia Metabolic Flux Across Brain Development

Jake Vaynshteyn, Isaac Marin-Valencia, Jeffry Alger, Pierre-Gilles Henry, Manuel Gonzalez Rodriguez

Background: The developing brain transitions from glycolysis-dominant to oxidative phosphorylation-dominant energy metabolism, yet the cell type-specific flux dynamics underlying this shift remain poorly understood. Prior metabolic models were largely derived from non-neural tissues such as liver and heart, limiting their applicability to the brain. Notably, isolated alterations in pyruvate dehydrogenase (PDH) flux — linking glycolysis to the TCA cycle — are sufficient to precipitate severe neurodevelopmental pathology, underscoring the need for cell-type-resolved flux analyses. To address this gap, we developed two computational models for quantitative flux estimation in glutamatergic neurons and glial cells.

Methods: C57BL/6J mice at postnatal days 7, 15, and 21 (P7, P15, P21) received [U-^{13}C]-glucose as a metabolic tracer. Cerebellum (CB) and forebrain (FB) were analyzed by GC-MS to quantify isotopologue enrichment across TCA cycle intermediates. Two models were applied: (1) a steady-state relative flux model normalized to citrate synthase activity, adapted from tcaCALC; and (2) a two-compartment dynamic model partitioning absolute fluxes (μmol/mg/min) between glutamatergic neuronal and glial compartments.

Results: The relative flux model revealed age-dependent PDH increases in both regions, rising from P7 (CB: 0.29 ± 0.05; FB: 0.32 ± 0.05) to P21 (CB: 0.96 ± 0.06; FB: 0.97 ± 0.05). The two-compartment model extended these findings with cell-type resolution: neuronal TCA flux (F_x) in the forebrain increased from 0.37 μmol/mg/min at P7 to 2.75 μmol/mg/min at P21, with parallel maturation in glial cells across both regions.

Conclusions: These complementary frameworks capture metabolic heterogeneity between glutamatergic neurons and glial cells across neurodevelopment, surpassing non-neural-derived models. This approach offers a tractable route to identifying metabolic targets in neurodevelopmental disorders.

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Submit your abstract here:

Medial Amygdala Neural Subtype Contributions in the Glucose Response to Stress

Jamie R.E. Carty, Natalie J. Spence, Azra Krek, Sabrina Petri, Kristen Beaumont, G. C. Yuan, Sarah A. Stanley

BACKGROUND: The MeA is stress responsive and has non-overlapping neural populations that project to several downstream brain regions including the ventromedial hypothalamus (VMH). MeA is a major driver of exclusively the SNS mediated glucose response to stress. MeAVMH neurons are enriched in several genes related to diabetes and obesity phenotypes. Consequently, our objective is to establish the genetic identities and functional mechanisms by which specific MeA neural populations modulate blood glucose in response to stress.

METHODS: We use Cre driven chemogenetic activation of several cell types that are enriched in MeAVMH neurons and assess changes in glucose and stress metabolism. Specifically, we use vGlut2-cre mice to assess glutamatergic neurons, vGat-cre mice to assess GABAergic neurons, Gk-cre mice to assess glucokinase-expressing neurons, and BNDF-cre mice to assess brain-derived neurotrophic factor-expressing neurons. In these different Cre lines, an activating cre-dependent chemogenetic virus (DIO-hM3DGq) is expressed in the MeA and, after 4-week to allow for viral expression, changes in glucose metabolism, the involvement of gluco-regulatory organs, and glucose-stress reactivity were assessed.

RESULTS: MeAGLUT and MeAGABA neurons contribute to changes in glucose metabolism, but do not further exacerbate the glucose response to stress. MeAGk neurons function as a counterregulatory response to stress-induced increases in blood glucose. MeABDNF neurons can utilize multi-organ recruitment to improve the metabolic response to stress.

CONCLUSIONS: These studies will establish that MeA neural-subtype activity and peripheral organ function have causal relationships that drive blood glucose stress responses and build the foundation for developing novel therapies to regulate amygdala circuit activity, improve glucose control, and so advance T2D treatment, independently of stress-induced anxiety behavior.

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In vivo photorelease of oxytocin using photoswitchable nanovesicles modulates hippocampal circuit dynamics and social behavior

J. Taura Iglesias, H. Tajarenejad, L. Nahar, X. Yu, Z. Qin, P. A. Slesinger

Background: Precise spatiotemporal control of neuropeptide release in vivo remains a major challenge for dissecting neuromodulatory mechanisms underlying brain function and behavior. We previously developed photoswitchable lipid nanovesicles (“azosomes”) that enable light-triggered cargo release. Here, we extend this platform to achieve controlled neuropeptide delivery in vivo and link it to circuit activity and behavior.
Methods: We combined azosome infusion with optofluidic cannulas and fiber photometry in freely behaving mice. Calcein-loaded azosomes were used to characterize in vivo release dynamics, including light power, pulse duration, and post-infusion stability. Oxytocin (OT)-loaded azosomes were validated using the OT sensor MTRIA-OT with dual-color photometry and pharmacological blockade using OVTA (Ornithine-VasoTocin Analog), a peptide-based oxytocin receptor antagonist. Behavioral effects were assessed in a social interaction assay, while circuit activity was monitored using MTRIA-OT/Vglut1-GCaMP imaging.
Results: Azosomes enabled robust, repeatable, light-dependent cargo release in vivo, with efficiency tunable by stimulation parameters. High-power stimulation achieved maximal release with short pulses, while lower power required longer durations. Azosomes retained functionality for several hours after infusion, with near-complete release maintained for ~2 hours. Photorelease of OT produced rapid, receptor-specific increases in MTRIA-OT signals without detectable leakage prior to stimulation, and elevated OT levels were sustained during behavioral testing. In the hippocampal CA2 circuit, light-triggered OT release reduced latency to initiate social contact and shortened interaction duration without altering contact frequency. Elevated OT reshaped signaling dynamics during social encounters and suppressed excitatory activity, reducing both frequency and amplitude of Vglut1-positive neuronal transients.
Conclusions: These findings establish azosomes as a platform for temporally precise neuropeptide delivery in vivo and demonstrate that controlled oxytocin release modulates hippocampal circuit dynamics and social behavior.

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Submit your abstract here:

CA1-specific hippocampus-ACC hyperconnectivity in major depressive disorder revealed by 7T fMRI

Jenna Jubeir, James W. Murrough, Yael Jacob

Background

Major depressive disorder (MDD) is associated with increased hippocampus–anterior cingulate cortex (ACC) functional connectivity (FC). Preclinical studies implicate CA1-specific hippocampal projections in stress-related pathology, but subfield-specific FC of the hippocampus–ACC pathway is unresolved due to the coarse spatial resolution of 3T fMRI. We leveraged 7T fMRI to test whether CA1 preferentially contributes to hippocampus–ACC connectivity alterations in MDD.

Methods

We analyzed 7T MRI data for 15 MDD patients and 19 controls. High-resolution T1 (0.7mm isotropic) and T2-TSE (0.4x0.4x2.0mm; coronal-oblique) images were used for ACC and hippocampal subfield segmentation (FreeSurfer 7.4.1). Resting-state fMRI (1.1mm isotropic) was preprocessed with fMRIPrep and AFNI. FC was computed in native space between hippocampal subfields and dorsal ACC (dACC) and rostral ACC (rACC). Group differences were tested using linear models with FDR correction.

Results

Among subfields (CA1, CA2/3, dentate gyrus, presubiculum, parasubiculum and subiculum), only left CA1 exhibited increased FC with ipsilateral dACC in MDD vs. controls ($t=3.39$, $p_{cor}=0.002$, $p_{fdr}=0.023$, $d=0.93$). A trend-level increase in left CA1-contralateral dACC FC was also observed ($t=2.91$, $p_{cor}=0.006$, $p_{fdr}=0.08$, $d=0.73$). No subfield–rACC FC was significant. Exploratory analysis in MDD group revealed no association between left CA1–dACC FC and depressive symptoms. In contrast, right CA1–dACC FC correlated with hedonic capacity (ACIPS, $r=0.58$, $p_{cor}=0.03$) and reflective rumination (RRS-reflection, $r=0.61$, $p_{cor}=0.02$).

Conclusions

Using subfield-resolved 7T fMRI, we identified that hippocampus–ACC hyperconnectivity in MDD localizes to CA1, mirroring preclinical evidence of CA1-driven circuit dysfunction. This study provides a novel translational link between human neuroimaging and preclinical circuit frameworks of depression.

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Submit your abstract here:

Background: Cerebral small vascular disease (cSVD) is an age-dependent disorder responsible for 25% of ischemic strokes and a major cause of cognitive decline and dementia, yet no therapies exist. Age-related loss of NOTCH3 activity promotes vascular cell degeneration and is a key driver of age-related cSVD. Mutations in NOTCH3 cause CADASIL, the most common monogenic form of cSVD, characterized by migraines, early-onset strokes, and dementia. Our lab's previous unbiased plasma proteomics in CADASIL identified immune-related abnormalities of high relevance to T cell chemotaxis. Given growing evidence that T cells regulate cerebrovascular health, we hypothesize that dysregulated T cell responses contribute to CADASIL pathogenesis.

Methods: To assess T cell involvement in CADASIL, we employed a multimodal approach combining CyTOF-based immunophenotyping and single-cell RNA sequencing of PBMCs from age- and sex-matched CADASIL participants (n=29) and controls (n=22) (aged 26-80 years), alongside high-throughput proteomic profiling of plasma and post-mortem brain vascular extracts from CADASIL and control subjects.

Results: CADASIL showed reduced T cell recruitment to the brain vasculature and a marked decrease in $CD8^+$ T cells compared to controls. Effector CD8+ T cells from CADASIL showed diminished expression of key activation markers. Consequently, CADASIL had a higher frequency of CD57+CD28-CD8+ T cells, a subset associated with cellular senescence. Notably, senescent-like $CD8^+$ T cells were elevated as early as in their 20s in CADASIL and were significantly associated with worse cognitive performance. Lastly, exposing NOTCH3 mutant vs isogenic iPSC-derived vascular cells with diseased vs healthy PBMCs showed reduced T cell adhesion in diseased vasculature, suggesting impaired T cell-vascular interactions in CADASIL.

Conclusion: Together, these findings raise the possibility that T cells may contribute to the pathogenesis of cSVD-related dementia, an area that remains poorly understood, with high therapeutic relevance for brain healthspan.

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Investigating the impact of P2RY12 genetic variants in a 3D iPSC model of alpha-synuclein aggregation

Jennifer Strong, Andrea Perez Arevalo, Raphael Kubler, Oriol Narcis, Daniele Mattei, Joel Blanchard, Towfique Raj

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by aggregation of α-synuclein (α-syn) and progressive neuronal loss. While neuronal pathology has been extensively studied, the role of glial cells in modulating α-syn uptake, clearance, and toxicity remains poorly understood. Emerging evidence suggests that microglia and astrocytes actively contribute to α-syn processing, yet how genetic variation influences these responses is unclear. The microglial receptor P2RY12 variant rs3732765 has been implicated in PD risk and altered immune signaling.
Methods: To define genotype-specific glial responses, we will integrate RNA sequencing data across human iPSC-derived models and postmortem datasets. In Aim 1, bulk RNA-seq of CRISPR-edited iPSC-derived microglia (A/A vs G/G) will identify P2RY12-dependent co-expression modules and stress pathways at baseline, followed by validation in genotype-stratified postmortem microglia. In Aim 2, single-cell RNA-seq of multicellular miBrain models containing A53T α-syn–overexpressing neurons will assess how P2RY12 genotype shapes microglial states and intercellular signaling across microglia, astrocytes, and neurons.
Results: We hypothesize that the protective rs3732765-A allele attenuates maladaptive microglial activation and proteostatic stress responses, limiting downstream astrocyte reactivity and neuronal dysfunction during early α-syn challenge.
Conclusions: This work will generate a genotype-resolved, multicellular atlas of early glial responses to α-syn and establish mechanistic links between P2RY12 variation and neuroimmune resilience. These findings may reveal protective immune pathways that can be therapeutically targeted in PD.

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Experience-dependent retrosplenial cortex activity and neuronal alterations in a mouse model of autism

Jeronimo Lukin, Khaled Althobaiti, Marta Garcia-Forn, Rodrigo Muñoz-Castañeda, Wei Wang, Zhuhao Wu, Silvia De Rubeis

BACKGROUND: Altered cortical circuit development has been strongly implicated in autism spectrum disorders (ASD). Pathogenic variants in DDX3X cause DDX3X syndrome, a neurodevelopmental condition frequently co-morbid with ASD. Our laboratory generated the first mouse model with construct and face validity for Ddx3x haploinsufficiency. Female Ddx3x$^{+/-}$ mice exhibit abnormal neocortical development and altered behavior during open field (OF) exploration; however, the cellular and circuit mechanisms linking these phenotypes remain poorly defined.

METHODS AND RESULTS: To bridge this gap, we mapped whole-brain neuronal activity in Ddx3x$^{+/-}$ and control female mice following OF exploration using iDISCO+ tissue clearing combined with Fos immunolabeling and light-sheet microscopy. Ddx3x$^{+/-}$ mice display a distinct experience-dependent activation pattern, revealing differentially engaged brain regions. Notably, enhanced activation was observed across cortical areas, including the retrosplenial cortex (RSP), a region critical for spatial information processing and priorly linked in ASD deficits.
To establish causal and regional specificity, we controlled RSP activity using chemogenetics via stereotaxic delivery of inhibitory DREADDs and assessed their effects on OF behavior in both genotypes. Additionally, we induced region-specific Ddx3x ablation through stereotaxic injection of a Cre viral vector into the RSP of Ddx3xflx/+ mice. Both manipulations showed a partial reversion of the observed maladaptive behavior. Additionally, using a Thy1-GFP reporter line, we examined experience-dependent dendritic spine remodeling and performed transcriptomic analyses to identify molecular signatures altered by Ddx3x haploinsufficiency.

CONCLUSIONS: Together, these findings implicate dysregulated RSP circuitry in abnormal spatial exploration in Ddx3x haploinsufficient mice and highlight experience-dependent, malleable circuit and molecular targets relevant to DDX3X syndrome and ASD.

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Title: Treatment Strategies in Cerebellar Intracerebral Hemorrhage: Comparative Outcomes and Case-Based Evidence for Minimally Invasive Surgery.

Authors: Jimin Shin, Kimberly Agosto, Mikhail Nasrallah, Tannishtha Som, Christopher P. Kellner

Background: Cerebellar intracerebral hemorrhages (cICH) are a devastating subset representing about 10% of all ICH. While surgical management is indicated in select cases, it is often followed by long-term neurological complications. We evaluated the differences in outcomes between treatment strategies for cICH, along with two examples of cerebellar minimally invasive hematoma evacuations (MIS).

Methods: We performed a single-center retrospective review of consecutive patients with cICH from 2018 to 2026. Baseline clinical and radiographic variables were collected. ICH volume was calculated by the ABC/2 method.

Results: 67 patients with spontaneous cICH were included in our single-institution analysis, of which two patients who underwent SCUBA evacuation were excluded from primary analysis. Median age was 67 years (IQR 55-79), 53.8% of patients were male, and the median presenting systolic blood pressure was 173 mmHg (IQR 144.5-201.5). Patients who underwent surgical intervention remained in the hospital longer (median 20.8 days IQR 10.4-31.2 days) than their counterpart (median 7.8 days IQR 3.9-11.6 days, $p < 0.001$). However, median discharge mRS ($p = 0.679$) and mortality ($p = 0.838$) remained similar for both groups.

Two patients underwent SCUBA evacuations. The average length of stay for these two patients was 32.3 days, and both patients were discharged to subacute rehabilitation facilities. The average evacuation percentage was 93.9% for MIS patients, as compared to 75.6% for patients who underwent traditional craniotomy.

Conclusion: Our data demonstrates that, while surgical intervention lengthens hospital stay, it does not worsen mortality nor affect functional status at discharge. Minimally invasive surgery can be a promising treatment modality in cICH evacuation, though randomized studies are necessary to evaluate its safety and effectiveness in this population.

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Peripheral immune interactions at the endothelium following stress and antidepressant treatment

Johana Alvarez, Hsiao-Yun Lin, Flurin Cathomas, Rachel L. Fisher-Foye, Huipeng Huang, Teagen Daly, Eva Kuzyk, Lyonna F. Parise, Kenny L. Chan, Aarthi Ramakrishnan, Molly Estill, Li Shen, Scott J. Russo

BACKGROUND: Preclinical and clinical studies link alterations in the immune system to stress-related disorders. Critically, blood-brain barrier (BBB) endothelial cells interface directly with circulating immune cells and their released factors. Current research highlights region-specific differences in brain endothelial permeability and immune cell migration following chronic stress. A mechanistic understanding of how these changes occur in stress-responsive brain regions, including the nucleus accumbens (NAc), remains incomplete. Furthermore, the effects of antidepressant treatment on BBB permeability and the peripheral immune system remain insufficiently characterized.

METHODS: We collected endothelial cell mRNA from the NAc of male mice following chronic social defeat stress (CSDS) using translating ribosome affinity purification. We completed differential gene expression (DGE) analysis and gene set enrichment analysis for stress-susceptible, resilient, and control animals. Concurrently, fluoxetine was administered to mice for 2 and 4 weeks following CSDS, after which we assessed BBB permeability using the Evans Blue Assay and immunohistochemistry.

RESULTS: CSDS strongly affects NAc endothelial cells in stress-susceptible mice, with greater DGE than in stress-resilient mice. Following gene ontology analysis, stress-susceptible mice demonstrate upregulation of genes associated with endothelial cell junction organization and adhesion compared to stress-resilient mice. Furthermore, we observed a significant negative correlation between Evans Blue permeability and two weeks of fluoxetine treatment.

CONCLUSIONS: Our work aims to 1) virally manipulate the expression of genes related to immune cell recruitment to the endothelium and BBB permeability and 2) determine the mechanism underlying decreased BBB permeability following fluoxetine treatment. This work will uncover regional differences in endothelial cell communication with the immune system following stress and antidepressant treatment.

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Neurodegeneration and inflammation in a novel spinocerebellar ataxia 13 preclinical model

Junxiang Yin, Michael Wu, Jennifer White, Swati Khare, Aamir R. Zuberi, Ming Gao, Cathleen M. Lutz, Kyle D. Allen, Ashley Stokes, Harry S. Nick, Michael F. Waters.

BACKGROUND: Neuroinflammation is a critical pathological feature underlying neurodegenerative diseases. Spinocerebellar ataxia 13 (SCA13) is a heterogeneous ataxia with neurodegenerative and currently without effective treatment. Our prior work identified human KCNC3 gene mutations as causative for SCA13. The precise nature of the inflammation and its link to neurodegeneration in SCA13 remains elusive.

METHODS: We engineered a single Kcnc3 R424H mutation (analogous to the human SCA13 KCNC3 R423H allele) into mice using CRISPR/Cas9. We performed thorough phenotypic analyses including motor function and brain segmental /cerebellar volume at multiple timepoints. We then investigated both neurodegenerative Purkinje cell (PC) loss and inflammatory responses within the cerebellum and systemically.

RESULTS: At 3 and 6 months of age, the R424H mice displayed profound neurological motor dysfunction, including high-frequency tremor, aberrant gait, and a decreased latency to fall. Electrophysiology revealed dysregulated spontaneous firing in PCs. Pathological examination confirmed progressive PC degeneration and cerebellar atrophy. Critically, we observed a pronounced activation of microglia and astrocytes within the cerebella of R424H mice. Pearson correlation analyses highlighted a strong inverse correlation between the number of surviving PCs and markers of inflammatory activation.

CONCLUSIONS: Our R424H mice establish a novel model of brain hypoplasia and neurodegeneration caused by dysfunction of a voltage-gated potassium channel mimicking SCA13R423H, exhibiting significant motor deficits, prominent PCs loss, cerebellar inflammation, and atrophy. This study suggests that the aberrant activation of inflammatory immune cells, notably astroglia and microglia, is associated with PC demise in the cerebellum. We propose that this abnormal neuroinflammation plays a significant and potentially aggressive role in driving the progression of neurodegeneration in SCA13.

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Submit your abstract here:

Theta-Band Activity in the Globus Pallidus Externa Reflects Cognitive Control Demands in an Economic Decision-Making Task

Justice Simonetti, Zarghona Imtiaz, Brian Kopell, Andrew Smith, Martijn Figee, Xiaosi Gu, Vincenzo Fiore

Background: Deep brain stimulation (DBS) recordings in Parkinson's disease patients have provided direct human evidence that the subthalamic nucleus (STN) and the hyperdirect pathway contribute to cognitive control. In contrast, the role of the globus pallidus externa (GPe)—a central node in the long- and short-indirect basal ganglia pathways—remains poorly understood. Here, we leverage rare intracranial local field potential (LFP) recordings from the human GPe in 10 patients undergoing DBS for severe obsessive–compulsive disorder (OCD) to examine its contribution during an economic decision-making task.
Methods: LFPs were recorded bilaterally from DBS electrodes implanted in the GPe of patients with severe OCD. Participants performed the Ultimatum Game, deciding trial-by-trial whether to accept or reject variably unfair monetary offer splits. Recordings were obtained pre-stimulation and after 2, 4, and 6 months of chronic therapeutic DBS. Behavior was modeled using a heuristic algorithm that parameterized each participant's "tipping-point" offer (TPO; acceptance threshold). The heuristic model was selected because it performed at least as well as, or better than, more complex canonical reinforcement-learning models.
Results: Left-hemisphere theta-band activity immediately following offer presentation was significantly elevated at DBS initiation relative to the 6-month time-point (cluster-based permutation test: n permutations=2000, mass=+24.61, p=0.025). This effect was specific to trials adjacent to each participant's tipping-point offer (−1, 0, and +1 relative to TPO) and was not observed for non-adjacent trials. Notably, these trials were not associated with significantly longer reaction times. These findings suggest that prior to chronic DBS, participants engaged greater cognitive control when evaluating offers near an internal decision boundary.
Conclusion: Human GPe theta signals decision-boundary cognitive control during economic choice before chronic DBS.

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Submit your abstract here:

Mapping offline activity in the retrosplenial cortex

Ann Pierre Louis, Justin Lines, Austin Baggetta, Bumjin Ko, Denise Cai

BACKGROUND: The retrosplenial cortex is involved in spatial navigation, the consolidation of spatial memory, and one of the initial brain regions affected in Alzheimer's disease. During sleep, network events in the retrosplenial cortex are aligned to hippocampal signatures that are key to offline memory processing, however cellular recordings during sleep in retrosplenial cortex are lacking. Understanding the role of retrosplenial cortex during memory consolidation processes has the potential to identify a novel therapeutic target in the treatment of neurodegenerative disease.

METHODS: We have developed a novel visuospatial task, named Quadfield, to capture rich encoding from the retrosplenial cortex during learning across days. During behavior, we image calcium activity from neurons in layers 2/3 of the retrosplenial cortex using Miniscopes in freely behaving animals. To test the causal role of retrosplenial cortex on spatial learning and memory we use an NMDA-mediated lesion in one cohort of mice as well as the inhibitory metabotropic DREADDs (AAV8-hSyn-HM4Di-mCherry) to limit the activity of the retrosplenial cortex during spatial learning and memory in another cohort.

RESULTS: Mice learn the task over 5 days of training and can correctly recall reward sites several weeks out. Mice had reduced initial recall following retrosplenial cortex lesion if cues were removed from the arena. From the recordings of calcium activity, we quantify neuronal activity in the retrosplenial cortex corresponding to elements of behavior, as well as neuronal activity present during offline recordings. Further, the inhibition of the retrosplenial cortex via pharmacogenetics reduced the initial recall in contextual fear conditioning.

CONCLUSIONS: Retrosplenial cortex is involved in the encoding of spatial learning and memory tasks, and retrosplenial cortex may encode landmarks in the environment to influence spatial learning and memory.

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Comparison of EMG, Video, and Actigraphy Signals for Detecting Motor Activity in REM Sleep Behavior Disorder

Kang Hyun Ryu, Giorgio Ricciardiello Mejia, Salonee Marwaha, Andreas Brink-Kjaer, Emmanuel H. During

Background: Electromyography (EMG), video-polysomnography (vPSG), and wrist actigraphy are each used to develop diagnostic algorithms for Rapid eye movement sleep behavior disorder (RBD). However, the extent to which they capture overlapping versus distinct motor phenomena remains unknown. We evaluated the respective contributions of actigraphy, EMG and vPSG to the measurement of REM-sleep motor activity.
Methods: Seventeen adults with RBD (Mount Sinai n = 9; Stanford n = 8) and eight control participants from an open dataset underwent vPSG and concomitant wrist actigraphy. Flexor digitorum superficialis EMG activity and video-detected movements were manually scored in 3-second mini epochs. Actigraphy was quantified using an acceleration-magnitude–based activity count model. Statistical and agreement analyses were performed to assess the motor events captured by all three, any two, or each modality independently during REM sleep. Results: In participants with RBD, actig-raphy-derived movement load was significantly higher during REM sleep than during non-REM stages, a pattern not observed in control participants. Across 12,941 3-second mini epochs, EMG, actigraphy, and video detected 1703, 1613, and 811 motor events, of which 413 were detected concurrently by all three modalities. Pairwise agreement was moderate and increased from EMG–actigraphy ($\kappa = 0.27$) to actigraphy–video ($\kappa = 0.41$) and EMG–video ($\kappa = 0.45$). Of EMG-detected events, 49.0% were also detected by actigraphy; of actigraphy-detected events, 37.2% were detected by EMG and 34.9% by video. Actigraphy activity counts were highest for events detected by all three modalities and lowest for actigraphy-only events.
Conclusions: Actigraphy-measured REM-related motor activity was elevated in RBD but not in controls. EMG, actigraphy, and video captured partially overlapping motor events in RBD patients, with actigraphy showing the highest sensitivity and video the lowest.

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Submit your abstract here:

Anxiety-Like Behavior Induces Lipidomic Alterations in the Nucleus Accumbens Shell

Authors: Katie Lynch, Joseph Landry, Jacquie Ferland, Alex Chisholm, Krishnarao Maddipati, Yasmin L. Hurd

Background: Anxiety disorders represent a major mental health crisis in the United States, affecting roughly 40 million people. Recent research has established a connection between dysregulation of the blood brain barrier in animals exhibiting anxiety-like behaviors. Critical to blood brain barrier pathology is the generation of lipid mediators signaling disruption, released from vasculature and endothelial cells. Many of these are derived from polyunsaturated fatty acids (PUFA's). A recent study from the Hurd Lab demonstrated that linoleic acid (LA), an essential PUFA, positively correlate with anxiety-like behaviors. Cannabidiol (CBD) administration attenuated both the increase in LA and anxiety-like behavior. However, the broader PUFA metabolome in the brain associated with anxiety-like behavior has not been characterized.

Methods: Male rats (n=48) underwent a 6-minute shock session with or without a lemon oil cue. One week later, they were re-exposed to the cue in an open field test to assess anxiety-like behavior. Following a one-week rest period, animals underwent three consecutive days of one 6-minute shock session, again followed by the open field testing. Animals were euthanized one hour after behavior measurements, and brains flash frozen. Punches of the nucleus accumbens shell (NAcSh) were analyzed using liquid chromatography–mass spectrometry.

Results: Cue-exposed animals exhibited significantly increased anxiety-like behaviors compared to controls. Lipidomic analysis revealed significant elevations in several pro-inflammatory lipid mediators, including 13-HODE, a byproduct of LA metabolism. CBD administration further increased 13-HODE levels.

Conclusions: Anxiety-like behavior is associated with dynamic alterations in the PUFA metabolome within the NAcSh. The increase of 13-HODE levels upon CBD administration suggests CBD's potential treatment mechanism as a selective modulator of arachidonate lipoxygenase (ALOX) pathways in the brain.

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Submit your abstract here:

Disrupted Long-Range Inputs to Dentate PV^+ Interneurons in Experimental Temporal Lobe Epilepsy

Katherine Toole, Anish Saxena, Chris Adam, Tristan Shuman

BACKGROUND: Temporal lobe epilepsy (TLE) is a neurological disorder characterized by recurrent seizures and is often comorbid with cognitive deficits, including impairments in learning and memory. The hippocampal dentate gyrus (DG) plays a critical role in these processes and is known to be disrupted in both TLE patients and animal models. Parvalbumin-positive (PV^+) interneurons provide fast, feedforward inhibition that is essential for limiting overexcitation in the DG. Previous work from our lab demonstrates that the spike timing of DG PV^+ interneurons is disrupted in TLE, impairing their normal function. However, it remains unclear whether dysfunction in these PV^+ interneurons arises from alterations in their upstream synaptic inputs.

METHODS: To test this, we administered a cre-dependent modified monosynaptic retrograde rabies virus to PV-Cre mice. TLE was induced using pilocarpine, and tracing experiments were conducted approximately 22 weeks post-induction. A cre-dependent helper virus was first injected into the DG to restrict rabies infection to PV^+ interneurons and enable single-synapse retrograde spread. This approach allowed us to map and quantify presynaptic inputs to DG PV^+ cells in control and epileptic mice.

RESULTS: Compared to controls, epileptic mice showed an overall reduction in long-range presynaptic input cells with a statistically significant loss of input from the medial entorhinal cortex (MEC). No differences were observed in the number of starter cells.

CONCLUSIONS: Our findings indicate that long-range cortical inputs, particularly from the MEC, onto DG PV^+ interneurons are selectively disrupted in chronic TLE. This loss of upstream drive may contribute to impaired feedforward inhibition and dentate gyrus dysfunction. Targeting these circuits may provide new therapeutic strategies for TLE.

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Submit your abstract here:

VoxLoc: Automated shape metric guided voxel localization for magnetic resonance spectroscopy

Keith Werling, Sairam Geethanath, Lazar Fleysher, Keren Bachi

Background

Magnetic Resonance Spectroscopy (MRS) is widely used to study metabolites in neurological and psychiatric conditions, but accurate single-voxel placement remains challenging, particularly for small/heterogeneous targets, with manual placement and ad hoc rotation schemes being the standard. Despite advances in neuroimaging software, no atlas-based, automated, and open-source solution exists for real-time modality agnostic voxel placement. We present VoxLoc, a fast, robust tool for accurate, real-time, repeatable voxel localization.

Methods

Voxel localization was evaluated using the test–retest Human Connectome Project 2025 structural dataset of 45 healthy individuals. Left and right amygdala were segmented with FSL-FIRST. Retest volumes were randomly rotated to simulate longitudinal variability. Grid search leveraging cube rotational symmetry and Broyden-Fletcher-Goldfarb-Shanno (BFGS) refinement determined voxel location via quadrature over the blurred distance function (DF) shape metric. Overlap ratios and cube-center distances were calculated after alignment of the test-retest volumes.

Results

Overlap ratios were high and tightly distributed (right: 0.88 ± 0.008, left: 0.89 ± 0.007; SD = 0.057/0.048). Test–retest cube-center differences were small (0.55 ± 0.05 mm; SD = 0.32/0.30 mm). Localization was fast, averaging ~30 secs on a 4.4 GHz Mac Mini M4 Pro using a 60^3 sampling grid and 33 rotational axes in the grid search.

Conclusions

The tool achieves accuracy comparable to Siemens AutoAlign (≈0.91 average overlap ratio) without requiring manual baseline positioning or registration. The DF-based framework generalizes to other shape or modality-

specific metrics and can incorporate tissue-avoidance constraints for improved tissue targeting and individualized. VoxLoc's precision, efficiency, and flexibility make it suitable for rapid deployment across diverse MRS studies. VoxLoc is currently under development as a Python package and will include an advanced visualization interface to support real-time quality control and interactive localization planning.

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Oligodendrocyte rejuvenation and blood–brain crosstalk in the setting of aging and Alzheimer's disease pathology

Kevin Spehar, Sarah M. Philippi, Henry Shell, Joseph M. Castellano

Background: Aging reduces overall brain function characterized by molecular, cellular, and cognitive changes. Since aging is a major risk factor for many neurological conditions, including Alzheimer's Disease (AD), its study offers insights into AD pathobiology. One strategy involves leveraging the systemic environment; studies show aged mice exposed to the young peripheral environment exhibit improved synaptic plasticity, reduced neuroinflammation, and improved hippocampus-dependent cognitive performance. Systemic treatment with youth-associated proteins demonstrates similar rejuvenating potential. While these studies characterized rejuvenating effects in immature and mature neurons and microglia, the oligodendrocyte (OL) lineage remain unexplored despite clear interactions with both. The OL lineage appears highly responsive to the systemic environment, but a thorough functional assessment has not been undertaken. Moreover, while recent AD studies have linked the OL lineage and amyloid accumulation, especially in terms of myelination dysfunction, whether the systemic environment regulates these processes is unknown.

Methods: Using single cell transcriptomic data and immunofluorescent imaging in brain tissue from young plasma-injected or control-injected APPNL-G-F mice, we evaluated how the OL lineage responds to systemic cues during aging and AD pathology.

Results: Our single cell analyses show that the aged OL lineage exposed to young blood exhibited changes in pathways related to differentiation, oxidative stress, growth, and migration. Additionally, we find that OL lineage numbers increased with age in APPNL-G-F mouse model of amyloid pathology, with significant decreases in myelination. Young plasma increased the number of myelinating OLs as well as myelin content in these mice.

Conclusions: Our results demonstrate that the young systemic environment regulates the aged OL lineage, suggesting it may be leveraged to rejuvenate this population in the setting of AD pathology to improve brain function.

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Longitudinal Changes in Corticospinal Tract Microstructure 6 Months After Intracerebral Hemorrhage

Kimberly Agosto, Daniel D. Cummins, Priti Balchandani, Thomas Perillo, Ziad Rifi, Jimin Shin, Mikhail Nasrallah, Kristian Varga, Christopher P. Kellner

Background
Motor recovery after intracerebral hemorrhage (ICH) is highly variable and may reflect delayed corticospinal tract (CST) remodeling. We evaluated whether diffusion metrics beyond fractional anisotropy (FA) detect longitudinal CST change over 6 months after minimally invasive surgery (MIS) for ICH.

Methods
We performed a longitudinal DTI study of 15 patients with spontaneous supratentorial ICH treated with MIS evacuation. Subject-specific CST tractography was generated early postoperatively and at 6 months. Ipsilesional, contralesional, and ipsilesional-to-contralesional ratio metrics for FA, mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and geodesic anisotropy (GA) were analyzed using paired Wilcoxon signed-rank tests.

Results
Over 6 months after MIS-treated ICH, the CST demonstrated ongoing metric-specific microstructural change. Within the ipsilesional CST, MD, RD, and AD increased significantly over time ($p=0.021$, $p=0.025$, and $p=0.016$, respectively), while FA remained stable ($p=0.478$) and GA showed a non-significant downward trend ($p=0.074$). Ratio-based analyses similarly showed significant increases in relative diffusivity, including rMD and rRD ($p=0.033$ and $p=0.029$), with a decline in relative GA (rGA, $p=0.044$), whereas relative FA did not significantly change (rFA, $p=0.244$). Relative AD increased with borderline significance (rAD, $p=0.050$). Contralesional metrics showed little cohort-level longitudinal change aside from a modest increase in AD ($p=0.044$). Exploratory analyses suggested that greater decline in rGA was associated with worse 6-month functional outcome, while contralesional GA may reflect inter-individual recovery differences.

Conclusions
The CST continues to undergo delayed microstructural remodeling over 6 months after ICH, characterized by rising diffusivity and declining geometry-sensitive anisotropy despite stable FA. Multi-metric diffusion profiling may therefore better capture secondary degeneration and recovery than FA alone.

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Title: Dynamic Mitochondrial Disruptions and Neurodegenerative Signature within the Dorsal Striatum in Relation to Opioid Exposure

Authors:Kion Winson, Konrad Dabrowski, Alex Chisholm, Yasmin L. Hurd

Background: Opioid misuse remains a public health crisis, contributing to significant overdose deaths and morbidity. Studies have recently linked opioid exposure to neurodegenerative-related changes including the development of hyperphosphorylated Tau. Mechanisms that underly the relationship between opioid use and neurodegenerative risk remain unclear. Here, we studied the dorsal striatum, a region in which hyperphosphorylated-Tau pathology was identified in opioid users.

Method: RNA-sequencing was performed on the putamen of 16 postmortem human heroin users and 14 age-matched controls. Preclinical model was also studied where brains were obtained from Long Evans rats (n = 40) that underwent heroin self-administration; brains were obtained at 1hr and 24hr following last drug exposure. Subregions of the dorsal striatum were collected and RNA sequencing conducted. Functional ontology analysis was performed using Enrichr (FDR < 0.05) and Ingenuity Pathway Analysis (IPA) to identify biological pathways related to differentially expressed genes (DEGS). Primary striatal and striatal-cortical cultures were prepared and treated with morphine (10□M/40□M) with gene expression measured with qPCR.

Results: In postmortem heroin users, 2347 significant (p-value< 0.05) DEGs were enriched related to multiple neurodegenerative ontologies. The rodent model also confirmed neurodegenerative ontologies as well as changes in nuclear-encoded mitochondrial genes. In-vitro cell culture model also identified significant alterations of regulatory mitochondrial genes.

Conclusion: Both human opioid users and animals that self-administer heroin show significant mitochondrial perturbation in the striatum related the neurodegenerative-like molecular phenotype. These consistent findings support a causal relationship of opioid experience with mitochondrial perturbations potentially underlying opioid-related neurodegenerative risk.

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Background

There is ongoing debate as to whether psychotic symptoms are most clearly understood within categorical diagnostic models or as part of a continuous, dimensional spectrum. Furthermore, it is difficult to predict if individuals at high risk of psychosis, and those with subthreshold psychotic experiences, are on their way to full blown disorder, likely to remain where they are, or if fleeting states should be regarded as a nonissue. As the brain often predicts what is to come before symptoms arise, we conducted an exploratory study examining relationships between polygenic risk scores related to polyunsaturated fatty acids, which make up a large percentage of the brain, and white matter microstructure metrics between and within those with psychotic-like experiences (PLE), diagnosed psychotic disorders (ICD), and controls.

Methods

Participants from the UK Biobank included individuals with an ICD-10 diagnosis in the schizophrenia, schizotypal, and delusional disorders category or mood disorders with psychotic symptoms, individuals reporting psychotic-like experiences, and stratified frequency-matched controls. White matter microstructure was assessed using neurite orientation dispersion and density imaging (NODDI) metrics. Associations were examined between these and polyunsaturated fatty acid (PUFA) polygenic risk scores using genetically informed causal mediation analyses and multigroup structural equation modeling.

Results

Multigroup structural equation modeling identified significant associations between PUFA PRS scores and NODDI metrics across several white matter tracts. Individuals with diagnosed psychotic disorders showed a greater number of associations, whereas individuals reporting psychotic-like experiences showed fewer and more localized associations.

Conclusions

Metabolic genetic liability may shape white matter organization in both psychotic symptom–experiencing groups significantly, but differently. While subclinical psychotic experiences may reflect a more plastic and potentially resilient neurobiological state, those with an established disorder have a greater number of more stable and pronounced traits consistent with cumulative genetic expression and illness-related neurobiological consolidation.

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Submit your abstract here:

A new murine model of X-linked d A new murine model of X-linked dystonia parkinsonism (XDP)

Ploense, Kyle L., Bonet, Justine, Shillingford, Darlinda, Brosh, Ran, Zhang, Weimin, Boeke, Jef D., Ehrlich, Michelle E.

Background: X-linked dystonia Parkinsonism (XDP) is an X-linked recessive, fatal movement disorder affecting approximately 5 in every 100,000 men in the Philippine island of Panay. The causative XDP mutation is the insertion of a SINE-VNTR-Alu (SVA) retrotransposon in the 32nd intron of the TAF1 gene, a crucial element of the ubiquitously expressed TFIID transcription factor complex.

Methods: Female C57Bl/6J mice homozygote for a conditional, humanized Taf1/TAF1 gene (courtesy of Dr. Boeke) are crossed with male mice expressing a Synapsin cre-recombinase-transgene. These mice underwent a panel of locomotor tests, including hindlimb clasping, accelerating rotorod, vertical pole, balance beam, and locomotor activity assay. Using standard IHC/IF techniques we analyzed the size of the striatum, percentage surface area occupied by striosomes, astrocytosis, microgliosis, and numbers of cholinergic interneurons (ChINs).

Results: At 1 month of age, there were no differences in body weight, clasping behaviors, motor function, or number of astrocytes. There was a small increase in activated microglia within the striatum, and also a reduced striosome area and number, as determined by IF with a mu-opioid receptor antibody. At 7 months, the hTaf1/Synapsin-cre+ mutant mice displayed increased hindlimb clasping and deficits on the accelerating rotorod. Furthermore, they exhibited freezing-like episodes and a lack of control over muscle movements, at which time they were euthanized. The mutant brains exhibited massive astrogliosis and activation of microglia as well as a decrease in striosome number and percent striatal area.

Conclusion: The above-mentioned motor abnormalities and anatomical findings provide support for using the hTaf1/ Synapsin-cre mouse to model progressive motor and morphologic aspects of XDP. Their 7-month course is also amenable to pharmacologic testing.

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Submit your abstract here:

Shisa7 in the Orbitofrontal Cortex as a Driver of Opioid Seeking

Lauren Park, Randall Ellis, Yasmin L. Hurd

Background: Opioid Use Disorder (OUD) continues to contribute significantly to overdose deaths in the United States along with high morbidity, and has one the highest relapse rates among substance use disorders. OUD is not adequately managed by existing FDA approved treatments, highlighting the urgent need for new therapeutic strategies. The orbitofrontal cortex (OFC) is critically implicated in craving and relapse behavior in OUD. In a human OFC bulk RNA-sequencing study conducted by our group, Shisa7 was identified by machine learning as the transcript most predictive of heroin or saline group classification. Shisa7 is an auxiliary subunit of GABAA and AMPA receptors, but little is known about its role in opioid seeking behavior.

Methods: Shisa7 was measured in the OFC of rats exposed to either heroin or saline in an intravenous self-administration paradigm, and Shisa7 coimmunoprecipitation (co-IP) and mass spectrometry (MS) were performed on the OFC to acquire differential protein expression.

Results: Shisa7 expression was reduced in the rat OFC after heroin experience and was positively correlated with drug seeking behavior. Co-IP/MS demonstrated that under control conditions, Shisa7 binds to GABAAR subunits a1, a2, b2, b3, y2, as well as AMPAR subunits GluA1-3. However, following heroin experience, Shisa7 binding was selectively increased at GABAAR subunit b2 (GABRB2) compared to saline controls.

Conclusions: Shisa7 and its related protein network are changed after chronic heroin use in a manner that may promote opioid seeking behavior. Shisa7 binding to GABAAR b2 is predicted to increase fast inhibitory neurotransmission; future studies will seek to validate this mechanistic connection. These findings implicate Shisa7 and its associated pathways as potential drug targets for reducing opioid craving and relapse.

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Rate-Distortion Signatures of Generalization and Information Trade-offs in Humans and Deep Vision Models
Leyla Roksan Caglar, Pedro A.M. Mediano, & Baihan Lin

Background: Generalizing visual recognition across noisy, degraded, or transformed inputs is effortless for humans but remains a fundamental challenge for artificial vision systems. Yet standard robustness metrics reveal little about how biological and artificial systems differ in the way they trade accuracy for robustness - a question central to understanding the organizational principles of the visual system and to building more human-like machine vision.

Methods: We introduce a rate-distortion (RD) theoretic framework that treats stimulus-response behavior as an effective communication channel and derives empirical RD frontiers from confusion matrices. Each system is summarized with two geometric signatures: slope β, capturing the marginal compression cost per unit of precision, and curvature κ, capturing how abruptly performance collapses as distortion increases. We applied this framework to human psychophysical data and 18 deep vision models across 12 controlled image perturbations spanning diverse architectures and training regimes.

Results: Biological and artificial systems follow a common lossy-compression principle, but occupy systematically distinct regions of β-κ space despite comparable average accuracy, establishing that RD geometry exposes structure invisible to accuracy-only metrics. Training regime shifts model geometry along β and κ independently: distortion-augmented training shifts curvature toward humans while reducing efficiency, whereas specialized or all-noise training can improve efficiency while shifting curvature past humans. This dissociation shows that human-likeness is axis-dependent and unreducable to a single robustness score.

Conclusions: RD geometry provides a compact, model-agnostic diagnostic for comparing generalization strategies across systems. These findings establish that closing the human-machine vision gap requires targeting tradeoff geometry, and offers a principled tool for distinguishing competing accounts of how the visual neural system balances precision and robustness, including characterizing how this balance breaks down in conditions affecting visual processing.

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Investigating the Association Between Screen Exposure and Attentional Indicators in Preschool Children

Author Name(s): Luke Joseph Duculan; Marco Rizzo, PhD; Floriana Milazzo, MPH; Rushna Tubassum, MPH, Yasemin Schmitt, Anna-Sophie Rommel, PhD

Introduction: Prolonged screen exposure in early childhood has been associated with adverse attentional outcomes in later childhood. However, its neurophysiological correlates during earlier developmental stages remain underexplored. We examined whether prolonged screen exposure in preschool-aged children is associated with frontal alpha power derived from electroencephalography (EEG), a neural marker of attentional engagement.

Methods: Screentime exposure was assessed using the parent-reported Digital Screen Exposure Questionnaire. Ninety-nine children (mean age 3.61±0.36 years) had screen exposure and EEG data available; 18 (mean age 4.13±0.64years) had preprocessed EEG data suitable for analysis. Prolonged exposure was defined as total daily screen use (in minutes) >75th percentile. Resting-state EEG was recorded while children viewed a silent 3-minute video. Peak frequency and absolute power within the alpha frequency band (8-12 Hz) were analyzed from frontal EEG electrodes. Associations between continuous daily screentime and frontal peak and absolute power were examined using linear regressions, controlling for child age at visit and sex. Demographics were compared between high (screentime >75th percentile) and low (<75th percentile) exposure groups using chi-squared and Wilcoxon rank-sum tests.

Results: Prolonged screen exposure was neither associated with frontal alpha peak (ß=0.0021, 95% CI=-0.0044, 0.0003, p=0.07) or mean power (ß=0.0033, 95% CI=-0.0124, 0.0191, p = 0.66). Lower maternal education, multiparity, and frequent screen use (≥3 days per week) were associated with prolonged screen exposure (p<0.05).

Conclusions: Prolonged screen exposure was not associated with frontal alpha power. Given the small analytic sample, however, limited power may have reduced the ability to detect subtle effects, and larger studies are needed.

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Submit your abstract here:

Understanding Psychiatric Crises in Older Adults: A Descriptive and Thematic Analysis of Suicidal Ideation in a Geriatric Population with Major Depressive Disorder

Mackenzie Hargrove, Matthew Dobbs, Sandy Salazar, Zoe Schreiber, Rachel Fremont

Background: Suicide among older adults, specifically 60 years and older, is a burgeoning public health crisis, especially as the population in the United States continues to age. Major depressive disorder (MDD) is not uncommon in older adults and is associated with an increased risk for suicidal ideation (SI), suicide attempt, and completion of suicide. Older adults experience a unique set of factors that may increase their risk, including medical illness, burden, and living alone. This study aims to describe differences in the demographics of older adults with MDD without SI compared to older adults with MDD and SI. Furthermore, we aim to explore emergent themes related to SI through qualitative analysis of Structured Clinical Interviews.

Methods: Convenience sample surveys and case summaries from the Depression and Anxiety Center Screening pilot study (n=52; 2016 -2026) were used to characterize the demographics and Psychiatric Symptomatology of this sample.

Results: This sample is mostly White (82.4%), non-Hispanic (90.2%), male (53.0%), with a college education (88.2%), working full time, part time, or retired (68.6%). Average age at onset of MDD is similar between the two groups (27 years). Almost half (42.9%) of the MDD with SI group, compared to the MDD without SI group (8.7%), experienced past psychiatric hospitalization. All past suicide attempts (47.6%) occurred in the MDD with SI group. Themes that emerged from the MDD with SI group include persistence of illness, extensive treatment history, adverse childhood experiences, comorbid anxiety, and history of substance use.

Conclusions: The themes that emerged from this study align with prior research and help further elucidate factors that may contribute to SI in this population.

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Title: Investigating the relationship between cerebral small veins and microbleeds using 7T QSM MRI in Alzheimer's Disease

Authors: Madison Chiu, Sema Yildiz, Trey Hedden, Bradley Delman, Priti Balchandani, Akbar Alipour

Background: Cerebral microbleeds (CMBs) are small hypointense round lesions that indicate leakage of blood products from cerebral vessels damaged by β-amyloid (Aβ) and typically are detected by T2*-weighted GRE and susceptibility weighted imaging (SWI) on MRI. They are indicators of cerebral small vessel diseases like cerebral amyloid angiopathy and Alzheimer's disease (AD), primarily affecting cortical small arteries. The possibility of small veins playing a role in the development of CMBs, attributed to venous pathology associated with cerebral small vessel diseases, is also worth considering. In this study, we utilized the QSM technique to analyze venous structures at ultra-high resolution in a cohort of patients with AD using 7T MRI. Our aim is to evaluate the feasibility of using ultra-high resolution QSM at 7T MRI to find a link between small veins and CMBs in individuals with AD.

Methods: In-vivo human imaging was performed using a 7T MRI scanner. Multi-echo magnitude and phase images were obtained using a 3D multi-echo GRE sequence. QSM reconstruction was performed using a post-processing pipeline comprising phase unwrapping, background field removal, and dipole inversion. We also obtained SWI images using the CLEAR SWI technique.

Results: The images were analyzed by two neuroradiologists. CMBs were defined as hyperintense, round lesions in the QSM images. For verification, their appearance was matched on the SWI images, where CMBs are hypointense and associated with. CMBs with a direct link to a vein were assessed in the QSM sequence. They were defined as CMBs with small vein connections.

Conclusions: QSM, as a postprocessing technique, elevates CMB detection sensitivity while facilitating precise visualization of the brain's venous vasculature.

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Spatiotemporal chemistry of the developing brain

Background: While mass spectrometry provides a foundational framework for studying brain metabolism, it lacks the anatomical specificity needed to pinpoint region-specific features relevant during early brain development, which heterogeneous maturation across regions like the forebrain and cerebellum makes it vulnerable to metabolic insults. This critical period requires significant energy, yet the spatiotemporal dynamics of this demand remain poorly understood. By combining isotopic tracer labeling of central carbon metabolism with MALDI-TOF mass spectrometry imaging (MSI), we aim to directly map the spatial dynamics of energy demand and elucidate the spatiotemporal chemical architecture of the developing brain.

Methods: C57BL/6J mice at postnatal intervals P0, P7, P15, and P21 were infused with [U-13C]-glucose to label tricarboxylic acid (TCA) cycle intermediates. Sagittal brain slices were analyzed via MSI to map targeted and untargeted metabolite distributions.

Results: Image analysis generated regions that tracked developmental changes between forebrain and cerebellum, creating clusters that showed age-related separation, indicating that chemical signatures change in tandem with anatomical development. Region-specific mapping identified signatures: GlcCer 44:03 and HexCer d44:1 in the forebrain, aspartate in cerebellar white matter, and serine in cerebellar gray matter. These signatures should be further evaluated as potential developmental markers of spatiotemporal metabolic vulnerabilities. Global changes in glutamate primarily drove early cerebellar development. Isotopic tracing revealed a marked increase in Glutamate M2 (two 13C carbons within the molecule) labeling by P15. Because M2 glutamate requires incorporation of 13C-labeled acetyl-CoA into the TCA cycle, this pattern suggests a metabolic shift from glycolysis to active oxidative phosphorylation to support mature neural energy demands.

Conclusions: Increases in Glutamate M2 labeling and the spatial reorganization of lipids and TCA intermediates reveal a dynamic biochemical architecture that undergoes an energy metabolism transition around P15. Describing these dynamics establishes a crucial metabolic baseline for future therapeutic interventions.

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Title: Characterizing Aperiodic Components and Beta Oscillations in the Basal Ganglia

Maren Cukor1, Brian H. Kopell2, Qi Xiu Fu1, Katherine Belilty3, Enkhjin Gansukh3, Emanuel Coleman1, Ignacio Saez4

Background:

Subthalamic beta (13-30 Hz) oscillatory dynamics in the subthalamic nucleus (STN) and substantia nigra have been associated with motor pathology in Parkinson's disease, but less is known about whether these oscillations are also present in other brain areas such as the thalamus. Here, we characterize periodic (beta) and aperiodic (1/f) components of local field potentials (LFPs) recorded intraoperatively from the thalamus, STN, and substantia nigra (SNr).

Methods:

We recorded microelectrode LFPs in 9 PD patients undergoing DBS surgery (awake, off-medication). We quantified beta-band (13-30Hz) power and aperiodic LFP components (offset and exponent) using specparam/FOOOF for each region along clinical trajectories, including the dorsal thalamus (n=6), STN (n=18), and SNr (n=18). We compared beta power estimates and aperiodic offset and exponent, as well as the proportion of electrodes showing significant beta activity across patients.

Results:

Only the aperiodic exponent showed a significant difference (p=0.005), whereas Aperiodic offset and beta amplitude did not differ significantly across the thalamus, STN, and SNr (p=0.41, p=0.74). In contrast, we found a greater proportion of electrodes exhibiting beta activity in the thalamus (83%) compared to STN (55%) and SNr (45%).

Conclusions:

These findings suggest that the value of spectral aperiodic components of thalamic activity are similar to STN and SNr, Similarly, the magnitude of beta oscillatory activity was similar across regions, but beta oscillations were more common in thalamic electrodes, suggesting that beta may be overrepresented in thalamic components of the cortico-basal ganglia-thalamo-cortical loops.

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BEHAVIORAL AND POPULATION LEVEL EFFECTS OF OXYCODONE RELAPSE IN MICE

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BACKGROUND: Opioid Use Disorder (OUD) relapse is a dangerous stage of the addiction cycle due to increased overdose risk following tolerance. The habenula is an epithalamic structure connecting limbic areas and monoaminergic nuclei. The habenula is enriched in cholinergic neurons, mu opioid receptors (MOR), and the soluble guanylyl cyclase receptor for nitric oxide (NO). NO mediated retrograde inhibition from the interpeduncular nucleus onto terminals of the medial habenula attenuates aversion during chronic nicotine exposure. We examine habenular calcium dynamics in response to oxycodone dose escalation and relapse during intoxication, tolerance, and withdrawal.

METHODS: Fiber photometry recordings were collected from male Chat-Cre mice (n=6) expressing GCaMP in cholinergic neurons with optical fibers implanted in the habenula. Calcium dependent fluorescence was aligned to saline and oxycodone injections and to Straub tail onset. Event locked calcium dynamics were quantified using peak and area under the curve analyses. Hotplate assay and somatic withdrawal signs were used as behavioral measures.

RESULTS: Oxycodone elicited a larger peak than saline during initial exposure, whereas repeated oxycodone exposure was associated with attenuated signal. Straub tail onset occurred with increased latency following dose escalation and relapse and was associated with attenuated calcium response. Hotplate response latency decreased and somatic withdrawal signs increased progressively.

CONCLUSIONS: Calcium signal attenuation during Straub tail onset reflects MOR engagement consistent with Gi/o coupled signaling, while increased latency of Straub tail reflects tolerance consistent with MOR desensitization. These findings support the habenula as a dynamic regulator of opioid addiction.

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TSH Receptor Haploinsufficiency Impairs Sensorineural Auditory Function Without Altering Thyroid Hormones

Maryam Mansoori, Steven Sims, Vitaly Ryu, Anisa Gumerova, Georgii Pevnev, Farhath Sultana, Weibin Zhou, Ofer Moldavski, Daria Lizneva, Ki Goosens, Tony Yuen, Pin-Xian Xu, Se-Min Kim, Rauf Latif, Terry Davies, Mone Zaidi

Hearing loss is a recognized yet understudied complication of thyroid dysfunction. Recent clinical observations of hearing loss in patients with Thyroid Eye Disease (Graves' ophthalmopathy) following therapy with an IGF-1 receptor monoclonal antibody (teprotumumab) have highlighted this association. Highly suggestive evidence of a mechanism for such an association has come from emerging evidence of thyroid-stimulating hormone receptor (TSHR) expression within the auditory pathway. Here, we investigated the expression and functional role of the Tshr in the auditory system using our Tshr-haploinsufficient mouse model. Auditory outcomes were compared with age- and sex-matched C57BL/6 wild-type (WT) controls. RNAscope and GFP-immunofluorescence were used to localize TSHR expression in the auditory pathway. Tshr-haploinsufficient mice exhibited Auditory Brainstem Response (ABR) threshold values significantly higher compared to WT, particularly at higher frequencies, including 22 kHz and 32 kHz (p-value<0.0001). Distortion Product Otoacoustic Emissions (DPOAE) amplitudes were also reduced, by 12 dB at the highest frequency, 32 kHz (p-value= 0.0164), suggesting auditory sensitivity and outer hair cell dysfunction. We detected Tshr mRNA expression and Tshr immunoreactivity in auditory structures along the peripheral and central auditory pathways. Tshr expression is localized to specific cochlear cell types and neuronal populations, suggesting a prominent role for Tshr in sensorineural auditory processing. Together, these findings identify Tshr as a previously unrecognized regulator of auditory function and a potential mediator of hearing loss in thyroid related conditions. This work highlights TSHR signaling as a critical determinant of auditory function with implications for the understanding of hearing impairment in patients with thyroid disease and potential development of novel therapeutic strategies.

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Hematopoiesis, the tightly regulated process by which the bone marrow generates leukocytes, red blood cells, and platelets, is essential for maintaining immune homeostasis and adapting to physiological stressors such as infection or inflammation. While peripheral nerves are known to regulate the bone marrow niche, the role of higher-order brain circuits in controlling hematopoiesis and leukocyte mobilization remains poorly understood. Here, using polysynaptic circuit tracing from the femur, we identify a direct neuronal connection between the locus coeruleus (LC) and the bone marrow. In a lipopolysaccharide (LPS)-induced inflammation model, we show that adrenergic LC neurons are robustly activated. Ablation of noradrenergic LC neurons significantly reduces hematopoietic stem and progenitor cell (HSPC) proliferation during emergency hematopoiesis, whereas chemogenetic activation of adrenergic LC neurons increases HSPC numbers in the bone marrow and spleen while reducing circulating leukocyte counts. In a mouse model of LPS-induced sepsis, LC ablation decreases survival and impairs thermogenesis and triglyceride mobilization: two critical mechanisms for adaptation to severe inflammation. Together, these findings identify the LC as a central neural regulator of the inflammatory response, linking brain circuits to immune cell dynamics and systemic metabolic adaptation during life-threatening inflammation.

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Background: Digital diary tools provide a valuable opportunity to collect data on patient experiences and emotions in real time to predict diagnoses and outcomes in treatment. Existing research primarily examines diaries as therapeutic interventions rather than predictive tools, and focuses on written diaries with structured questions. Little research exists on the predictive utility of audio diaries with open-ended prompts, allowing patients to elaborate on topics of their choice.

Methods: In the PREDiCTOR study, participants can record open-ended audio diaries through the MindLAMP app. We investigated characteristics of 152 psychiatric patients (mean[SD] age=28.8[8.21]; 60.9% female) completing a collective 862 audio diaries. A Chi square test was performed to assess the effects of diagnosis on whether participants submit audio diaries. An ANCOVA examined diagnostic group differences in the number of audio diaries submitted, controlling for days with the app installed. Theme clouds were generated from diary transcripts for key diagnoses and adverse events (ED visits, hospitalization, disengagement).

Results and Conclusions: While the results of the Chi square test were not significant, the ANCOVA yielded significant group differences ($F=2.68$, $p=0.042$), with Psychotic Disorders showing the highest average number of diary submissions (mean[SD]=34[24.7]), followed by Mood Disorders (mean[SD]=13.3[16.8]). Theme clouds highlighted topics such as emotional (dys)regulation across all diagnoses and particularly with those experiencing adverse events, and social connection within Psychotic and Mood disorders. Preliminary findings suggest audio diaries can be utilized to identify prominent characteristics within psychiatric diagnoses, provide insight into emotions and experiences outside of clinical interviews, and ultimately help individualize care.

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Bilateral and Extensive Intraventricular Hemorrhage Dissemination Predict Cerebrospinal Fluid Diversion Complication Rate

Megha Dhillon, Kimberly Agosto, Mikhail Nasrallah, Ysobel Ramirez, Jimin Shin, Tannishtha Som, Trevor Hardigan, J Mocco, Christopher P. Kellner

Background:
Patients with intraventricular hemorrhage (IVH) often require prolonged cerebrospinal fluid (CSF) diversion and permanent shunting, but radiographic predictors of diversion complexity are not well defined. We evaluated whether early residual IVH burden and anatomic dissemination predict ventriculoperitoneal (VP) shunt placement and drain-related burden.

Methods:
We conducted a retrospective single-center cohort study of patients with IVH requiring CSF diversion. Baseline clinical and radiographic variables included mGraeb score, segmented baseline and day-5 IVH volumes, and anatomic IVH extension pattern. Drain burden was defined as EVD replacement, clamp trial failure, VP shunt placement, infection, or tract hemorrhage. Multivariable logistic regression assessed predictors of VP shunt placement, drain burden, and poor day-5 IVH clearance.

Results:
Seventy-seven patients were included. Median age was 66.6 years (IQR 55.0–72.9), and 31 (40.3%) were female. Bilateral extension was present in 52 patients, third ventricular extension in 45, and fourth ventricular extension in 50; the most common phenotype was combined bilateral, third, and fourth ventricular involvement (n=29). In adjusted component models, bilateral extension independently predicted VP shunt placement (OR 19.0, 95% CI 2.90–371; p=0.012) and drain burden (OR 4.60, 95% CI 1.43–16.5; p=0.013). Higher residual day-5 IVH volume also independently predicted VP shunt placement (OR 1.05, 95% CI 1.02–1.10; p=0.0049) and drain burden (OR 1.06, 95% CI 1.02–1.12; p=0.0286). Greater anatomic extension count was associated with higher odds of both outcomes. Third and fourth ventricular extension alone were not independent predictors after adjustment.

Conclusions:
Bilateral IVH extension and higher residual day-5 ventricular blood burden were associated with greater CSF diversion complexity and may help identify patients at risk for prolonged or complicated diversion needs.

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A translational model of how aging erodes the neural mechanisms of directed exploration

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Exploration is essential for making new social connections, learning new skills, and staying engaged as we age – key behaviors that help maintain brain health into older adulthood. Unfortunately, older adults are much less likely to explore which, in turn, may accelerate cognitive and neural aging. A well-replicated result is that older adults are less likely than younger adults to engage in “directed” exploration, a strategy by which people direct their behavior towards opportunities they know the least about. However, beyond correlational work, a lack of causal studies means that it is unclear what neural mechanisms drive directed exploration. To address this, I established a mouse model of directed exploration with a probabilistic reward task, demonstrating that directed exploration decreases with mouse aging, replicating aging effects in humans. Using fiber photometry to analyze acetylcholine, a key neurotransmitter which is involved in directed exploration and which decreases globally with age, we demonstrated altered dynamics as animals explore choices on a probabilistic bandit task. Using a computational model of behavior, we explore the decision-making components of directed exploration, from choice patterns in young and old mice, with the goal of expanding these models to also capture human behavior.

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Characterizing cell type-specific isoforms of disease-associated Cav1.2 calcium channels in the developing cerebral cortex

Meilin Chen*, Arpana Arjun McKinney*, Vicente Pedrozo*, Denis Torre, Robert Sebra, Georgia Panagiotakos

Background: Precisely controlled calcium signaling is essential for the regulation of neural stem and progenitor cell (NSPC) behavior during cortical development, and its dysregulation has been linked to neurodevelopmental disorders. However, the mechanisms that enable temporal and cell type-specific control of calcium influx remain unclear. Alternative splicing of voltage-gated calcium channel (VGCC) subunits generates isoforms with distinct biophysical properties, representing a core mechanism for tuning calcium influx in developing cortical cells.

Methods: To investigate full-length ion channel isoform switching during cortical neuron differentiation, we performed in utero “Flashtag” labeling in embryonic day 13.5 mice, isolating radial glia stem cells, intermediate progenitor cells, and newborn neurons. Using fluorescence-activated cell sorting followed by paired long- and short-read RNA sequencing, we constructed an isoform-resolved transcriptome of the developing mouse brain.

Results: We identified NSPC- and neuron-specific isoforms of Cav1.2 α1 subunit (Cacna1c). Electrophysiological analysis of this NSPC-enriched Cacna1c isoform revealed a leftward shift in voltage-dependent channel activation compared to a canonical neuronal isoform, indicating distinct calcium influx dynamics. To determine potential in vivo functions for this isoform, we introduced it into developing cortical cells using in utero electroporation and followed the differentiation of electroporated cells across time. Our pilot data demonstrate an accumulation of electroporated cells in the germinal zones, with fewer cells reaching the cortical plate, suggesting a potential delayed differentiation or migration. Extending our analysis to auxiliary subunits, we identified NSPC-enriched Cacna2d1 and Cacnb2 isoforms.

Conclusions: These findings support the idea that NSPC-specific Cav1.2, comprised of unique combinations of pore-forming and auxiliary subunit isoforms, regulate calcium signaling dynamics critical for progenitor behavior and fate, with implications for understanding neurodevelopmental disorders linked to VGCC misregulation.

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Social Type Inference Through Observational Learning

Merima Šabanović, Anna Schinasi, Xiaoting Wu

Forming accurate social predictions without direct interaction is an evolutionarily advantageous strategy, particularly in contexts such as dominance conflicts where trial-and-error learning carries high costs. While most research on observational learning focuses on learning from others, animals also face the challenge of learning about social partners themselves. Whether observers can infer stable social behavior tendencies of conspecifics from observation alone to guide future interactions remains largely unexplored.

We developed a social observational learning paradigm in adult C57BL/6 mice combined with a social approach/avoidance test. Subjects completed a 5-minute baseline approach/avoidance test toward a cup-restrained target, observed a freely occurring social interaction between the target and a novel partner through a transparent divider for 10 minutes, followed by a 5-minute post-observation test with the same target. To test whether subjects could learn naturally occurring patterns of social behavior, targets were drawn from strains with distinct social phenotypes: affiliative (enrichment-housed C57BL/6), aggressive (FVB/N), and neutral (novel C57BL/6).

Subjects approached affiliative targets and avoided aggressive targets more following social observation compared to baseline, with no change toward neutral controls. Progressively restricting behavioral cue availability demonstrated that mere sensory exposure to the target was insufficient: these effects required observation of active social behavioral expression. Observational learning generalized across individuals of the same behavioral type only with repeated experience, but not across different target types, suggesting graded within-type generalization alongside discrimination between social categories.

Mice can infer the social tendencies of conspecifics through third-party observation and use this to guide subsequent approach/avoidance decisions in a manner consistent with the formation of distinct representations of social behavioral categories. Ongoing work using optogenetic inhibition of the mPFC, vCA1, and BLA is examining the circuit mechanisms supporting the acquisition and expression of social observational learning.

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An auditory navigation task for studying abstract cognitive mapping in mice

Michael Beauzile, Paul Philipsberg, Denise J. Cai, Tristan Shuman

Background: The hippocampal-entorhinal circuit supports cognitive maps that organize relationships between experiences, enabling flexible navigation. While medial entorhinal cortex (MEC) grid cells are well characterized in physical space, they may also encode continuous, non-spatial variables. However, most behavioral paradigms rely on physical space, which limits the ability to study how the brain represents and navigates abstract spaces. Thus, to identify whether the encoding principles of physical navigation apply to abstract stimuli, new tasks are needed that can dissociate physical and abstract space.

Methods: We developed a freely moving auditory navigation task in which mice move through an open field while auditory feedback varies along two continuous dimensions: pitch and amplitude modulation rate. The animal's position in physical space is mapped onto this tone space, requiring integration of sensory information to locate a target. We progressively increased task difficulty across training and quantified performance and navigation trajectories.

Results: Mice learned to associate auditory and visual cues with reward availability and adapted to increasing task difficulty while continuing performance. With consistent task demands, performance improved over time. During trials without auditory feedback ("tone-blind" trials), navigation time increased, and path efficiency decreased relative to trials with intact feedback.

Conclusions: Preliminary data suggest that mice learn to use auditory cues to guide search behavior in this task. Ongoing work will optimize training, implement calcium imaging in the hippocampus and MEC, identify grid-like representations of audio space, and test whether behavior reflects abstract cognitive mapping or alternative strategies. In addition, this task can be used to assess how neurological diseases such as Alzheimer's disease (AD) and aging disrupt abstract cognitive abilities.

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Biological Mechanisms in Sex Divergent Stress Response

Miguel Chicas, Christabel Mclain, Clementine Blascke

Background: Despite known sex differences in how both human and animal models respond to stress, the biological mechanisms responsible for driving these differences are not well understood. Stress has effects throughout the body and brain, and chronic stress exposure can modify gene expression and neural circuit functionality. It is important to understand the biological interactions produced by stress in females, which have previously been understudied, as this knowledge will help guide future treatments and research regarding female health. It is the goal of our project to explore the biological mechanisms driving divergent stress responses in males and females.

Methods: We investigated whether behavior after chronic variable stress differs according to sex and hormonal state. Male and female mice experienced either chronic variable stress or control conditions, followed by anxiety-related behavioral tests such as the open field and elevated plus maze. Female animals were estrous staged throughout the experiment to determine whether hormonal state at different timepoints affects the behavioral outcomes.

Results: After analyzing results, a general stress effect was observed between our control and stress groups. There were significant results between proestrus control and stress and diestrus control and stress, however, comparing these two stages under stress proved no significant difference.

Conclusions: While not significant, the data is promising in order to show that the sex factors, and specifically ovarian hormone levels, do influence behavior that mice exhibit following chronic stress. We may have to rerun this experiment with more animals considering the animals in each group changed every day, and there were only a total of 60 mice across all groups. Future experiments seek to analyze how stress affects brain-wide neuronal activity in males and females using lightsheet microscopy.

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Brain-wide reorganization of activity associated with aggression and decision-making

Mira Kondepudy, Antonio Aubry, Long Li, Romain Durand-de Cuttoli, Brian Sweis

Neural circuits active during the expression of aggressive behaviors can recruit critical nodes of the brain's reward system. Aggressive individuals may also differentially engage reward circuits during decision-making, even for non-aggressive behaviors. However, the link between aggression and decision-making remains unclear.

We explored how individual differences in aggressive traits mediate differential brain activation profiles during foraging behavior. Forty outbred Swiss Webster mice were screened for aggression toward a C57 intruder. Following screening, mice were tested longitudinally in the foraging task, Restaurant Row, trained to make economic decisions for food rewards. After 60 days of testing, mice were time-sacrificed during task engagement and whole-brain tissue clearing was performed to stain 275 regions for cFos expression, an activity-dependent biomarker of recent cell activity. Importantly, cFos expression was linked to task performance, not aggressive behavior.

Interestingly, we found that mPFC and NAc activity, regions critical for decision-making on this task, as a pair, best explained variance in aggression traits compared to any other pair of regions.

Then, we conducted a network analysis as a function of aggression levels and discovered 4 to 5 modules that independently clustered. We found that even though mPFC and NAc contributed to separate modules, both of these modules were preserved across aggression levels.

These data reveal that mPFC and NAc may serve as hubs of two functionally connected but independent networks relating task engagement to trait-level aggression.

Our work suggests how brain-wide network patterns recruited by cognitive demand can be mediated by aggressive traits, even for non-aggressive behaviors. These findings set the stage for future experiments causally manipulating key circuits that are both necessary for the expression of aggression and can drive dissociable valuation algorithms in the brain.

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TITLE

APOE variants differentially regulate lipid handling and barrier integrity in a human iPSC-derived outer blood-retina barrier model

AUTHORS

Mirella Maturano, Kevin Thomas Eade, Joel W. Blanchard, Louise Mesentier-Louro

BACKGROUND

Age-related macular degeneration (AMD) is characterized by lipid-rich extracellular deposits (drusen) that form under the retinal pigment epithelium (RPE) and lead to retinal damage. Variants of apolipoprotein E (APOE) show a clear pattern in AMD risk: APOE2 increases risk, APOE4 reduces risk, and APOE3 is considered neutral. However, the cellular mechanisms behind these differences are not fully understood.

METHODS

To study variant-specific effects in a human system, we generated isogenic iPSC-derived outer blood-retina barrier (BRB) tissues homozygous for APOE2, APOE3, or APOE4. The BRB model was established by co-culturing iPSC-derived RPE with vascular cells in a transwell system. Barrier integrity was measured using transepithelial electrical resistance (TEER). APOE localization was assessed by immunostaining. Cholesterol uptake assays were performed only in iPSC-derived RPE monocultures using BODIPY-cholesterol.

RESULTS

APOE2 BRBs showed lower TEER compared to APOE3 and APOE4, indicating reduced barrier integrity. Immunostaining showed higher total APOE signal in APOE2 BRBs. In RPE monocultures, APOE2 cells showed reduced cholesterol uptake and increased extracellular cholesterol accumulation. In contrast, APOE4 cells showed higher cholesterol uptake and greater intracellular lipid accumulation, while APOE3 showed intermediate results.

CONCLUSIONS

These findings show that APOE variants differently regulate cholesterol handling, APOE accumulation, and barrier function in a human isogenic model. The APOE2 variant is associated with reduced cholesterol uptake, increased extracellular lipid retention, and higher APOE accumulation, which may contribute to drusen formation. In contrast, APOE4 appears to improve intracellular lipid processing and maintain barrier integrity.

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Mitochondrial Complex I in Cholinergic Interneurons and Cognitive Impairment

Mohammad Jodeiri Farshbaf, Matthew Perkins, Jake Tetenman, Samantha O. Brown, Jessica L. Ables

Diabetes is the most common endocrine disorder in the United States and is strongly associated with increased risk of mental health problems. The comorbidity of diabetes and psychiatric conditions poses major challenges for effective treatment of either disorder. Impulsivity—a multifaceted behavioral trait linked to attention-deficit/hyperactivity disorder (ADHD) and substance use disorders—has been reported to increase in individuals with diabetes, yet the molecular mechanisms underlying this association remain unclear.

Cholinergic interneurons (CINs) in the nucleus accumbens (NAc) play a key role in behavioral control and are particularly vulnerable to metabolic stress. Using a modified multiple low-dose streptozotocin (STZ) protocol, we generated diabetic mouse models of both sexes and performed transcriptional profiling of CINs from the NAc. Our RNA-seq data revealed that mitochondrial complex I (MCI) genes in CINs show the most significant transcriptional changes after six weeks of sustained hyperglycemia. Interestingly, MCI gene expression returned to control levels after twelve weeks, suggesting dynamic adaptation of mitochondrial metabolism over time.

Pathway analyses indicated that diabetes reprograms mitochondrial metabolism in CINs in a sex-dependent manner, shifting the balance between carbohydrate metabolism and lipid oxidation across disease stages. Using operant conditioning tasks, we found that impulsive-like behavior emerges several weeks after the onset of hyperglycemia and coincides with mitochondrial transcriptomic changes in CINs. Moreover, diabetic mice exhibited impaired cognitive flexibility during task-switching paradigms.

Together, these findings demonstrate that diabetes disrupts mitochondrial complex I expression and metabolic homeostasis in cholinergic interneurons of the NAc, contributing to the emergence of impulsivity and cognitive inflexibility. Notably, human studies similarly link MCI abundance in the brain to task-switching ability, suggesting a conserved role for CIN mitochondrial function in cognitive control.

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Cerebellar microRNA-206 modulates sensorimotor gating and Purkinje cell excitability

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BACKGROUND: MicroRNAs are key post-transcriptional repressors of gene expression and are increasingly implicated in psychiatric disorders. Variants of the microRNA miR-206 are associated with affective and neurodevelopmental disorders including autism, schizophrenia, and bipolar disorder. Its expression has been detected in the PFC, hippocampus, and cerebellum in mice. However, its roles in neuronal function and behavior are unclear.

METHODS: We generated and behaviorally tested constitutive and conditional miR-206 knockout mice. We performed RNAScope detection of miR-206 expression in brain, immunofluorescence staining/counts and iontophoretic injection/Neurolucida360 tracing of Purkinje cells (PCs), snRNA-seq and spatial transcriptomics of cerebellum, HITS-CLIP and TRAP-seq of PCs, electrophysiological recordings, and intravenous delivery of PHP.eB AAVs expressing miR-206 in PCs.

RESULTS: Mice with targeted deletion of miR-206 exhibit sex-dependent behavioral differences, including stress-induced hypolocomotion, enhanced contextual fear memory retrieval, and cognitive deficits. Male miR-206 KO mice have impaired prepulse inhibition of the acoustic startle response (PPI), a form of sensorimotor gating that is disrupted in schizophrenia, bipolar disorder, and other mental health conditions. miR-206 in brain is exclusively expressed in postnatal cerebellar PCs, where it acts to control PPI, but is dispensable for PC cell fate specification, dendritic branching, and survival. Loss of miR-206 alters ion channel, synaptic, and neurodevelopmental disorder-associated gene expression pathways, and increases spontaneous firing frequency in PCs. Viral-mediated miR-206 expression promotes burst firing in PCs, and differentially shapes acoustic startle and PPI in WT and miR-206 KO mice.

CONCLUSIONS: We propose that miR-206 is a critical regulator of PC physiology and behaviors relevant to neuropsychiatric disorders.

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Title: Sodium-MRI for characterizing ionic dysregulation in Alzheimer's Disease

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Background: Sodium is a vital electrolyte that plays a central role in maintaining physiological homeostasis through osmoregulation and cellular function. In Alzheimer's disease (AD), studies have demonstrated a strong association
between Amyloid beta (Aβ) plaques, tau neurofibrillary tangles, and dysfunction of the NKA, a key regulator of ionic homeostasis. NKA impairment disrupts Na^+/K^+ gradients, leading to altered neuronal excitability and cellular stress. Advances in sodium-MRI enable the in vivo measurement of brain sodium
levels, providing a novel window into cellular homeostasis and energy regulation. In this study, we aim to evaluate the feasibility of 7T sodium-MRI in detecting AD-related ionic dysregulation.

Methods: All MRI measurements were performed on a 7T whole-body Magnetom scanner. Standard proton MRI was performed to acquire high-resolution T1-weighted anatomical images with the MP2RAGE sequence to assist with structural localization and co-registration. Sodium-MRI acquisition employed a gradient-recalled echo (GRE) sequence. This protocol was optimized to balance SNR, spatial resolution, and patient comfort while maintaining clinical feasibility. Individual total sodium concentration (TSC) maps were then co-registered to each participant's T1-weighted anatomical reference image acquired from the 1H MRI protocol.

Results: Voxel-based permutation analysis revealed elevated TSC in AD patients across diverse brain regions. Quantitatively, gray matter TSC in an AD patient was 40.85 ± 2.47 mM/L, compared to 32.58 ± 3.09 mM/L in the control, while white matter TSC was 34.37 ± 1.89 mM/L in patients versus 30.71 ± 2.11 mM/L in the control.

Conclusions: These results suggest that sodium-MRI can detect widespread ionic dysregulation that aligns with known pathological patterns of AD. Given its ability to non-invasively quantify sodium metrics, this technique offers a promising metabolic imaging biomarker for early disease detection.

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A multi-modal framework for characterizing cell types and circuits underlying context-dependent decision-making in mice

Myungji Kwak, Herbert Zheng Wu

BACKGROUND: The anterolateral motor cortex (ALM) plays a critical role in flexible, context-dependent sensorimotor decisions. In a delayed match-to-sample (DMS) task, ALM is required during the context odor and delay periods for accurate stimulus-response mapping. Two-photon imaging of ALM layer 2/3 identified context odor- and choice-selective neurons, including a subset encoding specific context-response contingencies, suggesting ALM supports flexible action selection through dynamic reconfiguration of local circuits. However, the underlying mechanisms including molecular identity of these functionally defined populations and their relationship to input-output connectivity remain unknown.

METHODS: We aim to address this gap by integrating functional imaging, circuit tracing, and spatial transcriptomics to characterize the same ALM neurons across all three modalities. We performed two-photon (2p) calcium imaging of ALM neurons during the DMS task, with circuit-defined subpopulations fluorescently co-labeled. Input-defined populations were labeled by injecting anterograde transsynaptic AAV1-Cre into the basolateral amygdala (BLA) and orbitofrontal cortex (OFC) in Ai14 mice. Output-defined populations were marked by injecting retroAAV-tdTomato into the striatum, BLA, and contralateral ALM. We developed a co-registration workflow to align 2p images with ex-vivo confocal images for downstream integration with spatial transcriptomics.

RESULTS: We confirmed context odor- and choice-selective populations in ALM layer 2/3 during the DMS task. Viral tracing labeled input- and output-defined populations co-expressing GCaMP, enabling simultaneous functional recording and connectivity identification. Preliminary analysis showed ~20% overlap between input-defined (BLA->ALM) populations and GCaMP expression. Co-registration achieved ~70% cell recovery in functional imaging planes, supporting feasibility for integration with spatial transcriptomics.

CONCLUSIONS: By characterizing the same neurons across function, cell type, and connectivity, this approach will reveal how context-dependent decision making is implemented by distinct ALM populations defined by molecular identity and circuit organization.

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Resting state brain activity can reliably predict drug cue-reactivity in stimulant use disorder: Evidence from multiple independent cohorts

Zihan (Nancy) Zhang, Tarik Bel-Bahar, Riaz B. Shaik, Nelly Alia-Klein, Rita Z. Goldstein, Muhammad A. Parvaz

Background
Stimulant (including cocaine and methamphetamine) use disorders have high relapse rates. Drug-cue reactivity is a key predictor of relapse risk, making cue-reactors more vulnerable to relapse than non-reactors. However, scaling robust cue-reactivity assessment in clinical settings is limited as it requires sustained attention to curated sets of drug-related and comparative cues. Here we test whether features in resting-state EEG can classify between cue-reactors and non-reactors. Classification was performed using two independent cohorts of individuals with cocaine use disorder (iCUD) and a sample of individuals with methamphetamine use disorder (iMUD).

Methods
Resting-state EEG power in delta, theta, alpha, and beta bands during eyes-open condition was analyzed from three datasets comprising 89 iCUDs (iCUD1), 37 iCUDs (iCUD2), and 49 iMUDs. P300 and LPP amplitudes elicited by drug and neutral picture cues were extracted and one-hot encoded for the classification between cue-reactors (LPP_drug > LPP_neutral) and non-reactors (LPP_drug ≤ LPP_neutral). Three sets of random forest models with varying data splitting strategies were applied to resting-state features for this classification.

Results
The top 5 resting-state predictors yielded >78% accuracy predicting frontal and medial P300 for iCUD1, and >88% accuracy predicting medial LPP for iCUD2. The top 5 predictors from iMUD obtained 90% accuracy predicting medial LPP and parietal P300. Relative frontal and parietal delta band power were top performing predictors of cue-reactivity across iCUD and iMUD.

Conclusions
Resting-state EEG features, especially delta band power, can robustly predict drug-cue reactivity for iCUD and iMUD, showing strong potential as objective biomarkers for identifying drug cue-reactors.

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Decreased neuronal activation during recall in middle age.

Naomi Yamaguchi, Austin M. Baggetta, Denise J. Cai

Background: Aging is associated with spatial memory impairments and cognitive decline, which are major concerns for an increasingly aging population. While deficits in learning rates, memory consolidation, and hippocampal neuronal activity have been widely studied in aged mouse models, the progression of these changes during middle age remain understudied. In particular, it is unclear whether hippocampal neuronal recruitment during spatial memory recall differs between young adult and middle-aged mice, and whether such alterations precede overt behavioral impairments.

Methods: We trained young adult and middle-aged mice to equivalent performance levels in a task involving water reward locations, allowing us to assess age-related differences in learning rates and recall accuracy. Seven days after training, mice underwent a recall session, followed by c-Fos immunolabeling across hippocampal subregions (CA1, CA3, DG) and the dorsal peduncular cortex to quantify neuronal activation during memory recall.

Results: Despite achieving comparable recall accuracy, middle-aged mice exhibited significantly slower learning rates compared to young adults. In addition, middle-aged mice showed reduced c-Fos expression across hippocampal subregions during recall.

Conclusions: These findings suggest that there is a decrease in hippocampal neuronal activation in middle-aged mice even when recall performance appears intact, highlighting early circuit-level alterations that may precede observable cognitive decline.

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Background: Drug addiction is characterized by heightened salience attributed to drug-related cues and impaired inhibitory control, underpinned by maladaptive recruitment of large-scale brain networks. However, traditional task-based studies focusing on regional activation or pairwise connectivity during static laboratory tasks cannot capture how coordinated whole-brain network activity unfolds over time in naturalistic environments. We investigated how time-resolved brain state dynamics during naturalistic drug cue exposure (a drug-themed movie) differ between individuals with opioid use disorder (iOUD) and healthy controls (HC).

Methods: Sixty-five iOUD and 31 HC viewed 17 minutes of 'Trainspotting' during fMRI. BOLD time series were extracted for 14 canonical brain networks, and a Hidden Markov Model identified discrete brain states from temporally concatenated network-level signals. The number of states was selected by minimizing AIC. Fractional occupancy, dwell time, appearance rate, and transition probabilities were compared between groups and scene types (drug vs. non-drug).

Results: Twelve HMM states were identified, exhibiting distinct activation profiles loading onto networks supporting attentional control, self-referential processing, visual-auditory processing, and language. The iOUD exhibited greater occupancy of states characterized by high salience, default mode, and sensorimotor network activity; HC preferentially occupied states marked by high executive control and visuospatial network engagement. Within iOUD, states defined by high executive control, default mode, and low visuospatial activity were visited more frequently during drug versus non-drug scenes. Notably, preferential engagement of default mode network states also correlated with higher scene-induced craving.

Conclusion: These findings suggest iOUD preferentially engage brain states characterized by heightened salience and default mode/sensorimotor activity during naturalistic drug cue exposure, while HC favor states supporting executive control. Altered brain state dynamics in iOUD may reflect maladaptive network coordination underlying drug-biased processing in ecologically valid contexts. The association between default mode state engagement and subjective craving further supports the clinical relevance of these dynamic neural signatures.

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Social buffering between chronically socially defeated susceptible mice induces recovery from depression-like phenotypes through empathetic behavior

Nathaniel Tjen, Hyoseon Oh, & Scott J. Russo

Major depressive disorder (MDD), characterized by persistent social withdrawal and impaired interpersonal functioning, is one of the most prevalent and debilitating psychiatric disorders globally, representing a substantial global health burden. In both human and rodent models, social environments are known to influence vulnerability and resilience to chronic stress, although it remains unclear whether reciprocal social interactions can actively contribute to recovery from stress-induced depressive states. In this study, we examined whether social buffering through cohousing between mice rendered susceptible following chronic social defeat stress (CSDS) could facilitate recovery from depression-like behaviors.

Following CSDS, mice were classified by their social behaviors through a standardized social interaction assay. Then, mice were cohoused for 21 days in defined pairings between control, resilient, and susceptible-stressed mice. Behavioral outcomes were measured using social interaction tests, resident-intruder assays, and home-cage analyses.

We found that cohousing stress-susceptible mice together led to improvement in social behavior, including increased social interaction and reduced social avoidance. In social interaction tests, susceptible-susceptible pairings presented higher SI index scores after social buffering, indicating recovery from traumatic social deficits. In resident-intruder tests, susceptible-susceptible pairings show increases in general sociability towards juvenile mice, indicating recovery from initial social interaction impairments. Notably, these mice also exhibited elevated levels of prosocial behaviors (huddling and allogrooming) during the social buffering period, suggesting engagement in empathy-like interactions.

Ultimately, these findings indicate that reciprocal social interactions between similarly stressed individuals can facilitate recovery from depression-like phenotypes in mice. Furthermore, they highlight the role of social buffering among stress-susceptible mice as a potential, powerful driver of behavioral recovery and suggest that mutual social support systems may play an active role in restoring social functioning following chronic stress.

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Cognitive and psychiatric profile of Parkinson's LRRK2G2019S gene mutation carriers

Nathaniel Westneat, George W. Huntley, Deanna L. Benson

Background: Cognitive and psychiatric abnormalities in Parkinson's commonly present during the prodromal stage of the disease, before motor dysfunction and subsequent diagnosis. To parse these non-motor trends in humans, we examined and compared multiple cognitive testing results across healthy, non-manifesting, and motor symptom-manifesting LRRK2G2019S carriers, in both men and women from the Parkinson's Progression Markers Initiative (PPMI) database.

Methods: To assess differences across several cognitive domains, we compared longitudinal test scores from the Montreal Cognitive Assessment (MoCA) across age and clinical status. We similarly compared self-report scores from the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-CS) to understand impulsive behavior across routine, goal-directed activities.

Results: We found no significant differences in MoCA scores among healthy, manifesting and non-manifesting groups in men or women, nor in normalized longitudinal comparisons with each patient's own original score. However, there were several differences in QUIP-CS self-reported behaviors. While men reported increased compulsive sexual behavior in both non-manifesting and manifesting carriers compared to healthy controls, women did not. However, both mutation-carrying groups in men and women reported significantly exacerbated compulsive-impulsive eating behaviors, compared to healthy controls.

Conclusion: While significant differences in MoCA cognitive assessments were not evident, there were marked differences in QUIP-CS impulsive-compulsive behaviors across non-manifesting and manifesting LRRK2G2019S carriers in both men and women. Increased impulsivity in the QUIP-CS test in LRRK2G2019S humans may be mirrored by the higher "False Alarm" rates (faulty inhibitory control) that we observe in the Continuous Performance Test by Lrrk2G2019S mice compared to wildtype controls. Further examination of these Parkinson's cognitive findings with each other longitudinally and with autonomic data is likely promising for further translation of our behavioral mouse results.

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Leveraging Electronic Health Record–Based Social Determinants of Health to Examine Psychiatric Crisis Care

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*Authors contributed equally

Background: Social determinants of health (SDoH) play a critical role in shaping health trajectories and treatment access among psychiatric patients. Electronic health records (EHRs) contain rich SDoH data that represent an underutilized resource for examining social determinants on psychiatric outcomes. This study examines associations between EHR-derived SDoH indicators with psychiatric hospitalizations and emergency department (ED) visits.

Methods: EHRs were derived from 625 patients (age: M[SD]=31.8[8.58]; sex: 51.68% male) seeking initial outpatient psychiatric treatment. SDoH variables were derived from the SDoH Psych Standard flowsheet. Of the 23 domains, 12 items were retained (<25% missing data). Logistic regression analyses stratified by sex investigated associations between SDoH and frequency and incidence of ED and hospitalizations with age included as a covariate.

Results: In sex-stratified analyses, primary insurance was significantly associated with hospitalization in both males (OR = 1.68, p = 0.020) and females (OR = 1.65, p = 0.02). Employment showed strong positive associations with total ED and hospitalizations across males (OR = 1.58, $p < 0.001$) and females (OR = 1.37, p = 0.002). In males, housing status (OR = 8.89, p = 0.009) and education (OR = 1.50, p = 0.026) were additionally significant, whereas these factors were not significant in females (ORs 0.66–0.91, $p > 0.60$).

Conclusion: Employment and insurance status are significant indicators of adverse psychiatric events at risk across sexes. Among males, housing status and education are significant indicators of risk. Identifying social risk patterns linked to crisis care may enact earlier risk identification and improve psychiatric outcomes by informing comprehensive care models.

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Dynamic geometry remapping of neural activity within frontal cortex during decision-making

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Background: Decision-making is a dynamic process and we often change our minds. What remains unclear is whether and how dynamic patterns of neural activity in frontal and subcortical areas encode this type of deliberative decision-making and how these dynamic activity patterns modulate how option attributes are encoded.

Methods: We trained two macaques to choose between one or two options that differed in their associated reward probability, flavor, and spatial location. While monkeys performed the task, we recorded the activity of 16,495 neurons across 9 frontal and subcortical areas. To characterize how population activity evolved during choice, we used a cross–task decoding approach to isolate periods where the neural activity was associated with distinct reward probabilities, which we refer to as probability states. We then assessed whether the neural population geometry and reliability of encoding of alternative attributes (flavor and spatial location) were modulated by probability states.

Results: As subjects deliberated between the options, we found that there were temporally specific neural representations associated with the probability of chosen and unchosen options. These probability states were primarily seen in ventrolateral PFC, inferior frontal gyrus (IFG) and amygdala population activity. In addition, probability states reshaped the geometry of population codes in area- and attribute-specific ways, while leaving single-neuron tuning preferences largely intact. Specifically, neural geometry related to flavor encoding changed across probability states in agranular insula and orbitofrontal cortex, with stronger flavor discrimination during unchosen probability states. By contrast, spatial location representations were mostly influenced by probability states within IFG and dorsolateral PFC.

Conclusion: Probability states dynamically reconfigure population-level coding geometry even though individual neurons largely preserve their tuning. This suggests that state transitions reorganize how information is represented but not what information is represented.

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Role of locus coeruleus PAC1 receptors in modulating whole-body energy metabolism under stress

Toh P, Duesman SJ, Shetty S, Keller B, Rajbhandari P, Rajbhandari AK

INTRODUCTION: Post-traumatic stress disorder (PTSD) is characterized by chronic dysregulation of the fear response in part due to heightened activation of the sympathetic nervous system (SNS). PTSD is comorbid with metabolic disorders and associated with maladaptive lifestyle factors, such as consumption of a high-fat diet (HFD). The locus coeruleus (LC) is a regulator of the SNS implicated in feeding and metabolism, however, its role in coordinating stress-induced metabolic dysregulation remains poorly understood. The LC expresses PAC1, a receptor for PACAP, a neuropeptide associated with PTSD symptom severity and metabolism.

METHODS: To investigate the role of LC-PAC1 neurons in coordinating stress and metabolism, male Adcyap1r1loxP/loxP mice were stereotaxically injected with AAV2-hSyn-GFP control virus or AAV2-hSyn-Cre-GFP to reduce PAC1 expression in the LC. Following recovery, mice were placed on a HFD (60% kcal by fat) and underwent stress-enhanced fear learning (SEFL). Mice were separated into two groups: a group receiving 15 weeks of a single, once/week reminder shock (RS+), or no reminder shocks (RS-). Body weights were recorded weekly preceding 72h of indirect calorimetry in metabolic chambers. PACAPergic projections to the LC were identified via retrograde tracing with CTB-AF647.

RESULTS: CRE/RS+ mice showed increased freezing during reminder shocks and attenuated weight gain. LC-PAC1 knockdown was predominantly associated with an increase in oxygen consumption (VO2), carbon dioxide production (VCO2), and energy expenditure (EE) in RS- groups. However, the opposite effects were observed in RS+ groups, where LC-PAC1 knockdown was associated with decreases in these parameters.

CONCLUSION: These findings suggest that the effects of LC-PAC1 knockdown on whole-body energy metabolism are altered by stress. Future studies will determine the role of the sympathetic response in mediating these metabolic effects.

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Title:
Medial entorhinal layer 2 stellate cell activity is sufficient to drive type 2 dentate spikes and pathological hypersynchronous events in healthy and epileptic mice.

Authors:
Paul A. Philipsberg, Emanuel M. Coleman, Zoé Christenson Wick, Yu Feng, Kaylin M. Pimshan, Cassidy Kohler, Clifford Kentros, Tristan Shuman

Background:
Type 2 dentate spikes (DS2s) are synchronizing events thought to be important for spatial memory in the healthy brain. Medial perforant path projections have long been thought to drive DS2s, however the specific contribution of medial entorhinal layer 2 (MEC2) stellate cells to DS2s has never been experimentally tested. Further, the extent to which mechanisms facilitating dentate spikes in heathy animals are coopted to produce pathological hypersynchronous events in epileptic animals remains unknown. Here we characterize dentate spikes and MEC2 excitatory firing in both healthy and epileptic mice, and optogenetically activate MEC2 stellate cells to elicit DS2-like events and pathological interictal epileptiform discharges (IEDs).

Methods:
We used dual-region silicon probe recordings in MEC and hippocampus to examine neural activity during dentate spikes in both heathy and chronically epileptic mice. We expressed ChR2 specifically in MEC2 stellate cells in order to optogenetically identify them and directly investigate their role in initiating DS2s.

Results:
We found that the firing rates of MEC2 excitatory cells increase preceding a DS2 and that this modulation of firing rate is increased in epileptic mice, which also have higher rates of DS2s. Further, we show that optotagged MEC2 stellate cells increase in firing rate more than non-optotagged MEC2 excitatory neurons. Finally, we show that activating MEC2 stellate cells can elicit DS2-like events, while stimulating with higher light power can drive IEDs even in control animals.

Conclusions:
These results provide new evidence that MEC2 stellate cell activity contributes both to physiological DS2s and pathological hypersynchronous events in epilepsy.

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Preliminary Magnetic Resonance Spectroscopy Study of Cannabidiol Effects on Amygdala in Opioid Use Disorder

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BACKGROUND: Opioid misuse and opioid use disorder (OUD) continue to pose major public health challenges. We investigated the potential of cannabidiol (CBD), a non-intoxicating cannabinoid, as a possible adjunctive strategy to opioid agonist treatment. In this pilot neuroimaging study, we examined CBD's effects on amygdala metabolite levels in OUD individuals maintained on methadone using magnetic resonance spectroscopy (MRS).

METHODS: Fifty-seven OUD participants receiving methadone treatment received either 800mg CBD (Epidolex®) or placebo oral solution for three consecutive days. MRS was used to quantify metabolites, including N-Acetylaspartate (NAA), Choline, Creatine, Myo-inositol, and Glx (Glutamate+Glutamine). Two MRS scans were conducted: the first ~90 mins after the initial CBD/placebo administration; the second, seven days after the final daily CBD/placebo dose. Spectral processing and metabolite quantification were performed using jMRUI. Preliminary analysis used independent t-tests to assess between-group differences.

RESULTS: Following quality control, data from 33 participants who completed both MRS sessions were studied regarding CBD/placebo groups (Group A, n=20; Group B, n=13). Demographic analysis showed no significant group differences. At the behavioral level, there was a trend toward reduced craving in one group. Preliminary statistical analysis revealed that NAA levels were significantly higher in Group A than Group B at Session 2 ($p = 0.034$). Patterns of other metabolite levels suggest a potential trend toward group-level separation, particularly for Glx (Group B>Group A).

CONCLUSION: Full statistical analyses are ongoing and will be presented. Preliminary findings to date suggest a potential neurometabolic effect of CBD as compared to placebo among methadone-maintained OUD individuals.

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Leveraging region-specific chemogenetics to validate dual-color fiber photometry recordings of dopamine and serotonin

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BACKGROUND: How the brain makes choices depends on separable neural systems and neuromodulatory pathways involved in different aspects of motivated behavior. We aimed to explore how dopaminergic and serotonergic circuits contribute to dissociable computations related to reward value. Modern optical imaging tools combine fluorescent biosensors with fiber photometry to enable real-time dopamine and serotonin measurements, even multiplexing simultaneous dual-color recordings. However, technical challenges arise in resolving signal processing issues related to spectral bleedthrough, cross-talk, or motion artifact correction.

METHODS: We attempted to address this by leveraging chemogenetics to independently perturb the VTA vs. DRN - the upstream sources of mesolimbic dopamine and serotonin - in order to isolate signal contributions to each channel. Here, across 44 mice, we co-transfected AAV9-hsyn-GRAB_5-HT1.0 and AAV9-CAG-RdLight1 and implanted optic fibers into one of six brain regions (NAc, mPFC, OFC, BLA, IPN, LDTg). These mice were also transfected with either AAV9-hSyn-hM3Dq-mCherry or AAV9-hSyn-hM4Di-mCherry in the VTA or DRN, in addition to a no-DREADDS sham control group. Freely-behaving mice were tested on our neuroeconomic spatial foraging paradigm, “Restaurant Row”, concurrent with dual-color recordings using the Neurophotometrics device. After mice were well-trained, we administered clozapine-N-oxide (0.25 - 4 mg/kg) vs. saline 30 min before testing via IP injection.

RESULTS: Preliminary analyses focusing on NAc recordings with inhibitory DREADDs in the VTA revealed a decrease in signal only in the red channel only on CNO days, compared to saline days or the green channel.

CONCLUSIONS: Bidirectionally manipulating sources of major neurotransmitter species using chemogenetics may be a useful approach for disentangling meaningful dual-color photometry signals from confounding noise.

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Permissive Role of Erythroferrone in Alzheimer's Disease Pathophysiology

P Na-Phatthalung, V Ryu, A Gumerova, M Levy, M Fribourg, M Planoutene, Z Tumoglu, L Kautz, T Yuen, M Zaidi, Y Ginzburg

Alzheimer's disease (AD) results from aberrant amyloid precursor protein (APP) processing, leading to neurotoxic Aβ and sAPPβ peptide accumulation. Currently available therapeutics lead to disappointingly small improvements in AD patients. Because BMPs maintain synapses and dendritic plasticity, and regulate homeostasis and repair in the adult brain, we hypothesize that hepcidin-regulator erythroferrone (ERFE) mediated BMP sequestration impairs neurogenesis, leading to memory loss and ultimately global cognitive decline.

We utilize the well-established 3xTg mouse model to dissect the contribution of ERFE to AD pathophysiology. Using RNAscope, we show that ERFE is expressed in the dentate gyrus and that Erfe expression is increased in 3xTg mouse hippocampus, the brain area involved most robustly in memory function and that both neurons and microglia express Erfe. Furthermore, we see evidence of ferroptosis in 3xTg mice, reversed in 3xTg;Erfe–/– mice. Next, we demonstrate prevention of memory defects in 3xTg;Erfe–/– vs. 3xTg mice using well-established validated behavioral studies, i.e. Novel Object Recognition (recognition memory), Y-Maze of Spontaneous Alternation (working memory), and the Morris Water Maze (spatial learning and memory). Finally, using proteomics technology, we demonstrate that BMP4-associated proteins (based on GO terms) provide the most robust separation between analyses of the hippocampus in WT, 3xTg, and 3xTg;Erfe–/– mice. Specifically, ERFE loss in the 3xTg mouse hippocampus results in enhanced expression of BMP4-associated proteins involved in chromatic organization and transcription regulation and a decreased expression of proteins involved in neuronal synaptic signaling.

Taken together, these novel results provide robust evidence of the permissive effect of ERFE in AD in 3xTg mice possibly as a result of its effect on BMP sequestration.

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Submit your abstract here:

Neural Encoding of Pneumonia

Rahul Sabnis1, Andrea Muñoz Zamora1, Ignacio Beccacece1, Verónica Burstein1, Michel Enamorado1, *

1Kimberly and Eric J. Waldman Department of Dermatology, Mark Lebwohl Center for Neuroinflammation and Sensation, Marc and Jennifer Lipschultz Precision Immunology Institute, and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029

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While the neural circuits underlying exteroception are well characterized, how the nervous system encodes interoceptive immune signals remains largely undefined. To address this, we used a model of Staphylococcus aureus pneumonia to examine how infection-derived signals are represented in the brain and how they influence behavior. C57BL/6 mice were infected intratracheally to induce pneumonia. Brains were subsequently extracted, immunostained, and analyzed using an automated brain-wide c-Fos quantification pipeline.

Strikingly, we found increased neuronal activity in hippocampal and amygdalar regions following infection, suggesting engagement of circuits potentially linked to pathogen sensing or stress-related responses. In addition, pneumonia altered activity in hypothalamic and immune-associated brain regions, indicating recruitment of circuits more directly related to physiological homeostasis and immune regulation. Together, these findings suggest that immune challenges are represented in the brain through distinct neural circuits, providing insight into how interoceptive immune signals shape brain function and behavior.

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mAION: Microglial remodeling in α-synucleinopathy converges with Parkinson's disease polygenic risk
Raphael Kubler, Daniele Mattei, Kosei Hirata, Oriol Narcis, Mikaela Rosen, Felix Crary, Beomjin Jang, Kailash BP, John F. Crary, Lot D. de Witte, Joel Blanchard, Towfique Raj

Background. Parkinson's Disease (PD) and dementia with Lewy bodies (DLB) are characterized by α-synuclein pathology and substantia nigra (SN) dopaminergic neuron loss. Genetic evidence implicates microglia, but which microglial states respond to pathology and whether these states are genetically predisposed remains unknown. We used single-cell transcriptomics and polygenic risk assessment to identify disease-relevant, genetically-predisposed microglial populations.

Methods. We sequenced 423,445 oligodendrocyte-depleted brain nuclei (36,214 myeloid nuclei) from 98 donors (AION nuclei cohort; 109 samples; amygdala, substantia nigra, cortex) and an additional 133,585 fresh myeloid cells from 21 donors (AION cell cohort; 36 samples; SN, cortex). For replication, we leveraged the AMP-PD cohort which contained 128,793 myeloid nuclei from 97 donors (443 samples; five brain regions).

Results. We identified eight distinct brain-resident myeloid cell states, including phagocytic and sensome (P2RY12-high), unfolded protein response (UPR; HSP90AA1-high), and perivascular (CD163-high). In α-synucleinopathy brains, P2RY12-high microglia were depleted (logFC ≈ -0.21), while HSP90AA1-high microglia expanded (logFC ≈ 0.57). These shifts were accentuated in Braak LB late-stage cases and consistently replicated across cohorts. Pseudobulk differential gene expression analysis pinpointed that HSP90AA1-high microglia upregulate glycolytic and lipid metabolic pathways while downregulating lysosomal, endoplasmic reticulum homeostasis, and phagocytic functions. Next, we tested state- and pathway-level enrichment for polygenic disease risk. We found that HSP90AA1-high microglia and the mitochondrial UPR pathway were significantly associated with PD GWAS (GP2) risk gene expression.

Conclusions. Our findings reveal genetic regulation of microglial state dynamics in α-synucleinopathy brains. PD polygenic risk is linked to microglial dysregulation while protective alleles constrain maladaptive reprogramming. These findings nominate microglial stress programs as genetically prioritized, disease-relevant therapeutic targets.

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Submit your abstract here:

Histone serotonylation-associated gene expression patterns in the dorsal raphe nucleus are regulated by hormonal status in females

Rasika Iyer, Giuseppina Di Salvo, Benjamin Weekley, Ashley Cunningham, Jennifer Chan, Ian Maze

Females are almost twice as likely as males to be affected by Major Depressive Disorder and other mood-related syndromes. One possible explanation for this disparity is that ovarian hormones contribute to mood by affecting the serotonergic system. Indeed, females are at greater risk for mood disorders at times when ovarian hormone levels are changing, and estradiol has been shown to modulate levels of serotonin receptors and the serotonin transporter throughout the brain. However, the impact of ovarian hormones on histone serotonylation, a novel epigenetic mechanism important for neural plasticity and stress responsivity, has not yet been investigated. In the present study, we explored how hormonal status affects serotonin levels, histone serotonylation enrichment genome-wide, and related gene expression patterns in the dorsal raphe nucleus (DRN) using enzyme-linked immunosorbent assays, CUT&RUN sequencing, and RNA sequencing. We found that female mice who underwent bilateral ovariectomy (OVX) displayed higher serotonin levels and greater genomic enrichment of histone serotonylation in the DRN compared to mice with intact ovaries. Furthermore, OVX induced elevated expression of histone serotonylation-marked genes involved in synaptic plasticity and epigenetic regulation. Ongoing and future work will therefore focus on probing the functional implications of these findings on neural signaling throughout the brain and investigating how histone serotonylation and serotonin levels change across the mouse estrous cycle.

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Dissecting the Impact of DDS-Associated Brg/Brm-Associated Factor (BAF) Complex Mutations on Excitatory Neurogenesis

Ratchell Sadovnik, Mark Youssef, Sarah E. Williams, Joseph D. Buxbaum & Nan Yang

Autism spectrum disorder (ASD) is a neurological condition caused by the disruption of essential neurodevelopmental processes. In an effort to identify genetic contributors, hundreds of genes have been identified that, when perturbed, can increase the risk of developing ASD and other developmental delay syndromes (DDSs). Central to these discoveries are chromatin binding proteins, such as the BRG1- or BRM-associated factor complex (BAF complex), a chromatin remodeling complex. These subunits combine to give rise to three main forms of BAF: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and non-canonical BAF (ncBAF). De novo rare variants to various subunits of the BAF family are implicated in ASD and DDS pathologies. While previous studies have revealed the nuanced influences of individual BAF complex subunits on specific regulatory networks in cancer, a thorough understanding of their individual contributions to ASD/DDS remains unexplored. I hypothesize that perturbations in different ASD/DDS-associated BAF complex genes will affect neurogenesis' complex- & module- specific mechanisms. Using CRISPR inhibition complemented with single-cell multi-omics, I aim to comprehensively study the influence of 11 BAF subunits linked with ASD/DDS on excitatory neurogenesis. This study will identify changes in gene expression caused by BAF gene perturbations, detect alterations in gene regulatory processes, and determine whether these changes are consistent or vary across a particular set of perturbations in the human neural context, which could inform the development of targeted therapies for ASD and DDS by identifying key regulatory mechanisms and potential drug targets within the BAF complex.

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Submit your abstract here:

TITLE: Hippocampal sharp-wave ripple dynamics during human social navigation

AUTHORS: Remington Eliasek, Gelana Tostaeva, Katherine Belilty, Daniela Schiller, and Ignacio Saez

BACKGROUND: The hippocampus supports navigation not only through physical environments but also through abstract relational spaces, including social space defined by the dimensions of power and affiliation. Sharp-wave ripples (SWRs) are brief high-frequency hippocampal events implicated in memory consolidation, replay, and the evaluation of possible future trajectories. These properties make SWRs a candidate mechanism for integrating prior social information and supporting upcoming social navigation decisions. However, the temporal relationship between hippocampal SWRs and decision-making during human social navigation remains unclear.

METHODS: We analyzed hippocampal intracranial LFP recordings from 10 neurosurgical epilepsy patients as they engaged in an interactive social navigation task. Participants made decisions that implicitly moved fictional characters along two latent, orthogonal dimensions of affiliation and power. We detected hippocampal SWRs using the deepest hippocampal channel pair that met prespecified quality-control criteria, including ripple-band event detection with duration and oscillatory morphology constraints, rejection of interictal epileptiform discharges, and surrogate-based false-positive assessment.

RESULTS: Preliminary group-level analyses showed modulation of hippocampal SWR rate around the time of social navigation decisions. Across all participants, peri-decision time courses suggested distinct temporal profiles for power versus affiliation trials. Overall, SWR activity during the decision period was not elevated relative to the pre-decision period and was numerically slightly lower (pre-decision: 0.176 ripples/s, SEM = 0.036; decision: 0.160 ripples/s, SEM = 0.031; n = 10).

CONCLUSIONS: Our preliminary findings suggest that hippocampal SWRs may contribute to the integration or evaluation of social-state information before an overt choice is made, rather than reflecting only the navigational choice period itself. More broadly, our results are consistent with a role for hippocampal replay-related processes in human social navigation through an abstract map of power and affiliation.

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Submit your abstract here:

Title: Linguistic Markers of Motivation: NLP-Based Analysis of Motivational Interviewing in Substance Use Treatment

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Background:
Motivational Interviewing (MI) promotes behavior change by addressing ambivalence. Key markers include change talk and sustain talk, whose balance predicts engagement. Human coding is resource-intensive; NLP offers scalable alternative.

Methods:
We developed an NLP pipeline using OpenAI's o4-mini model to classify utterances as change or sustain talk. A pilot sample (n = 5) refined the approach. Outputs were compared with human-coded labels. Logistic regression tested the effects of sentiment, phrasing, and length on accuracy, and principal components analysis identified underlying factors.

Results:
GLM showed a significant multivariate effect of MI behavior category on NLP outputs (Wilks' $\lambda = 0.932$, $F(6, 574) = 3.43$, $p = 0.002$, $\eta p^2 = 0.035$). MI behaviors predicted change talk ($F(3, 288) = 5.26$, $p = 0.002$, $\eta p^2 = 0.052$), but not sustain talk ($p = 0.221$). Reason statements elicited the highest change talk ($M = 1.67$), followed by ability ($M = 1.57$) & need ($M = 1.47$), with desire lowest ($M = 1.36$). Pairwise comparisons showed Reason > Desire/Need and Ability > Desire ($ps < 0.05$). Sustain talk showed little variability.

Conclusions:
NLP classification captures key MI language patterns, especially change talk, supporting scalable assessment of therapeutic processes and potential real-time use.

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Submit your abstract here:

Title: Cortical dynamics of cue reactivity and regulation in methamphetamine use disorder.

Authors: Riaz B. Shaik[1], Tarik Bel-Bahar[1], Zihan Zhang[12], Armaan S. Dullat[13], Areeb Siddiqui[14], Karmiella S. Ferster[1], Rachel Heisler[1], Sarah Abdelaziz[1], Jackie Curtin[5], Therese Mbah[6], Sam Edwards[1], Manassa Hany[7], Muhammad A. Parvaz[128]

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Background: Reactivity to drug-related cues predicts relapse. We examined the EEG late positive potential (LPP) to assess methamphetamine cue-reactivity in individuals with MUD, its variation across abstinence, and its regulation through cognitive reappraisal.

Methods: Forty-one adults with MUD completed an EEG task with two phases: passive viewing of methamphetamine-related and neutral cues, followed by regulation using cognitive reappraisal ('Look' vs. 'Decrease'). LPP amplitudes and cortical sources were measured during early (400–1000 ms) and late (2500–4500 ms) windows. Participants were grouped by abstinence duration (Early vs. Late).

Results: MA cues elicited larger LPP amplitudes than neutral cues during the pre-instruction phase [$t(40)=6.21$, $p<.001$], indicating robust cue-reactivity. Source analysis revealed increased activation in temporal-limbic, occipital, and somatosensory regions, with relative reductions in orbitofrontal and posterior cingulate areas (p-FDR<.05). The Late abstinence group showed higher LPP amplitudes than the Early group [$t(35)=2.68$, $p=.010$], and cognitive reappraisal significantly reduced LPP amplitudes [$t(28)=-3.21$, $p=.003$].

Conclusions: Cue-reactivity in MUD reflects increased temporal–limbic and reduced prefrontal engagement and increases with abstinence, consistent with incubation. MA cue-reactivity can be down-regulated via cognitive reappraisal, indicating preserved regulatory capacity.

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Title: Neuromodulatory Credit Assignment in Recurrent Neural Networks
Background: How neurons determine whether their activity contributed to successful behavior, the credit assignment problem, remains central to understanding motor learning. Dopamine alone cannot explain learning flexibility across varying arousal and internal states, pointing to broader neuromodulatory systems as a missing feedback channel. Noradrenaline, serotonin, and acetylcholine broadcast diffuse global signals, yet learning requires selective reinforcement of specific cells. Transcriptomic evidence reveals that individual neurons co-express dozens of G protein-coupled receptors (GPCRs), suggesting that combinatorial receptor logic may allow neurons to interpret these signals in a cell-specific manner, enabling local credit assignment within recurrent cortical networks.
Methods: We employed established recurrent neural network models, RFLO and MDGL, as generative frameworks to simulate motor learning dynamics under phasic and tonic locus coeruleus activation. Using the RFLO model, we introduced a modulatory receptivity matrix (B) to capture how neuromodulatory feedback targets individual neurons, then developed and validated a B recovery algorithm to infer this matrix from simulated neural activity. LASSO regression was subsequently applied to link recovered B values to MERFISH-derived GPCR expression profiles from motor cortex (M1).
Results: Both RNN models reproduced loop-like population dynamics consistent with calcium-imaging data from mice performing motor learning tasks. The B recovery algorithm reliably reconstructed the true modulatory receptivity matrix from simulated data, and LASSO regression successfully identified relevant GPCR combinations from among 100 candidates. Preliminary MERFISH profiling confirmed heterogeneous GPCR co-expression across excitatory and inhibitory neurons in M1.
Conclusions: This framework links molecular receptor diversity to circuit-level learning dynamics, suggesting that combinatorial GPCR expression implements cell-specific credit assignment in recurrent cortical networks, with implications for disorders of adaptive plasticity such as ADHD and post-stroke motor deficits.

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Submit your abstract here:

Modulating ΔFOSB levels alters nucleus accumbens medium spiny neuron activity

Rithika Lingala, Tamara Markovic, Angelica Minier-Toribio, Eric M. Parise, Arthur Godino, Leanne M. Holt, Veronika Kondev, Kanza Choudhry, Eric J. Nestler

ΔFOSB is a key transcription factor that drives persistent gene expression changes in the nucleus accumbens (NAc) in response to chronic stimuli. The NAc is composed primarily of GABAergic medium spiny neurons (MSNs), divided into dopamine receptor D1- and D2-expressing populations. Prior rodent studies demonstrate that ΔFOSB induction is highly cell-type- and stimulus-specific: cocaine induces ΔFOSB in D1 MSNs, while chronic stress increases its expression in D2 MSNs in stress-susceptible animals and in D1 MSNs in stress-resilient animals. In contrast, opioids and natural rewards induce ΔFOSB in both MSN subtypes. These patterns correlate with opposing synaptic effects, where ΔFOSB reduces excitatory synaptic strength and increases silent synapses in D1 MSNs, while producing opposite effects in D2 MSNs.

Despite these insights, how ΔFOSB alters in vivo MSN activity remains unclear. To address this, we used Cre-dependent viral strategies in D1-Cre and D2-Cre mice to bidirectionally manipulate ΔFOSB expression alongside calcium imaging via fiber photometry. We recorded MSN activity in response to social interaction, saccharin reward, foot shock, and cocaine-conditioned place preference (CPP).

ΔFOSB manipulation primarily affected responses to salient stimuli. Reducing ΔFOSB in D1 MSNs attenuated foot shock-induced calcium transients, whereas reduction in D2 MSNs enhanced them. Behaviorally, decreasing ΔFOSB in D1 MSNs and increasing it in D2 MSNs reduced social interaction. Notably, decreasing ΔFOSB in D1 MSNs—but not D2 MSNs—blocked cocaine CPP and reduced neural activity associated with entry into the cocaine-paired context.

Ongoing electrophysiological studies indicate that bidirectional modulation of ΔFOSB alters intrinsic excitability D1 and D2 MSNs. Together, these findings demonstrate that ΔFOSB bidirectionally regulates cell-type-specific NAc activity and shapes behavioral responses to rewarding and aversive stimuli.

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Effects of Sik3 sleepy mutation on hypothalamic function in mice

Ronit Witztum, Kerly Lozano, Yunayi Pei, Korey Kam, Andrew W. Varga

Introduction: The hypothalamus regulates diverse functions such as the sleep/wake cycle, metabolism, thermoregulation, and innate behaviors such as aggression and sex. The Sik3Slp/+ mouse model was identified by a forward-genetics screen for sleep duration. While Sik3Slp/+ mice exhibit abnormal sleep phenotype, sleep microarchitecture and other aspects of hypothalamic function have not previously been assessed.

Methods: Sleep architecture was analyzed in Sik3Slp/+ mice and non-transgenic littermates using 24hr video-EEG/EMG recordings (ages 2-8 months). Weight was tracked throughout life, while glucose tolerance (GTT) was tested at 10-12 months. Core body temperature was monitored for 3 weeks using intraperitoneal temperature sensors. Aggressive behavior of male Sik3Slp/+ and control mice was assessed during light and dark cycles using the resident intruder test (RI).

Results: Sik3Slp/+ mice showed increased total sleep time and total NREM time ($p< 0.001$) and slow oscillation density ($p < 0.0001$) but had shorter mean NREM bout length ($p< 0.0001$) with higher arousal index ($p< 0.001$). Spindle duration ($p = 0.001$) and power ($p = 0.005$) were reduced. Sik3Slp/+ mice gain excessive weight with age, and manifest significantly increased glucose levels during GTT. Core body temperature mesor ($p = 0.05$) and amplitude ($p< 0.0001$) were lower in Sik3Slp/+ compared to control mice. Aggression tests indicated a trend toward lower total aggression time in Sik3Slp/+ males in the dark phase.

Conclusion: Sik3Slp/+ mice sleep architecture suggests an increased sleep drive coupled with a less stabile sleep architecture, which we speculate may stem from altered neuronal calcium dynamics. The lower core body temperature, obesity, and tendency to lower levels of aggression in males, also support the hypothesis of hypothalamic dysfunction of this mouse model.

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Submit your abstract here:

Explaining abnormal sensorimotor adaptation in ASD mouse models using embodied artificial neural networks

Ross Kempner, Evan Schaffer

BACKGROUND: ASD mouse models exhibit various adaptation phenotypes such as increased adaptation during lever pulling and decreased adaptation to visual regularities during visually-guided wheel turning. At present, it is not known whether these phenotypes are connected. Given that ASD mouse models have S1DZ disinhibition, a region which receives peripheral proprioceptive inputs, proprioception is a candidate common cause. Although the tasks involve different degrees of proprioception and vision, prior research reveals that wild-type mice decide in the wheel-turning task using recent actions, suggesting that proprioception may play an under-appreciated role in the visual adaptation phenotype.

METHODS: To test whether the adaptation phenotypes share a proprioception-related cause, we built a biomechanically realistic arm model controlled by a neural network and trained it to perform the two tasks with the MotorNet python package. MotorNet streamlines an implementation of a simple recurrent neural network controlling an arm in a simplified task environment. The neural network receives hand coordinates for vision and muscle information for proprioception and controls by muscle activations. We tested whether altering proprioception recapitulates the two phenotypes.

RESULTS: We successfully recapitulated wild-type mice behavior in the two tasks. Scaling down the proprioceptive but not visual inputs from the arm to the neural network recapitulates the ASD mouse model visual adaptation phenotype.

CONCLUSION: In order to test whether a single mechanism may produce two adaptation phenotypes, we built a biomechanically realistic model. Scaling proprioceptive but not visual inputs recapitulates the ASD mouse model phenotype in a visual task not thought to assess proprioception. Ongoing work investigates whether this proprioceptive perturbation recapitulates the lever pulling phenotype and whether scaling proprioception recapitulates the ASD mouse model visual adaptation phenotype by impacting the model's memory of its actions.

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Submit your abstract here:

Title: Not all risk is equal: Environmental Subgroups Differentiate Morphometric Deviations and Substance Use Outcomes Among Youth with Family History of Substance Use

Co-Authors:
Sam Edwards, Faith Adams, Ayaan Mustafa, Srinivasan A. Ramakrishnan, Muhammad Parvaz, Shalaila S. Haas

Introduction: Family history of substance use (FHSU) is a well-established risk factor for adolescent substance use (SU), yet considerable heterogeneity exists among at-risk youth. Psychosocial and socioeconomic environments may differentially shape neurodevelopmental trajectories, suggesting that not all familial risk carries the same neurobiological signature. We investigated whether environmentally derived subgroups of FHSU-positive preadolescents show distinct patterns of morphometric deviations and differential SU outcomes across adolescence.

Methods: Participants from the ABCD Study (Release 5.0) were classified as FHSU-positive (n=1,955) or FHSU-negative (n=4,369). FHSU-positive youth were assigned to five psychosocial subgroups via K-means clustering on 33 sociodemographic variables. Normative deviation Z-scores for 150 FreeSurfer-derived morphometric measures were computed at baseline, Year-2, and Year-4 using CentileBrain sex-specific fractional polynomial models trained on 37,407 healthy individuals. SU outcomes at age 15 included low-level-use status, cumulative drug-use days, and SUD diagnosis. Cluster differences were assessed with ANOVA and pairwise differences with independent sample t-tests.

Results: FHSU-positive subgroups differed in age-15 SU outcomes ($F=2.77$, $p=0.02$). Subgroup 3, characterized by lowest family income, single-parent households, school disengagement, and few prosocial peers, showed the greatest difference from FHSU-negative youth across all timepoints ($T>2.63$, $pFDR<0.03$), indicating higher incidence of use. This subgroup also showed significantly greater negative deviation in bilateral lingual gyrus cortical thickness Z-scores across all timepoints ($T<-2.47$, $p<0.01$), most pronounced at Year-2 ($T=-4.53$, $pFDR=1.60E-05$).

Conclusions: Concentrated psychosocial disadvantage within FHSU-positive youth is associated with deviations in posterior cortical maturation, particularly in the lingual gyrus, a region implicated in visual processing and environmental salience. These findings suggest environmental context moderates neurodevelopmental risk, supporting environmentally informed subtyping for precision prevention.

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Submit your abstract here:

Title • Polygenic Risk for Major Depressive Disorder is associated with Late-Life Depression and Cognitive Impairment

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Background • While MDD is a known Alzheimer's disease (AD) risk factor, most AD cohorts lack comprehensive MDD history. Here, we examined if polygenic risk score (PRS) MDD is associated with history of MDD, geriatric depression, cognitive impairment, and AD biomarkers.

Methods • Leveraging the latest GWAS of MDD (EUR N=2,000,702, and Trans-ancestry N= 3,693,227), we calculated PRS-MDD in two cohorts: Health and Aging Brain Study-Health Disparities (HABS-HD) (EUR N=1,162; AMR N=1032), and Texas Alzheimer's Research and Care Consortium (TARCC) (EUR N=1,517; AMR N=967) using PRScs. We tested the association of PRS-MDD with a history of MDD (MDD), depression in the last two years (DEP2YRS), total geriatric depression score (GDS), cognitive impairment (CI), and plasma tau. We adjusted for age, sex, education, top five ancestry principal components, and APOE4 status.

Results • The PRS-MDD within EUR ancestral participants was associated with MDD (HABS-HD: p=1.11E-05, OR=1.34 | TARCC p=0.033, OR=1.18), total-GDS (HABS-HD: p=6.32E-08, effect=0.13 | TARCC: p=9.08E-04, effect=0.07), and DEP2YRS (TARCC: p=9.45E-04, OR=1.25; not available in HABS-HD). PRS-MDD was significant with: CI (HABS-HD: p=3.15E-03, OR=1.26; TARCC: p>0.05), and total tau (HABS-HD: p=0.02, effect=-0.02, TARCC: p>0.05). PRS-MDD was significant with: CI (HABS-HD: p=3.15E-03, OR=1.26; TARCC: p=0.024; OR=1.13), and tau (HABS-HD-ptau181: p=0.02, effect=-0.02, TARCC-total tau: p>0.05). The PRS-MDD calculated from trans-ancestry GWAS was significant with all depression variables and CI among self-identifying Hispanic participants, who had continental ancestry of Admixed Americans.

Conclusions • PRS-MDD predicted late-life depressive phenotypes, plasma tau, CI across two AD cohorts, and Hispanic/Admixed American participants, highlighting depression's genetic link across life stages. Ongoing work investigates additional AD cohorts.

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Submit your abstract here:

Role of a ventral respiratory nuclei neuropeptidergic tonality in fear and metabolic responses

Sanutha Shetty, Ramazan Yildiz, Pamela Toh, YoungUk Jung, Samuel Duesman, Aidan Warnock, Diego Espinoza, Sarah Stanley, Prashant Rajbhandari, Abha Rajbhandari

Introduction: Stress profoundly impacts whole-body energy metabolism, yet central neural circuits regulating stress-metabolic interactions remain poorly defined. We hypothesize that the ventral respiratory group (VRG), a brainstem respiratory rhythm generator, is a stress-responsive hub coordinating respiration with metabolic adaptation. The VRG contains heterogeneous neuronal populations, including the neuropeptide PACAP receptor PAC1R, a regulator of respiration and stress. We investigated the role of VRG-PAC1R in stress-induced metabolic adaptations.

Methods: In PAC1R floxed mice, we ablated PAC1R within the VRG using viral Cre-mediated deletion and analyzed fear behavior and cardiorespiratory output using stress-enhanced fear learning (SEFL) with telemetry. Using c-Fos mapping, viral tracing, and spatial transcriptomics in the VRG, combined with metabolic profiling in brown adipose tissue (BAT) and liver, we assessed central control of metabolic function under stress.

Results: First, SEFL robustly increased c-Fos activity in the VRG-PAC1R neurons. Using retrograde viral tracing, we identified neuronal projections from VRG to BAT and the liver, with a subset of these neurons expressing PAC1R. Second, PAC1R ablation disrupted cardiorespiratory rhythms and exacerbated fear sensitization following stressor exposure, independent of stressor intensity. Third, under SEFL conditions, PAC1R ablation reduced sympathetic innervation to BAT, suppressed energy expenditure, impaired thermoregulation, and downregulated the BAT thermoregulatory pathways. We also observed shifts in hepatic transcriptional profiles toward amino acid metabolism and gluconeogenesis. Further, PAC1R ablation under SEFL induced a glucose intolerance phenotype in mice. Spatial transcriptomic analysis of the VRG-PAC1R-ablated tissue revealed an altered excitatory-inhibitory balance within the VRG.

Conclusion: These findings reveal a neuropeptidergic brainstem-to-peripheral circuit integrating stress and metabolism, highlighting a previously unexplored brain-body pathway with therapeutic relevance for stress-related metabolic disorders.

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Submit your abstract here:

Systemic APOE4 induces inflammatory changes that negatively affect hippocampal function

Sarah Philippi, Brittany Hemmer, Hanxiao Liu, Monika Jain, Yihang Wang, Jian Luo, Michael Sewell, Manav Kapoor, Joseph Castellano

Background: Seminal brain aging studies found that perturbing the systemic environment (SE) through young blood exposure revitalizes brain function. Whether other modifications in the SE affect the brain, including how genomic variation affects peripheral organs to alter brain function, is unknown. The APOE4 allele increases risk for several brain disorders, including Alzheimer's disease, hemorrhagic stroke, vascular dementia, and Parkinson's dementia. We have shown that APOE4 shifts the plasma proteome relative to APOE3 in elderly humans without dementia, motivating our hypothesis that systemic alterations drive changes in brain function, which may be reversible through exposure to plasma proteins from more protective APOE genotypes.

Methods: We used a multi-omics approach following exposure to blood from opposing APOE genotypes and applied functional assays to probe cellular alterations mediated by shifts in the SE.

Results: We identified plasma proteomic shifts in immune pathways in APOE4 vs. APOE3 mice that were conserved with our human dataset, suggesting an inflammatory phenotype related to the APOE4 SE. Using bulk-RNAseq on hippocampi from APOE3 mice sharing APOE4 blood through parabiosis, we identified a transcriptomic profile reflective of altered immune activation and oligodendrocyte function. Using hippocampal snRNAseq of APOE3 mice exposed to APOE4 blood, we found proportional shifts in phagocytic microglia, while changing pathways associated with oligodendrocyte function. We applied confocal imaging, finding that exposure to the APOE4 SE induced microglial activation and oligodendrocyte dysfunction and loss of myelination. CellChat was used to identify how the APOE4 SE altered relationships among hippocampal cells, highlighting potential mechanisms.

Conclusions: Our results argue that the APOE4 SE is sufficient to induce CNS cell population changes, perhaps contributing to APOE4's increased risk for neurological disorders.

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Neurocomputational Evidence for Value-Based Decision-Making Alterations in Prolonged Grief Disorder

Seeley, S.H., Berner, L.A., Feder, A. & Schiller, D.S.

BACKGROUND: Grief is not a disorder, but ~5% of bereaved people experience debilitating grieving that predominates long-term (i.e., >one year) functioning: prolonged grief disorder (PGD). A neurocomputational perspective on grief suggests adaptation requires reconciliation of two competing internal models or beliefs, one accommodating and one rejecting the loss. However, this has yet to be empirically tested so specific learning mechanisms are unknown.

METHOD: N=22 bereaved adults (mean age 46 years, 80% female, 55% with PGD) who experienced a close loved one's death >1 year ago completed well-established probabilistic reversal learning tasks, one having a third "safe" (50/50% reward/loss) option, with hierarchical Bayesian estimation of reinforcement learning models and model-based fMRI.

RESULTS: Across tasks, people with PGD showed intact initial learning but impaired updating post-reversal ($p=.004$-$p=.049$). Unlike the typical or "integrated" grief group, PGD also lost discrimination between win and lose/safe options post-reversal in the three-choice task. Computational modeling revealed that influence of expected value on choice (inverse temperature, β) was lower in PGD, driven specifically by lesser devaluation of previously rewarded options after contingencies changed (-0.13 vs. -0.36, $p<.001$). Neurally, PGD showed reduced caudate activation for overall signed prediction errors, and for counterfactual prediction errors/expected values ($p<.02$-$.08$). Notably, behavioral and neural response to chosen options did not differ in PGD. The caudate is a key region for goal-directed, flexible learning, suggesting that PGD involves disrupted counterfactual processing, not general reward learning impairment.

CONCLUSIONS: We found convergent behavioral and neuroimaging evidence of alterations in flexible updating of action-value associations, consistent with the clinical presentation and phenomenology of PGD. Domain-general learning mechanisms may represent potential novel intervention targets for the ~30% of treatment seekers who do not respond to evidence-based treatment for PGD.

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Modeling the impact of deep brain stimulation for obsessive compulsive disorder on behavioral flexibility

Sarina Karmacharya, Keondre Herbert, Brian E. Russ and Peter Rudebeck

Background: Adaptive behavior relies on a balance between habitual and goal-directed systems. This balance is mediated by cortical-basal ganglia circuits and dysfunction within these circuits is implicated in obsessive-compulsive disorder (OCD). Recently, deep brain stimulation (DBS) of the anterior limb of the internal capsule (ALIC), that links frontal cortex and striatal regions, has been identified as an effective target for OCD. Stimulating this pathway modulates OCD-related circuit dysfunction, but the mechanisms remain unclear.

Method: Macaques were taught to perform two tasks that assess cognitive flexibility and are impacted in OCD: Go/No-Go and probabilistic reversal learning (PRL). In the Go/No-Go task, a centrally presented circle's color signals whether to make or withhold a saccade. In the PRL task, subjects first learn reward probabilities for stimuli and then must adapt when those contingencies are reversed. Guided by probabilistic-diffusion tractography, mini-DBS leads were implanted in the ALIC. Current ranging from 0.5-5mA at 130Hz was delivered and compared to non-stimulation. Reaction time, error rate, and reversal times were compared between stimulation and non-stimulation conditions.

Results: In Go/No-Go, the preliminary results show higher error rate in No-Go trials during 5mA stimulation, while the error rate decreased at 1.5mA compared to non-stimulation blocks. In PRL, following the reversal, the subject took longer to select the best option at 5mA, whereas reversal occurred faster at 0.5mA compared to non-stimulation blocks.

Conclusion: ALIC DBS affected both behavioral tasks: the subject showed enhanced cognitive flexibility at lower current levels, while higher current impaired behavioral flexibility. These findings show that in healthy subjects, DBS can alter performance and thus have implications for understanding how this therapy improves outcomes of OCD.

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Implementing Virtual Reality to study temporal dynamics of contextual fear memory linkage in humans
Shah D, Patel S, Kim C, Orederu T, Radulescu A, Schiller D

Fear generalization, the spread of conditioned fear responses to safe or related contexts, is a hallmark of anxiety disorders. Building on rodent research demonstrating that temporally proximal memories share overlapping neural ensembles and are susceptible to affective linking, this study investigated whether encoding interval between two distinct virtual reality contexts influences fear generalization from a conditioned to a non-conditioned environment in humans.

Participants were randomly assigned to a Near (~2-hour interval) or Far (~2-day interval) group and explored two virtual apartments across four sessions using Vive Pro 2 headset. Fear was conditioned in Apartment B via an animated zombie encounter, with physiological (tonic electrodermal activity, skin conductance response amplitude, heart rate) and behavioral measures (self-reported arousal and valence, source memory, attention) collected throughout.

Preliminary analyses on an initial cohort (n=12 Near, n=12 Far) confirmed successful fear conditioning, evidenced by a significant increase in tonic EDA during the zombie encounter relative to baseline ($p = .013$). Across converging measures, the Near group showed elevated physiological and self-reported arousal upon re-exposure to neutral Apartment A, with responses remaining comparable to those in the fear-conditioned context. The Far group's responses returned toward baseline, consistent with context-specific fear retention. The Near group also showed a trend toward greater source memory confusion between apartments, suggesting temporal proximity weakens contextual boundaries and facilitates retroactive interference.

Data collection has since been extended to n=16 per group, with analysis underway. These findings provide proof of concept for using immersive VR to study temporal memory linking in human fear conditioning, and suggest encoding interval meaningfully modulates fear generalization, with implications for understanding anxiety disorder mechanisms and optimizing timing of exposure-based therapeutic interventions.

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Real-World Emotion Processing in MDD: An Ecological Momentary Assessment Approach Using a Facial Affect Evaluation Task

Sibilla Masieri, Giada Dirupo, Jacqueline Beltrán, Yael Jacob, James W. Murrough, Laurel S. Morris

BACKGROUND: Major depressive disorder (MDD) is associated with alterations in emotion processing, including deficits in facial emotion recognition and blunted affective responses. This is observed in multiple contexts, especially via facial emotion recognition tasks. Most evidence comes from controlled laboratory settings, with limited ecological validity. This study examines emotion recognition performance in an ecological environment over the course of multiple days via smartphone based on task-based social affective assessment.

METHODS: 17 participants (MDD: n=6; HC: n=11) were enrolled in a clinical trial study which incorporated our social affective assessment task: Guess the Emotion. Participants were instructed to both identify and evaluate the emotional intensity on a 1-7 scale across five categories: no emotion, happy, anger, sad, fear. Two mixed-effects models were estimated controlling for age and sex with random intercepts for participant and day: a generalized linear mixed-effects model for emotion recognition accuracy, and a linear mixed-effects model for rating intensity, each including emotion × group as interaction term.

RESULTS: Emotion recognition accuracy did not differ significantly between groups. For intensity ratings, MDD participants showed significantly higher overall rating ($p = .001$), indicating they overrated rated emotional intensity. MDD Emotion × group interaction terms revealed significancy for happy ($\beta = -0.97$, $p = .005$), anger ($\beta = -1.26$, $p < .001$), and fear ($\beta = -0.82$, $p = .019$), meaning MDD participants rated these emotions more intensely relative to no emotion compared to HC.

CONCLUSIONS: These findings suggest MDD group is characterized by altered affective intensity perception rather than impaired recognition accuracy. Social affective assessment offers a promising avenue for future research by improving ecological validity beyond traditional laboratory settings.

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Title: Using the Possible Association between Subjective Assessments of Craving and Objective Assessments of Craving to Identify Biomarkers of Recovery in Substance Use Disorders

Authors: Souad Hassan, Sarah Abdelaziz, Rachel Hesiler, Muhammad A. Parvaz

Background: Relapse prediction is an important outcome in substance use disorders (SUD). A recent meta-analysis implicated objectively assessed drug cue-reactivity and self-reported craving as key predictors of relapse in SUD. Understanding the relationship between subjective assessments of craving and objective measures offers the potential to identify reliable biomarkers of craving. We reviewed literature on existing evidence on the association between subjectively ascertained craving and objectively measured cue-reactivity. It also evaluates whether this link is specific to certain substances or reflects broader addiction-related mechanisms.

Methods: We conducted a systematic search on PubMed and screened the studies using Covidence. We used MeSH keywords related to SUD, craving, cue reactivity, EEG, fMRI, and physiological arousal. Studies included: (1) individuals with a diagnosed SUD, (2) measured subjective craving and objective cue-reactivity, and (3) reported an association between the two. A narrative synthesis table compares associations across substances.

Results: A total of 38 studies met inclusion criteria, encompassing a range of substances. The majority of studies employed cue-reactivity paradigms and utilized neuroimaging, electrophysiological, or physiological measures alongside subjective craving assessments. Overall, 30 of 38 studies (79%) reported significant associations between subjective craving and objective measures, primarily involving reward-related brain regions. Negative or mixed associations were observed in a subset of studies, often involving prefrontal regulatory regions. Findings were consistent across substances.

Conclusions: This review aims to clarify when subjective craving aligns with objective cue-reactivity and when they differ. Early patterns suggest these concepts are possibly related. The final analysis will point out different methods that cause variation and identify situations where objective measures may be more reliable indicators of relapse risk.

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Gene-Target Prioritization for Opioid Use Disorder

Suzannah De Almeida, Sanan Venkatesh, Panos Roussos, Georgios Voloudakis

Background: Opioid use disorder (OUD) is a critical public health crisis with significant heritability, yet much of its genetic architecture remains elusive. While Genome-Wide Association Studies (GWAS) have identified loci like OPRM1, progress is hindered by phenotypic heterogeneity, inconsistent diagnostic criteria, and a lack of harmonization in genomic datasets. Furthermore, translating these genetic signals into specific cell-type-specific mechanisms remains a major bottleneck. We hypothesize that correcting for misclassification across various cohorts and integrating GWAS with single-cell genomics will identify biologically actionable genes.

Methods: This study leverages major European (EUR) and African (AFR) OUD GWAS cohorts. We employ a novel computational method to quantify and correct for phenotypic misclassification, thereby increasing statistical power for cross-ancestry meta-analyses. To bridge the gap between variants and tractable targets, we integrate these meta-analyses with ancestry-aware, single-cell gene expression models using Transcriptome-Wide Association Studies (TWAS). This approach allows us to localize genetically regulated gene expression changes to specific brain cell populations.

Results: By integrating OUD GWAS data from the Million Veteran Program (MVP) with cell-type-specific TWAS, we identified several significant gene-trait associations. Notably, FURIN mRNA levels are predicted to be significantly downregulated ($q<0.05$) in both inhibitory and excitatory neurons in individuals with OUD. Additionally, SCAI, a gene linked to synaptic plasticity, shows significant downregulation specifically within inhibitory neurons. We also identified novel candidates, including ZNF589 and SPINK8, which were previously undetected in bulk tissue analyses.

Discussion: Correcting for phenotypic heterogeneity and utilizing cell-type-specific data reveals novel mechanistic insights into the neurobiology of OUD. These findings prioritize high-confidence targets for therapeutic development. By incorporating diverse ancestries and high-resolution genomic data, this pipeline improves the reproducibility of genetic studies and advances personalized medicine strategies for OUD treatment across global populations.

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Striatal neuron adaptive scaling is circuit-based and selectively disrupted by the Parkinson’s linked LRRK2-G2019S mutation

S. Gupta, A. Tielemans, C.A. Guevara, P. Del Valle, A.R. Magee, G.W. Huntley, D.L. Benson

Background: The striatum receives dense glutamatergic projections from cortex onto two functionally opposing populations of striatal projection neurons (SPNs), D1R-SPNs and D2R-SPNs whose balanced activity encodes action selection, goal-directed behavior, and cognitive flexibility. These behaviors are commonly impaired in Parkinson's. The mechanisms by which corticostriatal circuits maintain balance and how they become vulnerable remains unknown.

Methods: Adaptation has been tested by selectively increasing or decreasing activity in identified populations of neurons for a sustained period. We used Cre-dependent tools to express excitatory or inhibitory DREADDs in SPNs or area PL neurons in adult male and female mice and measured synaptic activity in SPNs after sustained DREADD activation.

Results: Increasing or decreasing D1R-SPN activity for 48h produced multiplicative shifts in mEPSC amplitude in the same direction, contrasting with cortical homeostatic scaling where activity changes drive compensatory shifts in the opposite direction, suggesting that this adaptation is circuit-based and non-cell-autonomous. Scaling was selective to D1R-SPNs: mEPSC amplitudes in neighboring non-DREADD-expressing D2R-SPNs and mIPSC amplitudes in DREADD-expressing D1R-SPNs were unchanged. Contralateral D1R-SPNs (lacking DREADDs) scaled in parallel with ipsilateral manipulated D1R-SPNs. Chemogenetic-based circuit dissection revealed that scaling is driven by contralateral IT cortical projections and not PT neurons. Our prior work predicts that such adaptation would be impaired in Lrrk2G2019Smice and consistent with this prediction, D1R-SPNs could upscale but selectively failed to downscale.

Conclusions: These data show a non-cell-autonomous, direct-pathway-selective form of synaptic adaptation in corticostriatal circuits governed by contralateral IT cortical connectivity. The failure to downscale in Lrrk2G2019Smice likely contributes to the LTP impairments and behavioral deficits, suggesting that both Hebbian and homeostatic plasticity deficits converge to drive cognitive dysfunction in PD.

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Isoproterenol-induced c-Fos expression in PACAPergic neurons across cortico-limbic and brainstem regions

Sylvia Arrington Shannon, Sanutha Shetty, Samuel Duesman, Abha Rajbhandari

Background: Understanding bidirectional brain-body communications is critical in linking physiological and behavioral effects of stress. One such physiological effect of stress is increased heart rate, a key physiological "fight-or-flight" response. In this study, we aim to understand how changes in heart rate affects neuronal activity, particularly in interoceptive regions that are crucial for stress behavior.

Methods: Mice were anesthetized and baseline heart rate was measured for 5 minutes using the MouseOx telemetry system. They were then given an i.p. injection of isoproterenol (20mg/kg), a beta-agonist that increases heart rate, or saline, and heart rate was further recorded for 5 minutes. Mice were sacrificed 90 minutes after injection, and brains were harvested and flash frozen. Brains were sliced at 40um using a cryostat and were stained for cFOS and PACAP using immunohistochemistry. PACAP and cFOS expression were quantified in the nucleus tract solitarius (NTS), locus coeruleus (LC), medial amygdala (MeA), central amygdala (CeA), and posterior insular cortex (pIC).

Results: First, we found that isoproterenol significantly increased heart rate in mice. Next, we found that there was a significantly higher expression of cFOS positive cells in NTS, LC, MeA, CeA and pIC.. Finally, we also found that there was specificPACAPergic neuronal activity increase in the NTS in response to isoproterenol.

Conclusions: This research shows that increases in heart rate cause an increase in the neuronal activity of cortico-limbic and brainstem structures essential for stress regulation . These results establish a bidirectional communication between brain and body during stress behavioral and physiological response.

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Elucidating the role of lateral septum neurotensin expressing neurons in social pursuit

Teagan Daly, Rachel L. Fisher-Foye, Romain Durand-de Cuttoli, Hyoseon Oh, Antonio V. Aubry, Ansel Shirasu-Hiza, Carole Morel, Jaylen Herandez, Long Li, Scott J. Russo

BACKGROUND: Social trauma can alter the way in which the brain processes social interaction. As a result, interactions that should be rewarding are interpreted as threatening. Specifically, the inhibition of the neurotensin positive (NT+) neurons of the lateral septum are known to increase social investigation behavior in stress susceptible mice. Conversely, the activation of the NT+ neurons of the lateral septum are known to induce social avoidance behavior in stress resilient mice. However, the role of the lateral septum NT+ neurons in the motivation for social reward has yet to be explored.

METHODS: We use chemogenetics in neurotensin Cre-mice to manipulate NT+ neuron activity within the lateral septum during social self-administration, an operant task where mice lever press for a juvenile social partner. These mice are subjected to chronic social defeat stress (CSDS) where they are subordinated by a CD-1 aggressor for 10 days. Following CSDS, the mice are classified as susceptible or resilient in the social interaction task with a novel CD-1 mouse. To determine generalization of stress effects, the mice are then exposed to novel juvenile mice in the resident intruder task.

RESULTS: Preliminary results show that resilient mice lever press more than susceptible mice, suggesting that interaction with a juvenile social partner is more rewarding to this group. Additionally, we found that inhibition of NT+ neurons in stressed mice increased lever pressing.

CONCLUSIONS: This research will help to further establish the importance of lateral septum NT+ neurons in social interaction and potentially social motivation. This work provides valuable insight on the mechanism behind specific social deficits caused by traumatic events.

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Linking Pre-Intake Motivations and Treatment History to Intake Attendance: Insights from Semi-Structured Interviews in the PREDiCTOR Study

Theodore Servedio, Kendall Fording, Bree Foster, Bailey Todtfeld, Maya Valenzano, Nazly Suarez, Sophie Riviere, Isabella Melendez, Danielle Obergh, Joseph Colonel, Adam Davidson, Heather Thibeau, Rachel Jespersen, Yulia Landa, Guillermo Cecchi, Cheryl Corcoran, René Kahn, Shalaila Haas

Background: Engagement in mental health intake appointments is associated with reduced risk of emergency department (ED) visits and hospitalizations; however, intake non-attendance can delay or prevent treatment initiation for patients in need. Predicting intake non-attendance could enable health systems to implement proactive interventions that promote patient engagement and improve clinical outcomes. Patient-reported motivations for seeking care and treatment history collected during pre-intake interviews have yet to be evaluated as predictors of intake attendance.

Methods: Semi-structured open-ended interviews were conducted with 74 outpatient psychiatric patients from PREDiCTOR Study (mean[SD] age=30.15[7.80]; 62.16% female) prior to intake. Interview transcripts were qualitatively categorized to identify motivations for seeking care (intrinsic/extrinsic). Medication history, recent ED visits, and hospitalizations were extracted as binary variables from the interview. A Binomial Logistic Regression was conducted to assess the effects of these variables on intake attendance.

Results: Binomial logistic regression revealed that motivation type was the only significant predictor of intake attendance (β=1.63, p=0.012). Participants with extrinsic motivations had over fivefold greater odds of intake non-attendance than patients endorsing intrinsic motivations (OR=5.11, 95% CI [1.44, 18.14]). Age, sex, medication history, and prior ER or hospital utilization were not significant predictors (p>0.05).

Conclusions: Our findings suggest that internal drive is a more robust predictor of initial psychiatric treatment engagement. Incorporating pre-intake motivational screening may help identify patients at high risk for non-attendance. The next step will be to train and utilize a large language model to qualitatively categorize reasons for seeking care based on pre-intake interview transcripts.

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1Icahn School of Medicine At Mount Sinai, 2Florida Atlantic university, 3Brain Health Imaging Centre at the Centre for Addiction and Mental Health, 4Yale School of Medicine

Major depressive disorder (MDD) is a leading cause of disability and a major contributor to suicide worldwide. Chronic stress is a key risk factor for MDD and is often modeled in rodents using the chronic social defeat stress (CSDS) paradigm. This model classifies animals into two groups based on their responses to stress: those with depression-like behaviors (susceptible) and those who maintain normal behavior (resilient). However, the CSDS model has been predominantly studied in male mice, leaving a critical gap in understanding female-specific mechanisms, despite MDD being more prevalent in women.

Identifying sex-specific molecular drivers of stress resilience is essential for advancing personalized treatments. We adapted the CSDS model for female mice and employed RNA-sequencing to analyze transcriptional changes associated with susceptibility and resilience across multiple brain regions. Comparative analyses between sexes were conducted on the nucleus accumbens (NAc), a key brain region involved in stress responses. Weighted Gene Co-Expression Network Analysis (WGCNA) identified gene modules associated with resilience in males and females.

Our findings revealed significant sexual dimorphism in molecular responses to stress. However, approximately 40% of genes upregulated in the NAc of resilient mice overlapped between sexes. WGCNA identified convergent gene modules with one pair showing a 25% overlap—the highest across sexes. Within these modules, GPRIN1 and STX1A emerged as key driver genes positively correlated with resilience. Overexpression of these genes in male mice using viral manipulation induced pro-resilient effects.

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Title: "Ventral hippocampal circuit underlying discriminative fear encoding”

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Abstract: Fear conditioning is a fundamental form of learning that animals use to detect and defend themselves from dangerous situations, in which maladaptation often manifests in symptoms of many psychiatric disorders, including post-traumatic stress disorder (PTSD). Decades of research have extensively linked the ventral hippocampus (vHPC) to the encoding, expression, and extinction of fear memories, which mediate behavioral adaptation to environmental threats. However, many questions remain about precisely what is encoded among specific populations of vHPC neurons and what brain systems cooperate in processing this information during fear regulation. Previous work from our lab and others has highlighted the unique contributions of distinct vHPC GABAergic interneuron subtypes to various fear-memory processes. Recent results from our lab also point to a potential role of somatostatin interneurons (SST-INs) in the ventral cornu ammonis 1 (vCA1) region of the HPC in discriminative fear encoding. Providing the heterogeneous neuronal landscape of vCA1, whether this process is driven solely by SST-INs or through interaction with other INs is unclear. In addition, vCA1 excitatory projection neurons (PNs) project to various downstream regions implicated in valence processing, suggesting SST-INs (perhaps in concert with other local INs) may modulate distinct vCA1 output networks underlying discriminative fear encoding.

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Mapping Peripheral Neuroimmune Engrams

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Chronic inflammatory diseases are defined by severity, persistence and recurrence, suggesting that biological systems retain memory of inflammatory insults. While DRG sensory neurons are recognized as key mediators of inflammatory sensing, whether they encode and store these experiences remains unknown. Here, we identify a population of DRG sensory neurons that are activated during inflammation and retain information from prior insults. These neurons are defined by induction of the stress-responsive transcription factor ATF3, which is robustly expressed in dorsal root and vagal ganglion neurons across diverse inflammatory contexts, establishing ATF3 as a conserved marker of peripheral neuronal activation. To enable functional interrogation of these cells, we develop an ATF3-based genetic trapping system to permanently label and manipulate inflammation-activated neurons. Using this approach, we show that $ATF3^{+}$ sensory neurons are re-engaged upon subsequent homologous or heterologous inflammatory challenges and actively regulate inflammatory responses. Sensory neuron-specific deletion of Atf3 disrupts immune sensing, impairs myeloid cell recruitment, and delays tissue repair, while chemogenetic manipulation of ATF3-tagged neurons bidirectionally modulates disease severity. These findings suggest that ATF3 is a reliable marker of PNS activation and that ATF3+ neurons retain inflammatory information from previous challenges, supporting the existence of peripheral neuroimmune “engrams.” This work challenges the brain-centric model of memory and positions peripheral neural circuits as programmable therapeutic targets in chronic inflammatory disease.

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Investigating the extent and relevance of microglia plasticity for brain aging

Vinaya Sahasrabuddhe and Anne Schaefer

Aging is the highest risk factor for cognitive decline and neurodegeneration. Yet, the mechanisms underlying brain aging and the extent to which it is driven systemically or by dysfunction of specific cell populations—remain elusive. Among brain cell types, microglia—the brain's resident macrophages—exhibit some of the earliest age-related changes, including impaired neuro-supportive functions and heightened inflammation. However, it remains unclear whether these changes are intrinsic drivers of brain aging or secondary responses to the aging milieu. It is also unknown whether such alterations are stable and potentially irreversible or instead plastic and maintained by ongoing exposure to the aged brain environment.

To address these questions, I have established a microglia transplantation paradigm to transfer microglia across age groups using a genetic mouse model that lacks endogenous microglia. Further, I have applied this approach to test plasticity of brain region specification of microglia, finding adult microglia retain the ability to adapt to a new brain-environment. Having confirmed its validity to study microglia plasticity in vivo, I am now employing this approach to study microglia plasticity and function for brain aging.

By transplanting microglia across age groups, I am evaluating (a) how donor age and host environment influence microglial phenotypes to define the limits of microglial plasticity, and (b) how these interactions affect molecular and cellular indices of brain function. This work will provide mechanistic insight into how microglial aging shapes neural health, informing strategies for brain rejuvenation and the prevention of age-related neurodegenerative disease.

2026 Neuroscience Retreat

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Submit your abstract here:

Dynamic lipid remodeling shapes postnatal brain development

Background:

Brain development involves extensive metabolic and structural remodeling, including dynamic changes in lipid composition that remain incompletely characterized. Major lipid classes, including phospholipids, ceramides, and sphingolipids, integral to neurometabolic processes. Systematic characterization of these developmental lipid changes can provide insight into lipid-mediated mechanisms underlying neuronal maturation, synaptogenesis, and myelination. Here, we applied an untargeted LC-MS lipidomics workflow to define lipidomic changes across postnatal brain development in mice.

Methods:

Brain tissue from wild-type mice at postnatal days P0, P7, P15, P21, and P56 was analyzed using a high-sensitivity LC-MS lipidomics platform. Lipids were extracted following tissue homogenization and analyzed in both positive and negative ionization modes to maximize detection of lipid classes. Lipid species were annotated using established databases and grouped into ontological classes. Relative abundances were normalized to internal standards before analysis. Lipidomic changes were assessed at both class and species levels.

Results:

Lipidomic profiling of brain hemispheres revealed pronounced postnatal remodeling from P0 to P56. Early developmental stages (P0-P15) were characterized by phospholipid-enriched profiles, whereas later stages (P21-P56) showed increased abundance of sphingolipids, ether lipids, and glycosphingolipids. Significant increases (all $p \leq 0.014$) were observed in sphingomyelins, ceramide hydroxy fatty acid sphingosines, and hexosylceramides (3.6 to 30.6-fold).

At the species level (all $p \leq 0.006$), significant increases were observed in sphingomyelin, phosphatidylethanol-amine, phosphatidylcholine, and phosphatidylglycerol species, including SM 37:6; O3, PC 38:6, PG 36:2, PE 44:12, and (2.2 to 614-fold). Conversely, significant decreases were detected in phosphatidylcholine and phosphatidyl-ethanolamine species, including PC 32:1, PE 34:4 (6.4 to 49.9-fold).

Conclusion:

Postnatal brain development is characterized by coordinated, large-scale remodeling of the hemispheric lipidome. These transitions parallel membrane formation, synaptic maturation, and myelin assembly. This work provides a comprehensive lipidomic framework for future investigations into normal neurodevelopment and lipid dysregulation in neurological disorders.

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Protective Effects of Cognitive Performance in Early Stage Psychosis

Background: BrainAGE, a machine-learning-based age-prediction-metric, differs between healthy controls (HC) and psychosis-affected patients, yet the potential protective effect of cognitive ability is understudied. To test if cognitive performance associates with BrainAGE, we grouped patients into cognitive clusters and compared Global and Network BrainAGE across these clusters.
Methods: T1w images and cognitive data for 105 patients with affective and non-affective psychosis (mean[SD] age: 22.8[3.62], 40.95% female) and 54 HC (mean[SD] age: 25.0[4.15], 37.04% female) from the HCP_EP dataset were analyzed. Images were processed with Freesurfer and parcellated with Schaefer. Global and Network BrainAGE were computed via CentileBrain models. Cognitive metrics were processed with HYDRA to identify patient clusters (C). Group differences were compared with ANOVA and t-tests.
Results: HYDRA identified a 4-cluster solution (ARI=0.91). C4 (CogTotal=114) showed cognitive scores comparable to HC (CogTotal=113) and contains highest proportion of affective psychosis patients (40.00%). C2 showed lowest cognitive scores (CogTotal=90.6) and contains lowest proportion of affective psychosis patients (12%). C2 and C3 showed similar scores (both CogTotal=100). However, C3 showed reduced episodic memory=88.0 and C1 showed reduced processing speed=83.5. BrainAGE comparisons between all HC and patients were significant ($T>2.05$; $p<0.04$) for all networks, while between clusters, only brainAGE within the Limbic Network was significance ($F=4.389$, $p=0.008$).
Conclusion: Our findings suggest that BrainAGE in cognitive subtypes of patients with affective and non-affective psychosis is not uniform. Psychosis-spectrum disorders show differential brainAGE within the Limbic network based on cognitive subtypes. Cognitive subtyping may provide insights into within and cross-disorder heterogeneity of brain maturation.

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Submit your abstract here:

Niche Trajectory Reference Map of Whole Mouse Brain

Wen Wang, Sujung Crystal Shin, Joselyn Cristina Chávez-Fuentes, Guo-Cheng Yuan

BACKGROUND: The complexity of brain functions is intricately connected with its anatomical and molecular structures. Recent cell-atlas mapping studies have provided important insights into such connections. However, existing studies are primarily focused on individual cell types in isolation, whereas a systems-level view of the brain microenvironment (ME) organization remains lacking.

Methods: To address this issue, we have developed a novel, generally-applicable framework to represent the ME organization as a niche trajectory (NT), which delineates the spatially continuous variation of ME. The NT analysis framework differs from existing approaches in that treats a niche—a spatially localized group of cells—as its core unit. We therefore developed ONTraC, a graph neural network (GNN)–based algorithm specifically designed to reconstruct NTs from spatial transcriptomics data.

RESULTS: By applying ONTraC to a recently generated whole mouse brain MERFISH dataset, we have created an NT map at the brain-wide scale. The resulting NT accurately recapitulated major anatomic structures while also revealing fine-grained variation within individual compartments. Guided by this map, we identified coordinated ME-dependent changes of gene expression, regulatory activity, and predicted cell-cell interactions. Together, these findings highlight the utility of NT analysis for uncovering both neural and glial dynamics across brain microenvironment.

CONCLUSIONS: In summary, niche trajectory analysis provides a scalable and flexible framework for decoding ME variations. The whole-mouse-brain NT map may serve as a valuable resource for investigating the links between function and structural variations.

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Submit your abstract here:

Drugs of Abuse in Reward-Seeking

William McKernan, Veronika Kondev, Isla Racine, Elizabeth Kahn, Brian Kipp, Alexa LaBanca, Julia Sandu, Eric J. Nestler

BACKGROUND: Understanding the long-term effects of drugs of abuse on a molecular and behavioral level is an important goal to help people with substance use disorder, especially as the number of annual overdose deaths is on the rise. Dopamine, which signals through D1- or D2-type receptors, has been studied as a prominent neuromodulator of reward circuitry, given all drugs of abuse increase striatal dopamine levels. Despite decades of preclinical research, no dopamine-based pharmacotherapies have been approved, suggesting the need for studying targets outside the traditionally studied region of the striatum. The Nestler lab has shown that the ventral hippocampus (vHPC) receives dopamine input and contains distinct dopaminoceptive cells, both D1 and D2. We have previously shown that these cells have distinct roles in cocaine-context associative learning. The cannabinoid receptor type 1 (CB1R), was identified as a potent neuromodulator in these dopaminoceptive cells, and was found to be altered by cocaine-context associative learning.

METHODS: Here, we used CB1R knockdown and chemogenetics during saccharin self-administration to further investigate the role of endocannabinoid modulation of D1 or D2 vHPC cells in reward-seeking behavior.

RESULTS: CB1R knockdown in D1 cells increased responding for saccharin reward compared to controls. Using behavioral economics, we were able to model that CB1R knockdown in D1 cells reduces the value of rewards. During approach-avoidance conflict testing when mice are able to lever press for saccharin in the presence of a footshock, CB1R knockdown reduces saccharin responding.

CONCLUSIONS: We reveal endocannabinoid regulation specifically of vHPC D1 cells as an important modulator of reward seeking and approach-avoidance behavior. This provides a better grasp of CB1R receptors' role in reward circuitry, which could be targeted pharmacologically to treat reward deficits.

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Submit your abstract here:

Disruption of the LRRK2 substrate RAB12 Facilitates Neurotransmission and Causes Hyperactivity in Mice

Xingjian Li*, Yuanxin Chen*, Huaixing Wang*, Xue Zhang, Noah Guy Lewis Guiberson, Xianting Li, Jacqueline Burré, Junmin Peng, Hui Zhang, Zhenyu Yue

Background: RAB12 is a small GTPase and a validated substrate of LRRK2, a kinase genetically linked to Parkinson's disease (PD). While RAB12–LRRK2 signaling has been implicated in ciliogenesis and immune regulation, the neuronal function of RAB12 remains largely unexplored.

Methods: We investigated the role of RAB12 in synaptic physiology using Rab12 knockout (KO) mice. Behavioral analysis assessed locomotor activity. Electrophysiological recordings from striatal slices evaluated synaptic transmission. Live-cell imaging in cultured cortical neurons examined synaptic vesicle exocytosis. Biochemical fractionation determined subcellular localization of RAB12, and proteomic analysis of striatal tissue identified molecular changes associated with Rab12 deletion.

Results: Rab12 KO mice developed normally but exhibited increased locomotor activity in adulthood. Electrophysiological recordings revealed enhanced presynaptic release probability and increased excitatory input onto medium spiny neurons. Live-cell imaging showed that Rab12 deletion facilitated, whereas Rab12 overexpression inhibited, synaptic vesicle exocytosis. Biochemical fractionation demonstrated enrichment of RAB12 in synaptic vesicle–associated fractions containing presynaptic components. Proteomic analysis identified alterations in proteins involved in synaptic membrane trafficking pathways.

Conclusions: RAB12 functions as a negative regulator of synaptic vesicle exocytosis and excitatory neurotransmission in vivo. These findings establish a physiological role for RAB12 in synaptic function and provide a foundation for investigating how LRRK2-dependent RAB12 signaling contributes to neuronal dysfunction in Parkinson's disease.

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Submit your abstract here:

Title: Active Transcytosis of Peripheral Pathogenic IgG via Endothelial FcRn Drives Neurovascular Unit Dysfunction in Treatment-Resistant Depression\n\nAuthor/s: Xuanming Guo, Scott J. Russo\n\nBackground: Accumulating evidence implicates systemic immune dysregulation in treatment-resistant depression (TRD). However, how peripheral macromolecules like autoantibodies breach the blood-brain barrier (BBB) to drive central pathology remains elusive, often being mistakenly attributed to passive BBB leakage.\n\nMethods: We utilized chronic social defeat stress (CSDS) in mice to characterize peripheral antibody responses. Endothelial-specific FcRn knockdown mice were used to assess brain entry mechanisms. For clinical translation, we analyzed plasma from a well-characterized cohort of TRD patients (the LEAP study) using LEGENDplex assays to measure brain-reactive IgG.\n\nResults: CSDS induced robust activation of germinal centers in deep cervical lymph nodes (dCLN), triggering pathogenic, class-switched IgG2a/2b production. Rather than passively diffusing, these circulating IgGs were actively transcytosed across the intact BBB via the neonatal Fc receptor (FcRn) and accumulated in the perivascular space, causing profound neurovascular unit (NVU) dysfunction and depression-like behaviors. Clinically, TRD patients exhibited significantly elevated circulating brain-reactive IgG compared to healthy controls, which positively correlated with symptom severity (QIDS scores).\n\nConclusions: Our findings reposition the BBB endothelium from a passive victim to an active gatekeeper in psychiatric disease. Brain-reactive IgG serves as a viable blood biomarker for TRD subtyping, providing a mechanistic rationale for repurposing FcRn antagonists (e.g., Efgartigimod) as precision immunotherapies.

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Submit your abstract here:

AbiMatrix: Dimensionality reduction and spatial segmentation of brain tissue using mass spectrometry imaging

Yiqian Wu
Instructed by: Isaac Marin-Valencia

Background:
Mass spectrometry imaging (MSI) enables spatially resolved characterization of molecular distributions in tissue sections, providing a powerful framework for investigating molecular regional heterogeneity. This is particularly important for the brain because it links molecular composition to spatial location and provides insight into localized biochemical processes and underlying physiological or pathological mechanisms. This project addresses the challenge of extracting biologically meaningful spatial patterns from high dimensional and noisy MSI data by developing a standardized R-based pipeline for effective dimensionality reduction, spatial segmentation and region-specific metabolite analysis.

Methods:
In this study, The R-based pipeline reduces data dimensionality across both pixels and features prior to segmentation. ~90,000 pixels were filtered using total ion current (TIC) with a MAD-based threshold (z = -2.5), removing ~8% low-quality pixels while preserving tissue structure. Feature dimensionality was reduced from ~15,000 to ~4,500 m/z features by retaining the top 30% most variable feature. The reduced data were segmented using spatial shrunken centroid (SSC), followed by ROI-based extraction of mean metabolite intensity.

Results:
Spatial segmentation produced ~13-15 distinct molecular regions, with increased spatial radius improving cluster coherence and reducing fragmented assignments. The resulting segmentation revealed large-scale chemical compartments dominated by global molecular signals, while finer anatomical regions remained unresolved. ROI-based analysis enabled comparison of metabolite intensity across regions, linking chemical variation to spatial tissue organization.

Conclusions:
These results demonstrate the feasibility of linking chemical composition to spatial tissue compartments, with regional variations in metabolite intensity reflecting localized biochemical activity. The proposed pipeline enables robust identification of molecularly distinct regions and supports region-based metabolite analysis,

providing a foundation for studying spatial metabolic heterogeneity in the brain. Future work will focus on improving anatomical resolution and advancing cross-sample integration.

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Submit your abstract here:

Title: GRASP55 overexpression ameliorates molecular and histological features in the APP/PS1 mouse model of Alzheimer's disease

Authors: Yong Huang*, Yanzhuang Wang1, Min Goo Lee2, Michelle E. Ehrlich*, Sam Gandy*
*Department of Neurology, Icahn School of Medicine at Mount Sinai, 1Shenzhen University, Guangdong Province, China, 2Yonsei University, Seoul, South Korea.

BACKGROUND:
The Golgi apparatus is an essential cellular organelle responsible for protein processing and trafficking. Its structure is maintained by the Golgi reassembly and stacking proteins, GRASP55 and GRASP65. Previous in vitro studies have shown that GRASPs can significantly attenuate the neurotoxicities associated with the aggregated Aβ peptide in Alzheimer's disease (AD). In particular, transgenic GRASP55 overexpression mouse (under CAG promoter) has been reported to alleviate pathological features in mouse model of a form of cystic fibrosis (CF) and is well tolerated. Therefore, we hypothesize that GRASP55 overexpression may present a novel strategy to alleviate AD pathogenesis.

METHODS:
For generation of pCAG-GRASP55-Myc transgenic mice, the construct was digested and microinjected into fertilized eggs. Embryos were implanted into C57BL/6N surrogate mother to generate transgenic pups. CAG-GRASP55 transgenic mice were crossed with APP/PS1 (APPKM670/671NL/PSEN1Δexon9) mice to generate APP/PS1 × GRASP55 and GRASP55-only cohorts. Biochemical analyses and immunohistochemistry were performed to assess the effects of GRASP55 expression on Aβ production, plaque formation, and Golgi structure and function.

RESULTS:
GRASP55 overexpression was confirmed in the brains of APP/PS1× GRASP55 mice and was well tolerated. Notably, GRASP55 overexpression likely reduced Aβ production and plaques in APP/PS1 mouse brains and decreased associated gliosis. Further mechanistic studies are ongoing.

CONCLUSIONS:
Overexpression of GRASP55 in the mouse brain likely reverse Golgi fragmentation and ameliorate molecular and histological features in the APP/PS1 mouse model of AD. These findings suggest that pharmacological enhancement of GRASP55 expression may provide therapeutic benefit for individuals with, or at risk of

developing, Alzheimer’s disease.

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Submit your abstract here:

Bipolar and schizophrenia risk gene AKAP11 encodes an autophagy receptor coupling the regulation of PKA kinase network homeostasis to synaptic transmission

You-Kyung Lee, Cong Xiao, Xiaoting Zhou, Le Wang, Meghan McReynolds, Zhiping Wu, Xian Han, Eric Purisic, Henry Kim, Xianting Li, Zhiping Pang, Jinye Dai, Junmin Peng, Nan Yang and Zhenyu Yue

Human genomic studies have identified protein-truncating variants in AKAP11 associated with both bipolar disorder (BD) and schizophrenia (SCZ), implicating a shared disease mechanism driven by loss-of-function. AKAP11, a protein kinase A (PKA) adapter, plays a key role in degrading the PKA-RI complex through selective autophagy. However, the neuronal functions of AKAP11 and the impact of its loss-of-function remain largely uncharacterized.

Through multi-omics approaches, cell biology, and electrophysiology analyses in mouse models and human induced neurons, we delineate a central role of AKAP11 in coupling PKA kinase network regulation to synaptic transmission. Loss of AKAP11 distorts compartment-specific PKA and GSK3α/β activities and impairs cellular functions that significantly overlap with pathways associated with BD and SCZ. Moreover, we identify interactions between AKAP11, the PKA-RI adapter SPHKAP, and ER-resident autophagy-related proteins VAPA/B, which together mediate PKA-RI complex degradation in neurons. Notably, AKAP11 deficiency impairs neurotransmission, providing key insights into the mechanism underlying AKAP11-associated psychiatric diseases.

We further sought to determine how upstream signaling controls AKAP11 selective autophagy. Our results suggest that cAMP signaling may act as a trigger for AKAP11-mediated selective autophagy, potentially linking activity-dependent signaling to kinase network homeostasis and synaptic function.

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Submit your abstract here:

Asymmetric Social Representations in the Prefrontal Cortex for Cooperative Behavior

Authors: Yuan Cheng1†, Yusi Chen2†, Myungji Kwak1, Ross P. Kempner1, Rudramani Singha3, Jared Winslow4, Runqi Liu1, Umais Khan1, Tessa Spangler1, Alvi Khan1, Talmo Pereira5, Matthew Whiteway6, Evan S. Schaffer1, Nuttida Rungratsameetaweemana3, Nan Yang7,8, Herbert Zheng Wu1,8*

Background: Cooperation often requires individuals to adopt complementary roles, such as leaders and followers, to coordinate actions toward shared goals. Although such role differentiation is widespread across social species, the neural mechanisms that support role-dependent decision-making during real-time interactions remain poorly understood.

Methods: Here we developed a cooperative foraging paradigm in mice that enables quantitative analysis of social coordination. Multi-animal behavior was tracked using SLEAP-based pose estimation and aligned to task events. Neural activity in the medial prefrontal cortex (mPFC) was recorded using one-photon calcium imaging, and causal contributions were tested using chemogenetic and optogenetic manipulations. To uncover the computational principles underlying cooperative behavior, we applied multi-agent inverse reinforcement learning (MAIRL) to infer latent value functions guiding decisions.

Results: Mice spontaneously developed stable leader–follower roles during cooperative foraging, and these roles shaped distinct behavioral strategies and predicted learning dynamics. Disrupting mPFC activity impaired cooperative performance in a role-dependent manner. At the population level, mPFC neurons encoded trial-by-trial leader–follower interactions and represented the partner's position in an egocentric reference frame. These signals formed a role-dependent social value map that differed between leading and following animals. Computational modeling using MAIRL revealed latent value functions governing cooperative decisions that closely aligned with the structure of mPFC population activity.

Conclusion: Together, these findings show that cooperation is organized by emergent leader–follower roles and that the mPFC encodes asymmetric representations of social value to guide role-dependent decisions during cooperative interactions.

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Tittle: Single-Molecule Profiling of Hippocampal rDNA Chromatin Fibers during Pregnancy and Postpartum
Authors: Yueyan Zhu, Aileen Harnett, Molly Estill, Li Shen, Schahram Akbarian
Background: The postpartum period represents the highest-risk window for new-onset and recurrent bipolar disorder across a woman's lifetime. Estrogen and progesterone withdrawal following delivery is sufficient to precipitate anxiety- and depressive-like phenotypes in vulnerable individuals. Clinical studies also report gray matter volume changes during pregnancy and postpartum, the molecular basis of which remains unknown. Ribosomal DNA, which encodes the core machinery for ribosome biogenesis, represents a compelling yet understudied candidate locus underlying such structural dynamics. However, as a highly repetitive region, rDNA was largely inaccessible during the short-read sequencing era. Here we use Fiber-seq to explore rDNA epigenetic dynamics during pregnancy and postpartum.
Methods: Using a hormone-treatment pseudopregnancy mouse model, we collected ventral hippocampal tissue and performed single-nucleus multi-omics sequencing, Fiber-seq, and CUT&RUN.
Results: Single-molecule profiling reveals three epigenetically distinct rDNA chromatin states with altered distribution in the postpartum hippocampus. Compared to controls, the postpartum group showed a significant shift in state distribution. The postpartum hippocampus exhibits increased promoter accessibility at RNA Polymerase I (RPI) binding sites, suggesting elevated rRNA transcriptional activity. Single-nucleus multi-omics revealed concordant upregulation of Polr1d — encoding an RPI complex subunit — specifically in pyramidal neurons.
Conclusions: Postpartum hormonal withdrawal remodels rDNA chromatin architecture in the hippocampus, converging on enhanced RPI-driven transcriptional activity. Cell-type-specific upregulation of Polr1d suggests that elevated rRNA synthesis may alter translational capacity in mood-relevant circuits. This work establishes rDNA chromatin remodeling as a previously uncharacterized molecular event accompanying reproductive hormonal transitions, providing a foundation for future functional investigation.

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Submit your abstract here:

Computational and neural mechanisms of trace interval-dependent strategy selection in primate decision-making

Zachary R Zeisler, Liza London, Frederic M Stoll, and Peter H Rudebeck

When choices and outcomes are separated in time, the brain must bridge this gap to learn from rewards. We asked how non-human primates solve this problem by manipulating the trace interval between choice and reward in a probabilistic reversal learning task.

Four monkeys performed nearly 150,000 trials across 200 sessions while recording from frontal cortex, amygdala, and striatum. Longer trace intervals impaired choice accuracy and slowed learning after reversals. We fit a hybrid computational model assigning each trial a continuous weight (ω)
capturing the balance between model-based Bayesian strategy and model-free reinforcement learning, and this hybrid outperformed both pure alternatives.
Monkeys leaned on strategy during active learning and shifted toward habit once the block was mastered; critically, they relied more on strategy at longer trace intervals, suggesting temporal uncertainty recruits model-based computation.

In total, we've recorded over 7000 well-isolated single neurons on this task. Regional specialization emerged at the single-neuron level, with prefrontal cortex and anterior insula encoding stimuli, while amygdala tracks value, but this gave way to a striking population-level story: ω was continuously legible in how neural populations organized and moved through state space. Strategy-dominated trials produced more compact geometries, and ω tracked neural trajectory velocity, stability, and attractor structure from stimulus encoding throughout the trial across OFC, amygdala, striatum, and anterior insula—but not dACC. These findings reveal that the brain doesn't simply switch between learning algorithms; it continuously modulates the geometry of distributed population activity to match the computational demands of the moment.

Taken together, these results show that changing the temporal relationship between actions and outcomes dramatically reorganizes behavior and neural activity along with it, supporting adaptive learning under diverse conditions.

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Distinct Brain Ensembles Control Specific Peripheral Responses to Diverse Stressors

Ziche Chen, Alexander Leunig, Matteo Gianeselli, Thomas Rathner, Ana Oliveira Coelho, Jeffrey Downey, Abigail Glick, Gabriel Caumartin, Filip Swirski

BACKGROUND: Stress disrupts homeostasis and triggers coordinated responses from the nervous and immune systems. While individual neural circuits have been shown to regulate discrete immune or endocrine outputs, it remains unclear whether different stressors recruit shared or distinct brain-wide neuronal ensembles to control peripheral physiology. I hypothesize that psychological and physical stressors engage partially overlapping but distinct neuronal ensembles that encode stressor-specific neuro-body pathways, leading to differential physiological and immune outcomes.

METHODS: I combine unbiased whole-brain activity mapping with functional manipulation in mouse models of psychological stress (restraint), bacterial inflammation (lipopolysaccharide, LPS), viral mimic exposure (poly I:C), and cardiac stress (isoproterenol). Using TRAP2-based activity-dependent genetic labeling, I permanently tag stress-activated (cFos+) neurons and generate 3D brain-wide ensemble maps through tissue clearing and light-sheet microscopy.

RESULTS: Preliminary results reveal that each stressor induces a distinct but partially overlapping pattern of neuronal activation across the brain, accompanied by unique peripheral immune and physiological signatures. Notably, psychological and inflammatory stressors produce different ensemble architectures, suggesting stressor-specific neural encoding. To determine causality, I employ chemogenetic reactivation (Gq-DREADD) and inducible diphtheria toxin receptor (iDTR)-mediated ablation of stress-labeled ensembles. Reactivation of restraint stress–encoded ensembles recapitulates key endocrine and immune features of acute stress, including elevated corticosterone and leukocyte redistribution. Ongoing loss-of-function and region-specific manipulations are identifying conserved and stressor-specific nodes that are necessary for survival and immune regulation.

CONCLUSION: Together, this work establishes a systems-level framework linking brain-wide neuronal ensembles to stressor-specific peripheral responses. By defining conserved versus specialized neuroimmune circuits across diverse stress modalities, this study advances fundamental principles of brain–body communication and identifies candidate neural substrates for therapeutic targeting in stress-related and immune-mediated diseases.

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Submit your abstract here:

Condition-Aware Synthetic EEG Preserves Neural Signatures of Cognitive Processing in Healthy Controls and Alcohol Users and Enhances Decoding Performance

Zichen Zhao, Zihan Zhang, Riaz B. Shaik, Muhammad A. Parvaz

Background: Synthetic EEG provides a practical approach for addressing data scarcity and privacy constraints in addiction neuroscience. In this study, we compared synthetic EEG data generated by different models for their consistency to establish reliable baselines for subsequent synthetic EEG generation and evaluation within a context-aware workflow.

Methods: We used 64-channels EEG data available online from 8 alcohol users (ALC) and 8 healthy controls (HC), on a task with three visual-matching conditions (S1 object, S2 match, S2 no-match). We extracted Δ, θ, α, β, γ band-power from each channel. We then generated synthetic EEG with similar band-power vectors using stratified class and condition-specific sampling based on copula modeling and SMOTE-style log-space interpolation, tuned via a multi-metric evaluation suite that assessed utility, privacy, and distributional fidelity.

Results: Across all task conditions, the interpolation model produced synthetic EEG that closely matched the real recordings. Condition-wise tests showed small KS values (≈0.009–0.014 across Δ, θ, α, β bands) and maximum mean discrepancy values (−0.12 – −0.21), supporting high distributional similarity. Real-vs-synthetic classifiers performed at chance (50%) level (classification accuracies: 45.6% for S1, 50.3% for S2 match, and 49.1% for S2 no-match), underscoring robust consistency between synthetic and real data.

Conclusion: Together, these metrics show that the class-wise interpolation model generates robust synthetic EEG with strong real–synthetic correlation and low distinguishability. Establishing this validated baseline ensures that subsequent synthetic EEG generation ensures that all later fidelity, privacy, and synthetic data evaluations are grounded in accurate, well-characterized real-data performance.