The 17th Annual Neuroscience Retreat

MAY 2nd, 2025

ABSTRACTS

The 17th Annual
Neuroscience Retreat
#FBIRetreat25

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5. Afra Mahmud
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61. Hui Yang
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63. Jacob Abroon
64. Jacqueline Beltran
65. Jaume Taura
66. Jaylen Hernandez
67. Jazmine Chavez
68. Jenna Jubeir
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70. Johana Alvarez
71. Jonathan Barra
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76. Katherine Lynch
77. Kavya Harish
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79. Keondre Herbert
80. Kevin Braunscheidel
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Poster Session
Afternoon

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3. Corinne Smith
4. Khadijah Crawford
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6. Kion Winston
7. Konrad Dabrowski
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9. Lailun Nahar
10. Liting Song
11. Lyucheng Zou
12. Mackenzie Hargrove
13. Madeline Bacon
14. Malia McCollum
15. Manasa Kumar
16. Marcella Corwin
17. Marco Rizzo
18. Marcos Schaan Profes
19. Marvin Ntisem
20. Mason Dallegge
21. Matteo Gianeselli
22. Meilin Chen
23. Michael Maturana
24. Michelle Lu
25. Mohammad Jodeiri Farshbaf
26. Mu Li
27. Nancy Zhang
28. Natalie Hackman
29. Natalie McClain
30. Natasha Rice
31. Nathaniel Westneat
32. Neelima Valluru
33. Neha Ahmed
34. Nicole Bussola
35. Nishant Soni
36. Nitika Kamath
37. Nobuya Abe
38. Padmanayakege Chamithra Rupasinghe
39. Paul Philipsberg
40. Pauline Maciel August
41. Pavan Poojar
42. Philipp T. Neukam
43. Rachel Bercovitch
44. Rachel Brunn
45. Rachel Fisher Foye
46. Rasika Iyer
47. Renae Kurian
48. Rhyann Clarke
49. Noah Cabrera
50. Rintaro Shibuya
51. Risa Watanabe
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55. Samin Hassan
56. Samuel Allen
57. Samuele Petridis
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59. Sarah Claypool
60. Sarah Philippi
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62. Satoka Fujimoto
63. Shalaila Haas
64. Theodore Servedio
65. Shely Khaikin
66. Sonali Gupta
67. Susana Munoz Lara
68. Suzannah De Almeida
69. Swati Gupta
70. Takahiro Shimizu
71. Trevonn Gyles
72. Tri Dong
73. Ty Bell
74. Vinaya Sahasrabuddhe
75. Watit Sontising
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78. Yiran Tao
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ABSTRACTS

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Submit your abstract here:

Electrocortical Response to Deep Brain Stimulation of the Subcallosal Cingulate Cortex Tracks Depression Severity and Recovery

Aashna Desai, Elisa Xu, Jake Dahill-Fuchel, Tanya Nauvel, Sankar Alagapan, Martijn Figee, Chris Rozell, Ki Sueng Choi, Helen Mayberg, Allison Waters

Background: Treatment Resistant Depression (TRD) is a global public health concern correlated with high fatality rates. Deep brain stimulation (DBS) to the subcallocal cingulate has emerged as a promising treatment. While DBS shows immediate responses for motor conditions, psychiatric symptom responses to DBS can take months to show. We hypothesize that changes in cortical excitability over time can serve as a reliable patient selection biomarker, indicative of enhanced white matter and functional connectivity.

Methods: We measured cortical excitability using stimulation evoked potentials (EPs), which reflected immediate cortical response to DBS in the SCC in 13 TRD patients. Utilizing 256-channel EEG data, we generated a SCC specific brain source model depicting spatiotemporal patterns of voltage fluctuations at specific time points. We compared these source models at 4 weeks and 24 weeks post-DBS to understand the patterns of cortical excitability in different brain regions over treatment.

Results: Through longitudinal assessment of cortical excitability to DBS in TRD, we observed striking retest-reliability within patients (ICI .69-97). Our samples showed that patients who are responders have a faster latency and smaller magnitude at 24 weeks in comparison to 4 weeks. Patients who are non responders showed the opposite. Post-hoc analyses provide insight into the causal effects of DBS and facilitate identification of novel changes in excitability associated with treatment response.

Conclusions: The development of a SCC DBS patient selection biomarker holds significant promise for improving treatment outcomes and advancing research. By elucidating changes in cortical excitability using source modeling and EEG, we can enhance the efficacy of DBS for TRD patients.

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Submit your abstract here:

Astrocytic interleukin-3 instructs microglial synaptic pruning during neurodevelopment

Abi G. Yates, Annie Khamhoung, Lena Gaebel, Susana I. Ramos, Máté Kiss, Pacific Huynh, Teresa Gerhardt, Scott Russo, Nadejda M. Tsankova, & Cameron S. McAlpine

Background: Interleukin-3 (IL-3) is a critical mediator of glial communication and function in neurodegenerative diseases. Our previous work revealed that IL-3 and its receptor, IL-3Rα, are constitutively expressed by astrocytes and microglia, respectively, under healthy conditions, suggesting that IL-3 may play a role in brain homeostasis. Here, we aimed to investigate IL-3-mediated glial cell crosstalk and evaluate its contribution to neurodevelopment.

Methods: Wild-type (WT), Il3-/-, Il3fl/flAldh1l1Cre ERT2 and Il3rafl/flCX3CR1Cre ERT2 mice were used in this study. Brains were collected on postnatal day 3 (P3) for pups or 8-10 months old for adults. Brain structure and IL-3 signaling was evaluated by Golgi staining, immunofluorescence, flow cytometry and qPCR. Functional analysis was performed by brain iDISCO, behavioral assays and electrocardiograms (ECGs).

Results: First, we found that IL-3 expression in astrocyte progenitor cells (APCs) was greatest on days P0-5 in mice and the third trimester in humans. Consistent with this, microglial expression of IL-3Rα was greatest during this neonatal period. To explore the role of IL-3-mediated glial signaling in neurodevelopment, we characterized brain architecture by Golgi staining in Il3 knockout mice. We observed increased neuronal complexity and spine density in Il3-/- mice, compared to WT controls, suggesting impaired synaptic pruning. Indeed, an engulfment assay where the volume of engulfed synapses in microglia was reduced in Il3-/- mice. As a consequence, global and cell-specific Il3 knockout mice exhibited neuronal hyperactivity in the brain, which translated to increased anxiety, compulsive behavior and social aversion, and non-resolving elevated heart rate.

Conclusions: APC-derived IL-3 instructs microglial pruning of neurons during a critical neurodevelopmental window to establish proper synaptic connectivity for social behaviors and autonomic control.

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Submit your abstract here:

High-throughput investigation of NMDA-R related activity in alcohol use disorder.

Adam J. Tengolics, Isabel Gameiro-Ros, Iya Prytkova, Alison Goate, and Paul A. Slesinger

Background: Glutamatergic receptors, like N-methyl-D-aspartate receptors (NMDA-Rs), play key role in substance use disorder such as alcohol use disorder (AUD), as modulators of the reward circuit in the frontal cortex. Induced pluripotent stem cell (iPSC) derived glutamatergic neurons (iGlut) provide a novel, state-of-art method to examine the physiological functions underlying these chronic conditions in human neurons. We recently developed a new platform to study the function of human neurons in a high-throughput model to better understand AUD, and potentially identify novel drug therapies.

Methods: We developed the new platform using three healthy iPSC donor lines (provided by the Collaborative Study on the Genetics of Alcoholism). iPSC were differentiated into iGlut (Neurogenin-2 protocol/NGN2) and used to develop a high-throughput model based on NMDA-R-dependent activity, measured by Ca2+-imaging (GCaMP8f), patch-clamp electrophysiology, and multi electrode array (MEA). After validating the model, we compared the activity of neurons derived from 6 AUD (high PGS) and 6 healthy (low PGS) donor lines, and their response to ethanol.

Results: In Ca2+-imaging experiments, ethanol exposure slightly decreased NMDA-R related activity in neurons in the healthy low PGS group, but robustly decreased activity in the AUD high PGS group. We are currently comparing the changes in Ca2+ spikes with MEA experiments, which measures electrical activity (AP).

Conclusion: We demonstrate a new platform to examine NMDA-R dependent activity in human neurons and find that glutamate neurons from high PGS (AUD) donors are more sensitive to chronic ethanol treatment.

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Submit your abstract here:

Investigating the role 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) has been linked to neurodevelopmental conditions including Down syndrome and autism spectrum disorder. DYRK1A has primarily been described in the context of its role as an important mediator of astrocyte reactivity during neuroinflammation and neurodegeneration. However, little is known about the roles of DYRK1A in developing astrocytes, which serve essential functions during cortical circuit development and are increasingly implicated in neurodevelopmental disorders.

Methods. We previously employed a genetic strategy to target Dyrk1a deletion to cortical radial glial (RG) stem cells (Emx1Cre;Dyrk1a) and their progeny, which include excitatory neurons and astrocytes. Cortex-specific Dyrk1a inactivation led to alterations in the abundance of RG cells, neuronal subtypes, and cortical astrocytes. To dissect the effects of astrocyte-specific Dyrk1a deletion, independent of earlier changes in RG stem cells, we inactivated Dyrk1a using a tamoxifen-inducible approach (Aldh1l1-CreERT2;Dyrk1a) at the peak of astrogliogenesis.

Results. Our preliminary immunofluorescence staining suggests qualitative increases in the abundance of astrocytes and non-reactive microglia at postnatal day (P)14. We are quantifying these changes and further characterizing alterations in glial populations by interrogating transcriptional changes in astrocytes lacking one or both copies of Dyrk1a compared to controls. We are also conducting a time series across postnatal development to map the consequences of astrocytic Dyrk1a inactivation on early cortical circuits.

Conclusions. This study will elucidate Dyrk1a roles in developing astrocytes and in their communication with neuronal and other glial cells, shedding light on contributions of astrocyte dysfunction to developmental disorders.

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Submit your abstract here:

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

Adriana Mendez1, Mohammad Jodeiri Farshbaf2, Jake Tetenman2,3, Zim Kahn4, Hridika Tasnim4, Jessica L. Ables1,2

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 in the midbrain 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 organization and function of the extracellular matrix (ECM) in the habenulo-interpeduncular pathway to influence the development of mood-related neuropsychiatric disorders. 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 in rodents. We used targeted purification of polysomal mRNA (TRAP-Seq) in cholinergic neurons of the medial habenula (mHb) to examine changes to the expression of mRNA in diabetic and non-diabetic mice. We found that several pathways involved in the regulation of the ECM including activation of matrix metalloproteinases, collagen biosynthesis, and ECM organization are upregulated in mice with diabetes. By staining brain slices with biotinylated lectins, we also demonstrate that the structural organization including the area, total length, and branch points of the ECM in the interpeduncular nucleus (IPN), but not the mHb are significantly reduced in diabetic mice. Together, these findings identify the ECM as a possible mechanism by which diabetes is able to elicit changes to the central nervous system and influence the development of neuropsychiatric disorders. Ongoing experiments are focused on determining how diabetes-induced changes to the ECM impact mood-related behaviors.

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Submit your abstract here:

Grooming as a Post-stress Recuperative Behavior

Afra N Mahmud, Ann K PierreLouis, Naomi Yamaguchi, Denise J Cai, Zachary T Pennington

Background: The grooming behavior of rodents has been proposed to model various facets of neuropsychiatric illness, and in particular, an animal's level of stress. However, animals have been observed to exhibit both increased and decreased grooming in response to threatening/stressful events, making it unclear how stress affects grooming. Here we tested the hypothesis that both increased and decreased grooming in response to stress could explained by accounting for context and time.

Methods: We recorded grooming behavior across various levels of stress, from no stress (home cage), to low stress (exposure to an open environment), to moderate stress (return to shock-associated context without shock), to high stress (receiving footshocks). Additionally, we measured grooming in the home cage before and after being exposed to different levels of stress.

Results: Higher levels of stress led to decreased levels of grooming while in the stress-associated context. However, when stressed mice returned to their home cages, they increased grooming compared to non-stressed animals.

Conclusions: Grooming is suppressed when a stressor is present, indicating that decreases in grooming reflect higher stress levels. However, when stressed mice return to a safe environment, grooming increases, possibly as a recuperative behavior. This reconciles differences in previous literature and offers grooming as a model for post-stress recuperation.

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Submit your abstract here:

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

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 seen between 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 times. 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: Enrichment of hormone response elements motifs in differentially accessible chromatin regions and differentially expressed genes has been observed, particularly in astrocytes. Differential chromatin accessibility has been identified between treatment groups versus control.
Conclusion:
Hormonal fluctuations during the peripartum period result in alterations in chromatin accessibility within the ventral hippocampus. These modifications may exhibit cell-type specificity and are likely associated with hormone-responsive genes. Future investigations will involve the transfer of significant genes identified in our mouse model to human GWAS datasets related to psychiatric disorders, with the goal of pinpointing potential risk genes for postpartum mental health conditions.

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Submit your abstract here:

Association Between Prenatal Inflammatory Marker Levels in Relation to SARS-CoV-2 Infection and Child's Neurodevelopment at 2-4 Years Old.

Authors: Aisha Said, Jazmine Chavez, Rushna Tubassum, Marco Rizzo, Frederieke Gigase, Veerle Bergink, Lot de Witte, Anna-Sophie Rommel

Background: The SARS-CoV-2 infection triggers an immune response which induces inflammation. Pregnancy already involves changes in the immune system, and SARS-CoV-2 can further intensify the immune response, leading to elevated levels of inflammatory markers like C-reactive protein (CRP) and interleukins (e.g., IL-6). Maternal immune activation during pregnancy has previously been linked to poorer child neurodevelopment. Earlier studies regarding this topic were performed at 6 to 18 months and suggested negligible correlation, however, comparing the Ages and Stages Questionnaire (ASQ) from 6 and 36 months and Social Responsiveness Scale (SRS-2) from 2 to 4 years for longitudinal results allows us to explore the relationship between maternal infection, inflammatory markers, and potential impacts on a child's longer-term development.

Hypothesis: We hypothesized that we would not find significant evidence to support a potential association between the adverse social development of 2-4-year-olds and maternal immune activation based on earlier studies.

Methods: For each participant, we will calculate the mean levels of interleukin (IL)-1β, IL-6, IL-17A, and high-sensitivity C-reactive protein (HS-CRP) during pregnancy. We will then use regression models to investigate the association between mean inflammatory marker levels and child development using ASQ at 6 and 36 months and SRS from 2 to 4 years. We will stratify our sample by SARS-CoV-2 infection status during pregnancy (positive/negative).

Results: We found no significant association between prenatal exposure to SARS-CoV-2 and neurodevelopmental outcomes at the age of 2-4 years.

Conclusion: These findings offer reassurance concerning the longer-term effects of prenatal SARS-CoV-2 exposure on neurodevelopment.

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Submit your abstract here:

Astrocytic and vascular changes associated with neocortical vulnerability in Alzheimer's disease

Alec K. McKendell, Sofia Magalhaes, Aurélien M. Badina, Elizabeth McDonough, Lisa Lowery, Jennifer I. Luebke, Dan E. Meyer, Patrick R. Hof, Merina T. Varghese

BACKGROUND: In Alzheimer’s disease (AD), specific neocortical neurons become vulnerable while others remain resistant. Novel spatial imaging methods, like highly multiplexed immunofluorescence (MxIF), alongside computational analysis can identify factors associated with this regional vulnerability. Astrocytes are heterogeneously distributed support cells in the brain implicated in many AD-related pathological changes.

METHODS: We performed MxIF staining for 26 markers on postmortem human samples from an AD-susceptible brain area, the dorsolateral prefrontal cortex (PFC) and an AD-resistant brain area, the primary visual cortex (V1). Donors included AD (n = 3, clinical dementia rating CDR 3, Thal stages 3-4, Braak stages V-VI), mild cognitive impairment (n = 4, CDR 0.5, Thal 1-3, Braak I-V), and age-matched healthy females and males (n = 5, CDR 0, Thal 0-1, Braak I-II). Using QuPath for image analysis, the images were segmented for aldehyde dehydrogenase 1 family member L1 (all astrocytes), glial fibrillary
acidic protein (reactive astrocytes), collagen IV (vasculature), and amyloid β peptide (Aβ).

RESULTS: Reactive astrocytes were increased near Aβ plaques with worsening CDR in the V1. Juxtavascular reactive astrocytes were decreased in layer 1 of the PFC and increased in the V1 white matter with worsening Thal stage. Characterizing astrocytes specifically around Aβ-laden vessels will help determine if this is a specific response to cerebral amyloid angiopathy.

CONCLUSIONS: These preliminary results suggest a heterogenous astrocytic response near vasculature and Aβ deposits between neocortical regions with varying vulnerability to AD. We are investigating astrocyte morphology and cell states to assess how populations vary across the neocortex with worsening cognition and how these may be associated with selective neuronal vulnerability in AD.

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Submit your abstract here:

TIMP2-mediated extracellular matrix homeostasis regulates amyloid pathology in mouse models of β-amyloidosis

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 pathological changes, including amyloid-β (Aβ) accumulation and neuroinflammation, processes linked to extracellular matrix (ECM) remodeling. Our previous work showed that TIMP2, a youth-associated blood-borne factor, regulates ECM homeostasis by modulating MMP2 activity. While we have established TIMP2's ability to revitalize brain function in aged animals, its potential role in AD pathology and ECM-mediated disease mechanisms remains unexplored.

Methods and results
Using multiple mouse models of amyloid pathology (5xFAD and APP-KI), we find that TIMP2 expression is decreased compared to controls, a pattern we also observed in human AD hippocampi. TIMP2 deletion in both APP-KI and 5XFAD models results in increased amyloid burden, enhanced astrogliosis, and reduced MMP2 activity, accompanied by accumulation of specific ECM components. Notably, despite elevated astrocyte recruitment around plaques, TIMP2-knockout mice show larger and more numerous plaques with increased astrocyte-to-plaque distances. The effects on amyloid accumulation occur independently of APP processing changes, suggesting disrupted amyloid clearance mechanisms. We next found that targeting ECM through intrahippocampal chondroitinase ABC (ChABC) administration in 5xFAD mice leads to less plaque burden and size while enhancing astrocyte recruitment and MMP2-plaque interaction, effectively normalizing ECM alterations. Furthermore, viral-mediated TIMP2 overexpression in APP-KINL-F mice improves cognitive performance, reduces plaque load, and restores ECM homeostasis.

Conclusions
These findings establish TIMP2 deficiency as an exacerbating factor in amyloid pathology, highlighting its restoration as a promising therapeutic strategy for AD treatment.

Supported by 24AARF-1201458.

2025 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Submit your abstract here:

Mapping neural heart-brain connections

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INTRODUCTION
Brain-heart communication is increasingly recognized as key to cardiovascular disease. The heart and the brain are intimately connected through a dense network of sympathetic, parasympathetic and spinal cord neurons that both provide brain control of the heart and relay sensory information back from the heart to the brain. Characterizing which neuronal populations in the brain project onto the heart will allow directed targeting of these populations and provide insights into how the brain can influence heart disease

METHODS
We use retrograde polysynaptic viral tracing coupled with transgenic mouse model to trace from the right and left ventricle of the heart to map brain areas and neural pathways that control the heart. We also map neural pathways in heart disease models, focusing on hypertrophic heart disease caused pulmonary arterial banding and transverse aortic ligation.

RESULTS
We discovered differences in brain control of the two ventricles and distinct neuronal populations that only project onto one or the other ventricle (i.e. primarily control only one ventricle). In hypertrophic heart disease, these connections are altered, with certain brain regions being more connected to the left

ventricle. These findings suggest distinct neural circuits modulate the left and right ventricles, potentially contributing to differing vulnerabilities in cardiovascular disease.

CONCLUSION

Mapping the neural connections between the heart and the brain in health and disease, with spatial differentiation of brain connections to the right and left ventricles provide valuable insights into physiological and pathophysiological brain control of the heart.

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Cannabidiol attenuates heroin seeking in male rats associated with normalization of discrete neurobiological signatures within the nucleus accumbens with subregional specificity

Alexandra Chisholm, Jacqueline-Marie Ferland, Randall J. Ellis and Yasmin L. Hurd

Background: Opioid use disorder involves cycles of compulsive use, abstinence, and relapse. Cannabidiol (CBD), a non-intoxicating cannabinoid, is under investigation as an anti-relapse treatment. CBD attenuates cue-induced heroin-seeking in a rodent model of relapse and reduces cue-induced craving and anxiety in abstinent individuals with heroin use disorder. The neurobiological mechanisms by which CBD may exert its anti-relapse effects are unknown. The objective of the current study was to evaluate the effects of CBD administration on heroin-seeking in conjunction with transcriptomic profiling in the nucleus accumbens core (NAcC) and shell (NAcS).

Methods: Male Long Evans rats self-administered heroin for 15 days, followed by 14 days of abstinence. Rats were injected with vehicle or CBD (5 or 10 mg/kg, i.p) 24 hours before a drug-seeking session. Tissues were extracted 1.5 hours following the drug-seeking session. NAcC and NAcS tissue were dissected, and bulk RNA sequencing was performed.

Results: CBD attenuated cue-induced heroin-seeking. RNA-sequencing of the NAcC and NAcS revealed shared transcriptomic alterations the NAc subregions in response to heroin, with a more robust impact of heroin in the NAcS. Although CBD had minimal impact on the heroin-induced perturbations in the NAcC, it normalized components of the transcriptomic signature altered by heroin in both NAc subregions. Within the NAcS, CBD normalized particular subsets of genes that correlated to heroin-seeking. Such genes were specifically linked to the extracellular matrix, astrocyte function, and their upstream regulators related to immune function.

Conclusions: These findings underscore the NAc subregional signatures of heroin-induced neurobiological perturbations and provide novel biological targets relevant for CBD's apparent anti-relapse effects.

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Submit your abstract here:

Early abnormalities in cholinergic innervation and behaviorally-evoked ACh transients in mPFC of mice carrying a Parkinson's gene mutation

AR Magee, SJ Allen, NH Westneat, DL Benson, GW Huntley

BACKGROUND

In prodromal Parkinson's, cognitive impairment has been associated with changes in cholinergic modulation of PFC, but the basis is unknown. Here, we interrogated young adult male wildtype mice and mice carrying a G2019S mutation of LRRK2 kinase anatomically, to assess cholinergic innervation density in area PL, and functionally, using a GRAB3.0 ACh biosensor combined with fiber photometry to investigate behaviorally-evoked ACh transients.

METHODS

Cholinergic axons and terminals were identified by crossing wildtype (WT) and Lrrk2-G2019S (GS) mice with ChAT-Cre; tdTomato reporter mice and by immunofluorescent labeling for vesicular acetylcholine transporter (VAChT). Confocal images were analyzed with ImageJ. An AAV-GRAB-ACh3.0 ACh sensor was targeted to area PL. Signals were reported by fiber photometry during a modified 2d instrumental learning task.

RESULTS

The density of cholinergic axons and terminals in GS mPFC was significantly sparser compared to that in WT mice, suggesting that ACh signals could be weaker. In an instrumental learning task, when mice were on a continuous reinforcement schedule of reward, there were no genotype differences in ACh signals reported by the biosensor during the ITI, when mice were anticipating the upcoming trial. Notably, when the reward contingency unexpectedly shifted to a random interval schedule, WT mice displayed a significant increase in the ACh transient during the ITI, while the increase in GS mice was significantly reduced.

CONCLUSIONS

Our data suggest that in humans, early cognitive impairment in PD reflects both sparser cholinergic innervation of PFC and smaller behaviorally-evoked ACh transients. Ongoing experiments are examining

whether these changes worsen with age or can be rescued with chemogenetic activation of cholinergic projections to the mPFC, and if such changes occur in females.

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Submit your abstract here:

Title: Uncovering the role of the MS4A locus in Alzheimer's Disease

Authors: Alexandra Münch, Grace Peppler, Michael Sewell, Edoardo Marcora, Anne Schaefer, Alison Goate

Background: Accumulating evidence from genome wide association studies posit that myeloid cells play a central role in Alzheimer's Disease (AD) etiology. Microglia have thus emerged as attractive cells to target therapeutically. Such drug targets may lie within the MS4A locus, a region associated with AD risk and the primary locus associated with CSF levels of soluble TREM2, a biomarker of microglial activity which correlates with slower cognitive decline. This region contains multiple MS4A genes which encode structurally related transmembrane proteins primarily expressed by immune cells. We previously nominated a causal variant within this locus, rs636317, whose risk allele is predicted to disrupt CTCF binding and is associated with increased expression of MS4A4A and MS4A6A. Despite their emerging potential as therapeutic targets, the functions of these tetraspans remain poorly characterized.

Methods: Using CRISPR-edited iPSC-derived microglia (iMGL) we directly test the hypothesis that the candidate functional variant 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 and CLEC7A, we perform omics and targeted functional assays in MS4A4A/MS4A6A knockout and rs636317-edited iMGLs. In parallel, we generated microglia-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. We observe that knock-out of MS4A4A/MS4A6A, affects TREM2 shedding, signaling, lysosomal mass, and phagocytosis.

Conclusions: We hypothesize that decreased expression of MS4A4A and MS4A6A promotes protective microglial responses related to TREM2 signaling, ameliorating plaque containment and subsequent cognitive decline.

2025 Neuroscience Retreat

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Submit your abstract here:

Developing a neuroeconomic approach to study altruistic decision-making

Alexandra N. Ramirez, Brian Sweis

Understanding the psychological and neural mechanisms underlying prosocial decision-making can shed light on interpersonal dysfunctions observed in virtually every neuropsychiatric disorder. Prosocial behaviors are defined as those that aim to benefit another. More specifically, altruistic behaviors aim to benefit another at a cost to oneself. Recent studies have reported a variety of prosocial behaviors in rodents ranging from comforting and helping behaviors to prosocial choice. To date, the neural computations underlying cost-benefit decision processes when considering the needs of another remains underexplored in rodent models. To investigate this, I conceptualized and developed a novel social paradigm in mice rooted in principles of behavioral economics and foraging theory. In this task, mice forage for food rewards at four spatially distinct zones (“restaurants”). An “actor” mouse forages for food with the opportunity to feed both itself and a “recipient” mouse placed in the center of the arena. These mice are co-housed dyads where, in task, they are separated by an opaque or mesh divider in order to assess the effects of social interaction on prosocial choice. Mice were able to forage for two different flavors in order to introduce an element of subject value. Two of the four restaurants feed both mice (“both”), while the other two restaurants feed only the actor (“self”). Preliminary results revealed that mice in the mesh group shifted preferences toward less preferred flavors compared to their opaque divider counterparts. Upon closer look, this was due to a redistribution of time spent foraging: mesh mice detracted time investments away from their preferred “self” flavor, re-allocated instead toward their less preferred “both” flavor. These results suggest that mice modulate their behavior to benefit a conspecific, with ongoing efforts to identify the neuroeconomic mediators of this effect.

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Submit your abstract here:

Protocol for Clinical Pharmacology and Target Validation of a Bioactive Dietary Polyphenol Preparation (BDPP)

Alexia Lizzano*, Sibilla Masieri*, Camille Dupiton*, Haritz Irizar, Brian Lee, James Murrough

Background: This study will evaluate the clinical pharmacology and tolerability of the BDPP dietary supplement and assess its dose-dependent effects on baseline and stress-induced inflammatory markers. A total of 84 participants will be recruited over four years. Following screening and randomization, participants will be assigned to one of four BDPP dose groups, with study procedures spanning approximately six weeks. Plasma phenolic metabolites and inflammatory markers will be analyzed across treatment groups at visits 1 and 3, with stress-induced markers assessed at visit 4. Findings from this study will enhance understanding of polyphenols' pharmacological effects, informing future research on dietary supplements and health outcomes.

Methods: N=84 comprising solely of healthy controls (as determined by the DSM-V). The study will recruit participants and compile their data for a total of 4 years. Screening measures will take place prior to randomization in order to determine eligibility. After randomization, study procedures will take place over a total of approximately 6 weeks, and each participant will be randomized into either the low, medium, high dose or placebo groups.

Results: We will analyze how plasma levels of phenolic metabolites and of inflammatory cytokines at visits 1 and 3 vary by treatment group and how the treatment effect changes between visits. As well as assessing the difference in stress induced inflammatory markers at visit 4. These analyses will be conducted using normality testing, linear regression, generalized linear model, contrast testing, and mixed effects models.

Conclusion: The study will provide key insights for future analysis of the effects of polyphenols. Moreover, the findings will provide a deeper understanding of stress related markers of inflammation and the effects of BDPP on these markers.

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Submit your abstract here:

The Role of Alzheimer's Disease Risk Allele APOE4 in Neural Stem Cell Function and Development

Alison Salinas, Allison Bond

Background: Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to degeneration of multiple brain regions, including the hippocampus, ultimately causing memory impairments and cognitive dysfunction. Apolipoprotein E4 (APOE4) is one of the strongest genetic risk factors for late-onset AD, but the mechanism of increased risk is not well understood. APOE deficiency in a knockout mouse model suggests that APOE may play a role in normal brain development. Additionally, APOE is expressed in neural stem cells (NSCs) within the dentate gyrus of the hippocampus during both development and adulthood. Adult NSCs in the dentate gyrus generate new neurons through neurogenesis, which contributes to normal learning and memory function but is impaired in AD patients. We hypothesize that APOE plays a role in hippocampal development and APOE4 alters normal development, contributing to disease in adulthood.

Methods: We will use human APOE variant knock-in mice comparing APOE4/4 risk allele mice to the neutral allele APOE3/3 mice. We will use birth-dating methods to create a timeline of NSC differentiation into neurons and glia, and we will use immunohistochemistry staining of stage-specific markers to track their maturation trajectories. We will also use clonal lineage tracing to analyze the behavior of individuals NSCs and their resulting progeny.

Results: We expect that APOE4 will alter the maturation and behavior of NSCs. We expect that APOE4 will delay the maturation trajectory of NSCs and neurons and alter gliogenesis contributing to an increase in astrocytes during development and in adulthood.

Conclusions: Our research will further our understanding of how the APOE4 risk variant may alter development and lead to disease. This is important in establishing early detection methods and future therapeutic targets to prevent cognitive symptoms in APOE4 carriers.

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Submit your abstract here:

Psychiatric Symptom Changes in MCI-D Patients Given a Single Infusion of Ketamine: A DSM-5 Cross-Cutting Symptom Measure Analysis

Amelia Karim, BA, Arianna LaBarbiera, BA, Catherine McDonough, MS, Tanya Peguero Estevez, MD, Adriana Feder, MD, Georges Naasan, MD, Andrew Delgado, PhD, James Murrough, MD, PhD, Rachel Fremont, MD, PhD

BACKGROUND: Mild Cognitive Impairment with Depression (MCI-D) is increasingly recognized as a distinct condition, marked by greater behavioral symptoms, functional impairment, neurobiological abnormalities, and a higher dementia risk compared to MCI alone. However, its broader psychiatric profile remains unclear, and standard antidepressants show poor efficacy. This study examines transdiagnostic psychiatric symptoms in MCI-D and evaluates ketamine's effects in MCI-D using the DSM-5 Cross-Cutting Symptom Measure (CCSM).

METHODS: Eleven MCI-D participants (age = 71.45 ± 8.09) received a single IV ketamine infusion (0.5 mg/kg) in an open-label pilot study. Psychiatric symptoms were assessed via CCSM at baseline, post-infusion, and multiple follow-ups (24h, 48h, 72h, 1w, 1m). Linear mixed models with random intercepts analyzed CCSM changes over time. Planned comparisons of estimated marginal means (EMM) assessed response variability and symptom differences.

RESULTS: Eight out of 13 domains revealed significant effects. Depression ($p=0.0019$) showed improvements up to 1 week, with the greatest improvement at 48 hours (EMM difference=-2.2, 95% CI[-3.0, -1.4]). Anger ($p=0.0019$) was improved up to 1 week. Mania ($p=0.0019$) symptom improvements were sustained through 1 month. Anxiety ($p=0.0019$), somatic symptoms ($p=0.0146$), and sleep problems ($p=0.0019$) improved significantly through 72 hours. Memory ($p=0.0019$) showed improvements lasting 1 week, peaking at 72 hours (EMM difference=-1.7, 95% CI[-2.7, -0.79] and personality functioning ($p=0.0019$) also showed improvements lasting 1 week.

CONCLUSION: Ketamine improved depression, memory, personality functioning, and other psychiatric symptoms in MCI-D, and the effects lasted mostly up to one week before returning to baseline, highlighting the need for broader psychiatric assessment in ketamine research.

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Submit your abstract here:

Effective Brain Network Connectivity Correlates of Psychological Resilience in World Trade Center Responders

Ananya Iyer, Saren H. Seeley, Adriana Feder, Robert Pietrzak, M. Mercedes Perez-Rodriguez, Daniela Schiller

BACKGROUND: Altered connectivity among large-scale brain networks (default mode; DMN, central executive; CEN, salience; SN) is well-established in PTSD, with weaker top-down control of SN thought to contribute to symptoms such as hyperarousal and emotional reactivity. Less established is these networks' functioning in highly resilient individuals, such as World Trade Center responders who have never developed WTC-related psychopathology despite substantial trauma exposure.

METHODS: We used resting-state fMRI data from a parent study of WTC responders (N=89) to investigate effective network connectivity (i.e., influence of network X on network Y) via Granger causality analysis. Planned contrasts compared three groups: WTC-related PTSD (n=29), high WTC-exposed responders with no psychopathology ("highly resilient", n=32), and lower WTC-exposed controls (n=28). We also examined whether self-report and cognitive measures were correlates of effective network connectivity.

RESULTS: We identified a group difference in effective connectivity, with greater influence of CEN on SN in highly resilient responders versus lower WTC-exposed responders ($p = .012$, $pFDR = .07$, $d = .67$). CEN-to-SN connectivity in the PTSD group was lower than the highly resilient group but higher than the lower WTC-exposed group, though not significantly different from either. Higher CEN-to-SN connectivity was associated with better cognitive function in the full sample (Montreal Cognitive Assessment $r = .44$, $p < .001$) and with higher estimated IQ in the highly resilient group (WTAR $r = .55$, $p = .007$). Additionally, in the PTSD group, greater DMN-to-CEN connectivity was associated with greater clinician-assessed past-month dysphoric arousal and negative affect CAPS-5 symptoms ($r = .54$-$.57$, $p < .01$).

CONCLUSIONS: Greater top-down control of SN by CEN may represent a compensatory adaptation after substantial trauma exposure in highly resilient individuals, and is associated with better cognitive function.

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Submit your abstract here:

Title: Investigating PACAP-Cholinergic Interactions in the Nucleus of the Solitary Tract via Fear Response

By: Andrew Fajardo

Advisor: Dr. Abha K. Rajbhandari

Background

Post-traumatic stress disorder (PTSD) is characterized by persistent maladaptive fear responses and is closely associated with the vagus nerve, a major component of the parasympathetic nervous system. The nodose ganglion, a collection of sensory neurons located within the vagus nerve, plays an essential role in facilitating communication between the brain and many body systems. This thesis explores the role of neuropeptide Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) and its co-localization with cholinergic neurotransmitters in the Nucleus of the Solitary Tract (NTS), which serves as a key brainstem region involved in autonomic regulation.

Methods

By quantifying and manipulating the activity of the excited neurons to be soon later used with different viral injections going forward. Through vagus nerve stimulation paired with our model of PTSD- Stress-enhanced fear learning (SEFL) we were able to pinpoint specific PACAP-expressing neurons in the NTS that are associated with the cholinergic system that are related to the parasympathetic nervous system.

Results:

In our PACAP-GFP project there was a higher co-localziation within the mice that did receive stressed enhanced fear learning, as all signals were primarily shown within the anterior portion of the NTS. There were indeed differences between the posterior, medial, and anterior portions of the NTS where PACAP-expressing neurons co-localized with cholinergic neurons. Additionally, in our PACAP-Cre experiment, vagus nerve stimulation was shown to alter the expression patterns of PACAP-expressing neurons, indicating a potential modulatory role of the vagus nerve in regulating PTSD-related autonomic dysfunction.

Conclusion:

Overall, our studies indicate that the vagus nerve could regulate PTSD stress-mediated changes in behavioral outputs in murine models and that PACAP-cholinergic interactions in the NTS are functionally linked to stress adaptation and autonomic regulation.

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Title: A data driven exploratory study of cross regional phase amplitude coupling as a functional connectivity biomarker in depression networks

Andy Ho Wing Chan, James J. Young, Tarik Bel-Bahar, Riaz Shaik, Fedor Panov, Saadi Ghatan, Ji Yeoun Yoo, Anuradha Singh, Madeline C. Fields, Lara V. Marcuse, Nathalie Jette, Helen S. Mayberg and Muhammad A. Parvaz

Background: Depression is prevalent in temporal lobe epilepsy patients. Functional connectivity (in networks) between regions such as amygdala (affective), hippocampus (affective), superior temporal (salience), medial orbital frontal (default), superior frontal (default) and rostral anterior cingulate (salience) regions have been shown to be altered by depression. However, their connectivity in relation to depression in patients with epilepsy is unclear. Intracranial EEG (iEEG) recordings provide a unique opportunity to study functional connectivity, specifically by examining the coupling between the phase of low frequency neural oscillations in one region and the amplitude of high frequency neural oscillation in the other region, or the phase-amplitude coupling (PAC). Here, we examined functional connectivity differences between depressed and non-depressed epilepsy patients, using the PAC measure.

Methods: Resting state iEEG and depression severity characterized by Beck's Depression Inventory (BDI) scores were collected from 17 patients, 8 of whom had at least moderate depression (BDI>19; D) while the other 9 patients were considered as the non-depressed (BDI>19; ND) cohort. PAC was computed across all the pairings of the six brain regions.

Results: We found a distinct PAC signal by delta phase coupling with beta amplitude. Significant between-group differences in PAC were observed between anterior cingulate and hippocampus (D>ND), hippocampus and superior frontal (D>ND), and amygdala and superior frontal (D<ND) regions ($p<0.05$).

Conclusions: The observed PAC patterns are consistent with neuroimaging literature in depression, underscoring the utility of PAC as a biomarker of depression-related functional connectivity alterations in epilepsy.

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Submit your abstract here:

Investigating PET tracer 18F-PI-2620 binding in the choroid plexus

Anna Marin, Ryan Wales, Vanessa Xu, Cody Ruais, Jasmin Richard, and Trey Hedden

Background
The PET ligand 18F-PI-2620 is used to quantify tau pathology in Alzheimer's disease (AD). A challenge in accurate quantification is the binding localized to the choroid plexus (CP), adjacent to the hippocampus. It remains unclear whether this "off-target" binding is characteristic of tau tracers or driven by biological mechanisms. Our study examined correlates of 18F-PI-2620 CP binding to enhance measurement reliability and better understand its interpretation for the pathophysiology of AD.

Methods
Data were collected from 127 older adults (89 normal controls and 38 cognitively impaired) who completed 2 PET/MR sessions, with 18F-florbetaben to measure amyloid and 18F-PI-2620 for tau.

Results
Tracer binding in CP was positively associated with binding in the Braak II region ($p<0.001$). In normal controls only, it was associated with binding in the Braak III and IV regions ($p=0.006$; $p=0.004$). There was an effect of race, such that Black/African American (B/AA) participants (n=13; M=1.53 SUVR) had elevated CP binding compared to White participants (n=97; M=1.25 SUVR; $p=0.02$). We separately examined a small number of individuals with very high levels of CP binding (>1.8 SUVR; n=8; 56% White). Exploratory analyses in the full sample showed no association between CP binding and amyloid load, CP volume, or hippocampal volume.

Conclusions
Consistent with a prior report, our results show that high signal in CP may be partially driven by binding to melanocytes in the epithelium of CP, reflected in the race effect. In addition, our observation of a small number of individuals with very high uptake suggests other mechanisms are likely involved. Candidate factors include the deposition of tau and/or amyloid in CP and the tracer binding to other materials such as iron deposits.

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Submit your abstract here:

TWO-DAY CPET DOES NOT IDENTIFY POST-EXERTIONAL MALAISE IN ME/CFS PATIENTS

Donna Mancini, Patrick Quan, Anna Norweg, Tadahiro Yamazaki, Dane Cook, Michelle Blate, Benjamin Natelson

BACKGROUND: Post-exertional malaise (PEM) is an exacerbation of neurological symptoms after physical or cognitive exertion, significantly impacting functional ability and quality of life. Two consecutive cardiopulmonary exercise tests (CPETs) performed 24 hours apart are increasingly used to evaluate disability in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as declines in CPET on day 2 are thought to reflect PEM. Reports have described a reduction in peak oxygen consumption (VO2) or the anaerobic ventilatory threshold (VT) on day 2.

METHODS: Accordingly, we performed maximal bicycle ergometer CPETs on 2 consecutive days in 53 patients with ME/CFS (mean age 39.5 +/-9.5, BMI 24.1 +/-3.4, 11 men and 42 women) and 23 age matched sedentary control subjects (age 37.5 +/-10 yrs, BMI 24.1 +/-3.6, 5 men, 18 women). Peak VO2 was reported as the highest 30 sec average. We also measured VE/VCO2 slope throughout exercise. For eligibility, all patients with ME/CFS reported post-exertional symptom worsening [≥3 on 0 to 5 Likert scale].

RESULTS: All subjects achieved maximal effort as indicated by a peak respiratory exchange ratio (RER)≥1.1. There were no significant changes in peak VO2, VT, or VE/VCO2 on repeat exercise tests for both groups, p>0.05. There were also no significant differences in peak VO2, VT, or VE/VCO2 between ME/CFS and age-matched sedentary controls, p>0.05. Mean VE/VCO2 indicated normal ventilation efficiency for both groups over both test days (VE/VCO2 <34).

CONCLUSIONS: PEM is a cardinal symptom of ME/CFS. Our objective data suggest that 2-day CPET cannot identify patients with PEM because patients were able to reproduce their measures within 24 hours. Symptom-based data, over several days after 2-day CPET, may be better measures of PEM in ME/CFS.

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Title: Electrophysiological Markers of Response Inhibition in Schizophrenia

Authors: Siddiqui A, Bel-Bahar TS, Shaik R, Ferster KS, Khan AA, Velthorst E, Parvaz MA

Background:
Individuals with schizophrenia (SCZ) exhibit deficits in cognitive control and response inhibition, which are commonly assessed using event-related potentials (ERPs) in Go/No-Go tasks. The N200 and P300 ERP components are key neural markers associated with conflict monitoring and inhibitory control, respectively. This study examines these ERP responses in SCZ and healthy control (HC) individuals during No-Go trials, focusing on midline electrodes Fz, Cz, and Pz.

Methods:
EEG data were recorded from SCZ (n=6) and HC (n=11) participants while they completed a Go/No-Go task. ERPs were computed at Fz, Cz, and Pz during No-Go trials, and statistical comparisons between groups were performed using independent samples t-tests.

Results:
SCZ individuals showed marginally greater (more negative) amplitudes at Fz (: $t(15) = 1.652$, $p = 0.119$).
In contrast, SCZ individuals showed significantly lower (less positive) P300 amplitudes at Pz ($t(15) = 2.615$, $p = 0.020$), compared to HC.

Conclusion:
While N200 did not show significant differences between groups, the reduced P300 amplitude at Pz in SCZ suggests impaired neural processing of response inhibition. These findings align with prior research linking reduced P300 to deficits in cognitive control in schizophrenia. The results highlight posterior ERP alterations as a potential biomarker for inhibitory dysfunction in SCZ and support further investigation into the neural mechanisms underlying cognitive control deficits in this population.

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Submit your abstract here:

Investigating the contributions of Rabs 5, 8, 10, & 11 to AMPAR trafficking in wild-type corticostriatal cells.

Arianna Bassini, Alexander Tielemans, Deanna Benson

Parkinson's (PD) contributes to the onset of debilitating symptoms, both non-motor and motor. The non-motor symptoms typically begin to set in earlier and are largely associated with the glutamatergic system —corticostriatal circuitry. Leucine-rich repeat kinase 2 (LRRK2) is one of the most common genetic causes of both sporadic and familial PD. The G2019S (GS) mutation to LRRK2 significantly increases LRRK2's kinase activity. Striatal spiny projection neurons (SPNs) carrying the LRRK2G2019S mutation show impaired trafficking of AMPA receptors (AMPARs) — a type of glutamate receptors. AMPAR trafficking is essential to neuroplasticity, which is a key part of cognition. A subset of Rab GTPases have been implicated in AMPAR trafficking in other neurons, some of which are phosphorylation targets for LRRK2. While these Rabs have been studied in other contexts, their specific contribution to AMPAR trafficking in SPNs has not yet been studied. This research aims to investigate their roles by generating lentiviral knockouts for the subset of Rab GTPases, using them in different combinations to transfect wild-type corticostriatal cultures, and then comparing surface AMPAR levels.

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Title:
Differential Prefrontal Hemodynamic Responses to Emotional and Drug Related Cues in Individuals with Opioid and Alcohol Use Disorders

Authors:
Armaan S. Dullat, Riaz B. Shaik, Siddhartha Peri, Karmiella Ferster, Gopi Neppala, Brittany Tocco, Aleka Kakkera, Yasmin L Hurd, Iliyan Ivanov, Muhammad A. Parvaz

Background:
Understanding how the brain processes emotional and drug-related cues in individuals with opioid use disorder (OUD) and alcohol use disorder (AUD) can offer insights into addiction-related neural mechanisms. Such cue-reactivity, typically assessed via fMRI and EEG has shown to be predictive of clinical outcomes such as relapse. We used functional near-infrared spectroscopy (fNIRS) to measure oxygenated (HbO_2) and deoxygenated (HbR) hemoglobin levels in the prefrontal cortex (PFC) in response to opioid- and alcohol-related cues in individuals with OUD and AUD, respectively.
Methods:
We recruited 12 OUD and 25 AUD participants from the Addiction Institute of Mount Sinai's in-patient treatment centers. Each participant completed a cue-reactivity task while wearing an fNIRS headset with prefrontal cortical coverage, viewing images classified as pleasant, unpleasant, neutral, or drug-related. Hemodynamic responses were analyzed across different prefrontal regions.
Results:
Independent t-tests revealed that HbO_2 levels were significantly higher in AUD individuals compared to OUD individuals in the left orbitofrontal cortex (OFC) when viewing unpleasant cues. Additionally for unpleasant cues, HbR levels were significantly higher in AUD individuals in the left OFC compared to OUD individuals, indicating differences in deoxygenation patterns. OUD participants did not show significant differences in prefrontal activation compared to AUD participants across conditions. Importantly, age and sex did not influence these findings.
Conclusion:
These preliminary results suggest that AUD individuals engage the left OFC more strongly when processing unpleasant stimuli, while OUD individuals do not exhibit significant differences in prefrontal activation across conditions. These findings highlight distinct neural mechanisms in AUD versus OUD and may inform targeted interventions.

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Title: Pharmacological manipulation of brain activity impacts intrinsic neural timescales.

Authors: Atsushi Fujimoto, Catherine Elorette, Satoka H Fujimoto, Lazar Fleysher, Peter H Rudebeck, and Brian E Russ

Background:
Intrinsic timescales are akin to a brain areas' temporal receptive field over which information is integrated. Such timescales change from rest to being task engaged, but how administration of different drugs changes this measure remains unknown.

Methods:
Macaque monkeys (N = 11, 5 females) underwent anesthetized functional MRI scans when either no drug or different pharmacological agents (chemogenetic actuator DCZ at low or high dose, D1 antagonist SCH-23390, or D2 antagonist haloperidol) were administered. A subset of monkeys also underwent awake fMRI scans with a probabilistic choice task. Measures of the intrinsic neural timescale, including the amplitude and decay function (tau), were estimated by fitting an exponential decay model to an autocorrelation function computed on the fMRI time-series.

Results:
Replicating previous reports, baseline taus were higher in cortical than in subcortical areas. DCZ generally increased taus, but only at a high dose known to impair behavior. SCH broadly decreased the amplitude parameter but did not alter the taus across the brain. By contrast, haloperidol increased taus predominantly in cortical areas. The data from the task-fMRI experiment differed substantially from the resting-state, most notably with a profound reduction of cortical taus and an increase of subcortical taus.

Conclusions:
Our data show that pharmacological manipulations that alter behavior induce regionally specific changes in the intrinsic neural timescales. These effects were primarily seen in cortical regions, likely through their differential action on endogenous receptors. Task engagement also affects timescales across the brain, likely through changes in cognitive states. Thus, pharmacological modulation of behavior may reflect changes in the way that information is temporally processed in the brain.

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Submit your abstract here:

How does the brain accumulate cognitive maps?

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

Background: It has been postulated that the brain uses cognitive maps, or internal neural representations, to enable flexible behavior. Both the engram and spatial navigation literatures have shown that distinct cognitive maps are used to encode two different environments. However, recent work suggests that linking two distinct memories neuronally can enhance memory strength by sharing neural resources, suggesting that some aspects of the two cognitive maps are no longer distinct. Others have hypothesized that increased similarity between cognitive maps may link experiences across environments and provide a mechanism to increase learning rates. As animals learn reward locations in multiple environments, it's unclear if each new environment would be represented as a distinct cognitive map (low representational similarity) or share neural resources (high representational similarity) to influence behavior.

Methods: We combined in vivo calcium imaging with miniature microscopes in dorsal CA1 with a novel spatial navigation task consisting of a circular track with eight distinct water reward ports, where two ports gave water and six did not. We built four separate circular tracks, each with distinct visual cues, to study how mice accumulated cognitive maps.

Results: Mice increase their rate of achieving high lick accuracy after switching to each new circular track. We also observed that the number of neurons shared between each new circular track with the previous circular track did not change as mice accumulated maps.

Conclusions: Our preliminary data suggests that two measures of representational similarity between cognitive maps (measured through neuronal overlap and population vector correlations) do not change as mice accumulate cognitive maps. Future analyses will focus on what aspects of cognitive maps remain distinct and what aspects increase in similarity as learning rates increase in new tracks.

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Submit your abstract here:

Regulation of the Opioid System by Ketamine and its Therapeutic Potential in Opioid Use Disorder
A.Osman, A.Dawoud, A.Gupta, I.Gomes, L.Devi, Y.L.Hurd

Background: A major challenge in the treatment of opioid use disorder (OUD) is relapse, even after protracted abstinence, often driven by negative affect states including depression. Recently, a single sub-anesthetic dose of ketamine was shown to produce long-term antidepressant effects, with emerging evidence implicating the endogenous opioid system. Here we characterized interactions between ketamine and the opioid system at the mRNA, protein and receptor signaling level. Additionally, effects of ketamine exposure during protracted abstinence on measures of relapse are assessed using a heroin self-administration paradigm.

Methods: Adult male Long Evan rats received saline, 3mg/kg or 10mg/kg ketamine injections (intraperitoneal) and sacrificed 24h, 72h or 7 days later. Brain samples were collected for qPCR, ELISA, and GTP□S signaling. A separate cohort of rats were catheterized and trained on a 14-day heroin Fixed Ratio 1 schedule. Rats were subsequently subjected to 14-days of abstinence during which animals received vehicle or ketamine on days 9, 11 and 13 of forced abstinence. Rats were then assessed for cue-induced and heroin primed drug-seeking sessions.
Results: Acute ketamine exposure altered transcription of opioid related genes in the nucleus accumbens (NAc) shell, with 10mg/kg ketamine eliciting more robust and longer lasting effects compared to 3 mg/kg. Additionally, 10mg/kg ketamine increased μ opioid receptor protein and signaling in the NAc 7 days post-acute exposure. Behaviorally, ketamine significantly reduced heroin primed drug seeking.

Conclusions: Ketamine exposure was associated with long-term changes to the endogenous opioid system in the NAc providing novel insight into its long-term mechanisms. Additionally, ketamine exposure during abstinence from heroin reduced measures of relapse, indicating ketamine may have therapeutic potential in the treatment of OUD.

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Title: Juvenile social isolation dysregulates frontal VIP inhibitory circuits to induce social withdrawal

Authors: A Kawatake-Kuno, K Okamura, J Saez, J Riceberg, A Bansai, A Smith, S Fulton, I Maze, P Kenny, K Hashimoto-Torii, H Morishita

Background: Social isolation during a juvenile window is known to dysregulate medial prefrontal cortical (mPFC) circuits and social behavior in adulthood. While previous studies have examined the long-term consequences of juvenile social isolation (JSI) on adult circuitry and behavior, little is known about the immediate impact that JSI has on social development. Our preliminary study found that, at the end of isolation, JSI leads to heightened social withdrawal in males. At the circuit level, our pilot single-cell RNA-sequencing (scRNA-seq) of the P35 mPFC showed that VIP interneurons exhibit the largest number of differential expression genes (DEGs) amongst all cell-types in response to JSI. In this study, we test the hypothesis that JSI alters mPFC-VIP neural circuits—leading to excessive social withdrawal.

Method: To identify neural changes in mPFC-VIP interneurons following JSI, we performed cell-type-specific fiber photometry GCaMP imaging and optogenetic manipulation during social reciprocal tests. To investigate upstream inputs that alter mPFC-VIP neural activity, we conducted dopamine sensor imaging within the mPFC in JSI males.

Results: The GCaMP imaging results identified hyperactivation of mPFC-VIP interneurons in response to stimulus mouse's investigation in jSI males. Optogenetic inhibition of mPFC-VIP neural activity significantly reduced social withdrawal. Our pilot imaging also observed an increase in dopamine levels in response to stimulus mouse's investigation, uniquely in jSI males.

Discussions: The GCaMP imaging and optogenetic manipulation results collectively indicate that hyperactivation of mPFC-VIP interneurons in response to a stimulus mouse's investigation leads to social withdrawal in jSI males. Additionally, dopaminergic inputs are a potential upstream source of these mPFC-VIP neural changes, which will be explored in our future study.

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Association of specific resilience factors with mental health outcomes: Further validation of the Mount Sinai Resilience Scale

Aysha Khan, BA; Hira Ali, MPH; Andrew Delgado, PhD; James Murrough, MD PhD; Adriana Feder, MD; Jonathan DePierro, PhD; Dennis S. Charney, MD

Background: Factors such as strong social support, realistic optimism, facing fears, and physical activity contribute to resilience, helping individuals manage trauma symptoms and reducing the risk of mental disorders. This study utilizes the Mount Sinai Resilience Scale (MSRS, DePierro et al., 2024), a recently validated measure of psychological resilience. By focusing on MSRS subscales, which emphasize cognitive and behavioral factors fostering resilience, this work aims to advance an understanding of fine-grained relationships between specific resilience factors and psychological outcomes.

Methods: A representative U.S. sample was recruited via Prolific, an online research platform, in July 2024. Participants provided demographic data and completed measures of resilience (MSRS), PTSD (SPSS-A), depression (PHQ-8), and anxiety (GAD-7). Inverse probability weighting addressed missing data in Pearson correlations, examining resilience, trauma, and mental health outcomes with FDR-adjusted p-values.

Results: The sample comprised 1794 participants (mean age = 44.68, SD=15.34; 48.2% male, 50.4% female; 71.2 % White). MSRS domains of meaning and purpose, providing social support, facing fears, cognitive flexibility, physical exercise, and spirituality were significantly associated with psychopathology outcomes. Notably, the facing fears, physical exercise and meaning subscales demonstrated larger associations with mental health outcomes compared to other factors.

Conclusions: These findings demonstrate that certain resilience domains are more strongly associated with psychopathology outcomes, supporting the importance of psychotherapeutic approaches that integrate these personal strengths.

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Altered Brain State Dynamics in Major Depressive Disorder

B. Ülgen Kilic, Laurel Morris, Yael Jacob

BACKGROUND: Major depressive disorder (MDD) is one of the world's largest health problems. Neuronal mechanisms suggest dysfunctions in large-scale brain networks such as the Default Mode Network (DMN). However, how spatio-temporal activation patterns differ from baseline in MDD remains unknown.

METHODS: An unsupervised data-driven framework was applied to cluster time points of resting-state fMRI scans of 38 healthy controls (HC) and 38 MDD patients into temporally recurrent and spatially discrete configuration patterns (brain states that are repeatedly visited in time). High- and low-amplitude fMRI timeseries were mapped onto canonical resting-state networks. We then quantified the overall time spent in each state (fractional occupancy), the average number of consecutive appearances of a given state (dwell time), and the transition probabilities between states. Linear regression models were used to examine the association between brain state characteristics and MDD symptomatology, controlling for age, sex, and medication.

RESULTS: Four distinct brain states were identified: high-amplitude Visual Network (VIS+), low-amplitude Visual Network (VIS-), low-amplitude DMN (DMN-), and high-amplitude Limbic Network (LIM+). MDD spent more time in the DMN- compared to HC ($t=2.687$, $p=0.009$), but HC exhibited longer dwell times in this state compared to MDD ($t=-3.309$, $p=0.002$). Higher dwell times in DMN- correlated with lower anhedonia scores among both MDD and HC ($r=-0.510$, $p=0.042$ and $r=-0.648$, $p=3.8\times10^{-5}$, respectively), while higher fractional occupancy within the MDD group correlated with higher depression ($r=0.517$, $p=0.008$) and anhedonia scores ($r=0.532$, $p=0.008$). The MDD group showed significantly lower transition probabilities from LIM+ to VIS+ compared to HC ($t=2.59$, $p=0.011$), which inversely correlated with anxiety and depression symptoms (all $p<0.05$).

CONCLUSION: Dysfunctions in DMN- and the altered transitions between LIM+ and VIS+ are critical to MDD symptomatology in the resting-state brain.

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Patient- and Clinician-Rated Therapeutic Alliance and Outcomes: A Literature Review

Bailey Todtfeld, Debora Gonzalez, Theodore Servedio, Maya Valenzano, Heather Thibeau Rachel Jespersen, Yulia Landa, Lauren Lepow, Marc Aafjes, Jeffrey Cohn, Somnath Saha, Guillermo Cecchi, Cheryl M. Corcoran, René S. Kahn, Katie Aafjes-van Doorn, Mary Catherine Beach, Baihan Lin, Shalaila S. Haas

Background: Approximately 30% of people receiving outpatient psychiatric care disengage from treatment within 12 months. This, and other negative outcomes, may be attributable to poor patient-clinician relationships. Research shows stronger therapeutic alliance (TA) correlates with better long-term outcomes. This review expands upon previous research by examining these relationships across diagnoses, rater perspectives, and versions of the Working Alliance Inventory (WAI), offering insights for interdisciplinary approaches to intervention and prevention in mental health.

Methods: PsycINFO, PubMed, and Google Scholar were searched for peer-reviewed articles on the relationship between TA and treatment disengagement, increased symptom severity, and functional impairment. Selected papers used the WAI, or shortened versions, rated by clinicians and/or patients. We investigated bond, task, and goal subscales to evaluate associations with outcomes.

Results: Twenty-seven papers were included. High TA in clinician- and patient-rated assessments was associated with lower treatment disengagement and improved symptoms/functioning. Among clinician-rated alliance subscales, higher task/goal scores were associated with improved symptoms/functioning. No clinician-rated dimension was correlated with disengagement. For patient-rated alliance, higher bond dimension scores were associated with lower disengagement and improved symptoms/functioning.

Conclusions: These findings underscore how TA dimensions, as rated by each member of the dyad, are critical for achieving positive patient outcomes. A patient's sense of connection to their clinician may explain the critical role of bond for treatment outcomes. Further study of behavioral measures extracted from audiovisual recordings of clinical encounters may offer an opportunity to identify early indicators of connection between patients and clinicians to facilitate individualized therapeutic success.

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Submit your abstract here:

The distinct role of human LRRK2-G2019S in impairing immune cell homeostasis and immune response in periphery and brain

Bik Tzu Huang, Xianting Li and Zhenyu Yue

Background: Leucine-rich repeat kinase 2 (LRRK2) variant G2019S is found in both familial and sporadic Parkinson's disease (PD). Many LRRK2 G2019S mouse models created thus far have yet to show a robust Parkinson's disease phenotype. We propose to establish a new mouse model of humanized LRRK2-G2019S (hLRRK2 G2019S), which allow for better PD modeling by leveraging human gene regulation and limiting the compounding effects from mouse lrrk2.

Methods: Early characterizations of this model focused on male mice because of the increased severity of PD in males. Baseline measurements of CBC blood analysis from hLRRK2 G2019S, LRRK2 G2019S KI, and WT mice were done at 2 and 8 months. LPS was injected into hLRRK2 G2019S and WT male 3-month mice through i.p. Weight, open field, rotor rod and immunohistochemistry of the brain was consequently performed after 21 days post injection.

Results: In contrast to control and Lrrk2-G2019S KI mice, hLRRK2 G2019S show altered immune cell number at 2 months, which persisted even at 8 months of age. LPS induced inflammation showed hLRRK2 G2019S had heightened mortality to LPS and trend of dopamine neuron vulnerability compared to WT. Preliminary assessment of activated microglia and astrocytes, show reduced numbers in hLRRK2 G2019S mice. In vitro primary microglia cultures show increased LRRK2 kinase activity in hLRRK2 G2019S along with heightened LRRK2 response to immune activators, LPS and interferon-γ.

Conclusions: Our ongoing study shows the humanized LRRK2 G2019S model is distinct from the previously reported mouse knock-in LRRK2 G2019S. Humanized LRRK2 G2019S mice display impaired immune cell homeostasis in periphery and a robust immune response in microglia and potential enhanced neuronal vulnerability in SNpc, underlying LRRK2 pathogenesis in PD

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Youth-associated protein TIMP2 regulates microglial state in the context of aging and Alzheimer's pathology

Brittany Hemmer, Catarina Ferreira, Sarah Philippi, Samuele Petridis, Annie Phan, Joseph Castellano

Aging is the strongest risk factor for Alzheimer's disease, but mechanistic understanding for this connection remains unclear. The aged CNS can be rejuvenated by exposure to factors present in young blood. We've shown that youth-associated, blood-borne factor TIMP2 is critical for memory, synaptic function, and extracellular matrix homeostasis, processes that may be driven by changes in microglia. Here we sought to determine how TIMP2 regulates microglial state in contexts of aging and AD.

Though its expression in neurons has been established, we report TIMP2 is expressed in microglia, where it co-localizes with lysosome-associated CD68. RNAseq analysis of TIMP2 KO primary microglia revealed pathways associated with increased activation, immune response, and senescence. Mice lacking TIMP2 display accelerated neuroinflammatory phenotypes, including increased hippocampal microgliosis by 3 months of age, persisting through 7months. We sampled extracellular proteins by in vivo microdialysis, finding increased stress and inflammatory proteins in KO hippocampus. We find that microglia release TIMP2 under baseline conditions, with increased release in response to myelin debris. We created mice that allowed us to induce TIMP2 deletion in microglia, resulting in increased activation, senescent marker expression, and altered phagocytosis. Deletion of the neuronal pool of TIMP2 increases microglial activation, arguing that microglia are responsive to extracellular pools of TIMP2. Based on this, we asked how restoring the extracellular TIMP2 pool from the systemic environment regulates microglial function by treating aged WT mice systemically with TIMP2, which resulted in decreased microglial activation and increased synapse phagocytosis. snRNAseq analysis revealed TIMP2-mediated changes in microglia populations associated with phagocytosis and inflammation. Together, our results argue that microglia are responsive to youth-associated proteins like TIMP2, which regulate aging and AD-associated phenotypes.

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Title: A Novel Chemogenetic Approach for Identifying Cell Types with in vivo Calcium Imaging
Authors: BumJin Ko, Madeline Bacon, Yosif Zaki, Denise J. Cai

Background: Single-photon miniscope technologies are commonly used to record calcium dynamics from hundreds to thousands of cells in vivo in freely behaving mice. However, current miniscope tools are limited to recording from one cell type, sacrificing the ability to monitor the activities of multiple cell types simultaneously.

Method: Here, we present a novel technique to record calcium dynamics from two distinct cell types simultaneously, in vivo in freely behaving mice. We combined calcium imaging and chemogenetics to record from a broad class of neurons and post-hoc identify cell types among our recorded neurons using chemogenetics.

Result/Conclusions: We recorded calcium dynamics from all neurons and identified the inhibitory neurons among the recorded population. We then injected mice with the DREADD agonist and observed that a small fraction of neurons displayed robust calcium oscillations, which we used to identify the putative hM3Dq+ cells. Notably, this effect was not present after saline injections. We describe three ways in which we isolated the neurons that responded robustly to DREADD activation, demonstrating correspondence between these measures. Moreover, we demonstrate that we can reliably evoke these calcium oscillations in the same neurons across multiple days. To ensure this calcium oscillation is not driven by a poly-synaptic effect, we performed in vitro slice experiments where we bathed on the DREADD agonist onto slices expressing the same virus cocktail, and we demonstrate that only hM3Dq+ cells display calcium oscillations. Finally, we apply this approach to ask whether these putative GAD+ neurons display interesting dynamics. We found that inhibitory neurons are more likely to participate in synchronous burst events in hippocampus, consistent with the role of inhibitory neurons in orchestrating activity.

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Socioemotional Context Modulates Interpersonal Dynamics in BPD
Cameron Le Roux, Matthew Schafer, Xiaosi Gu, Harold Koenigsberg, Daniela Schiller
BACKGROUND: Borderline Personality Disorder (BPD) affects 1.7% of the population and 22% of psychiatric inpatients. Relationship instability, a hallmark feature, fuels suicidality in BPD. However, how interpersonal fluctuations arise and manifest along the fundamental dimensions of power and affiliation remains unclear.
METHODS: We used the Social Navigation Task (SNT) to assess interpersonal instability and its contingency on socioemotional triggers in BPD. In Study 1, online participants (n=239) played a negative SNT version in which they were wronged by the first character (Day 1), received a reminder of this event or a reminder plus an apology (Day 2), then evaluated their SNT relationships and played the Trust Game (Day 3). For analysis, participants were grouped by Borderline Symptom List scores (None-Mild vs. Moderate-High). In Study 2, a community sample (n=19) of healthy control (HC) and BPD participants completed the neutral SNT during MRI and were re-tested online at least four weeks later.
RESULTS: In Study 1, BPD traits did not affect interaction with the first character (Day 1). In both BPD trait groups, first character affiliation difference (Day 3–Day 1) was greater in Reminder+Apology versus Reminder-Only participants. However, a similar effect of the apology on first character power difference emerged only in the Moderate-High BPD group. Greater power differences were linked to higher reactive aggression in Moderate-High, but not None-Mild, BPD participants who received the apology. The apology also increased first character trust in both BPD trait groups. In Study 2, preliminary data suggest greater test-retest stability of SNT power decisions and relationship outcomes in BPD versus HC participants.
CONCLUSIONS: These findings suggest atypical interpersonal dynamics in BPD are reactively modulated by the social environment and manifest primarily along the power dimension.

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Title: Neural representations of task-based fMRI signal in macaque prefrontal cortex

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

Background: Functional magnetic resonance imaging (fMRI) is the dominant method for assessing the relationship between brain activity and behavior in humans. Studies investigating the neurophysiological basis of fMRI signals have focused on temporal cortex, reporting that up to 97% of neurons within an fMRI defined face-responsive area also selectively responded to faces. However, it is unclear whether the same fMRI-neurophysiology relationship holds in prefrontal cortex (PFC), which is known to have different neural timescales and a higher degree of mixed selectivity compared to other brain areas.

Methods: Two female macaques (Macaca mulatta) performed two distinct behavioral tasks during fMRI and neural recordings: 1) a probabilistic associative learning task with two contexts: novel (requiring learning) and familiar (previously learned); 2) a category selectivity task designed to assess face responsiveness.

Results: In Task 1, we found a region in ventrolateral PFC that more strongly responded to reward in the novel learning context. In Task 2, we found a nearby region in orbitofrontal cortex responsive to faces. During simultaneous neural recording from these fMRI-defined regions, we found that in the vlPFC region of interest (ROI), 93/195 (47.7%) of neurons were selective for reward in the novel learning context and 36/156 (23.1%) of neurons were selective for faces. In the OFC ROI, 61/131 (46.6%) were selective for reward in the novel learning context and 38/167 (22.7%) of neurons were selective for faces.

Conclusions: Our results indicate that the fMRI-neural activity relationship in PFC differs from that in temporal cortex. Our findings have implications for the interpretation of neuroimaging investigations of human PFC.

Funding: Mount Sinai, NIH

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Spatially Resolved Multiomics Profiling of Single Cells in Complex Tissues

Cheen Euong Ang

The recent development of spatial omics methods has enabled single-cell profiling of the transcriptome and 3D genome organization with high spatial resolution. Expanding the repertoire of spatial omics tools to a spatially resolved single cell epigenomics method will accelerate understanding of the spatial regulation of cell and tissue functions. Here, I will provide a summary of our current effort for the development of spatial multiomics imaging technique.
We reported a method for spatially resolved epigenomic profiling of single cells using in-situ tagmentation and transcription followed by multiplexed imaging. We demonstrated the ability to profile histone modifications marking active promoters, putative enhancers, and silenced promoters in individual cells, and generated high-resolution spatial atlas of hundreds of active promoters and putative enhancers in embryonic and adult mouse brains. We have recently expanded the technology to allow simultaneous profiling of the transcriptome and the epigenome and the methylome. We envision these imaging approaches will be enriched our understanding of how gene expression is spatiotemporally regulated by the epigenome.

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Military sexual trauma and genetic vulnerability: quantifying the association effects with serious mental illnesses in the Million Veteran Program

Chenyu Liu, Sanan Venkatesh, Georgios Voloudakis*, Panos Roussos*

BACKGROUND: Serious mental illnesses (SMIs) such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD), are among the most disabling health conditions. While these conditions have a well-established polygenic basis, exposure to traumatic experiences has also been shown to be a strong risk factor. Veterans facing unique environmental stressors are at an increasing risk of developing SMIs. This study aimed to investigate the impact of military sexual trauma (MST) compared to combat exposures (CE) on the risk of each SMI diagnosis. We also examined the relationships between MST, SMI polygenic scores (PGSs), and SMI outcomes.

METHODS: Individual-level SMI PGS were constructed for individuals of European (EUR) and African ancestry (AFR), respectively, using genotype information from a total of 542,030 participants (430,579 EUR; 111,664 AFR) in the Million Veteran Program (MVP). Phecodes representing relevant ICD-9-CM/ICD-10 diagnostic codes were used to determine each SMI diagnosis. We constructed logistic models to investigate the independent and interactive effect of MST and PGSs on each SMI diagnosis.

RESULTS: In this study, MST demonstrated a consistent association with all SMI diagnoses across all analyses and both ancestries, except for SCZ diagnosis in AFR. In the EUR cohort exposed to military combat (n=118,193), MST had the strongest association with all SMI diagnoses compared to all combat exposures, increasing the risk more than twofold in the top 10 percentile when stratified by SMI PGS. The odds ratio for PGS terms were significant regardless of MST history across each diagnosis in EUR. The interaction term PGS*MST was not significant in the interaction model.

CONCLUSIONS: MST and PGS are strong and independent risk factors for SMI.

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COMPARING SOCIAL DEFEAT STRESS MODELS: INTRODUCING THE ACCELERATED CHRONIC SOCIAL DEFEAT STRESS PARADIGM

Chloe Manca, Hyoseon Oh

BACKGROUND: Major depressive disorder (MDD) is a mental disorder characterized by persistent feelings of sadness, hopelessness, and loss of interest. Animal models are essential for studying the mechanisms behind depression and its impact on behavior. The chronic social defeat stress (CSDS) paradigm is commonly used to induce social stress in adult male mice but its application to adolescent rodents is limited due to the model's time-consuming nature. To capture results from key developmental periods, an accelerated version of this model has been developed. The accelerated social defeat stress (AcSD) paradigm uses a 4-day protocol with 2 physical attack sessions per day.

METHODS: In this study, male C57BL/6J mice were used for testing, and male CD-1 mice were used as aggressors. We compared behavior between CSDS and AcSD cohorts using the social interaction test (SI) with C57 and CD-1 targets, the resident intruder test (RI) with same sex, same strain, juvenile mice, and an open field test.

RESULTS: Results showed that AcSD mice exhibited stress-related behaviors. In the open field test, AcSD mice traveled less distance and spent more time in corner zones compared to controls. In the SI test, they interacted less with CD-1 and C57 target mice. Similarly, in the RI test, the AcSD mice spent less time interacting with CD-1 mice.

CONCLUSION: These findings indicate that the AcSD paradigm offers an alternative to the traditional CSDS model. The 4-day protocol captures the critical developmental stages, allowing for a more accurate representation of social stress in adolescent mice.

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Revisiting ketamine and dissociation: Ketamine's antidepressant and antisuicidal effects not predicted by psychoactive experience

Audrey Evers, Chris Kelly, PhD, Sanjay Mathew, MD, James Murrough, MD, PhD

Background: Ketamine has shown promise in clinical trials for its rapid antidepressant and antisuicidal effects in treatment-resistant depression (TRD), but the role of its dissociative properties remains unclear. As interest in psychedelic treatments grows, the assumption that ketamine's psychoactive effects contribute to its therapeutic efficacy has gained traction, despite mixed findings. Given these inconsistent results, we sought to replicate previous analyses using data from Murrough et al., 2013, a landmark trial that demonstrated robust antidepressant effects of ketamine.

Methods: Data were from a two-site, double-blind RCT comparing a single ketamine infusion (0.5 mg/kg) to midazolam in TRD patients (N=73) assigned in a 2:1 ratio. Dissociation was assessed using the Clinician-Administered Dissociative States Scale (CADSS). Depression outcomes were measured via the Montgomery-Åsberg Depression Rating Scale (MADRS). Only participants receiving ketamine (N=48) were included in analyses. Treatment response was defined as ≥50% MADRS reduction from baseline. Logistic regression examined the relationship between dissociation and response at 24 hours and 7 days. Linear regressions modeled dissociation's association with MADRS scores, percentage change in depression, and changes in suicidal ideation from baseline to 24 hours and 7 days.

Results: Dissociation during ketamine infusion did not predict response at 24 hours (OR = 1.05, 95% CI [-0.01, 0.11], p = .05) or 7 days (OR = 1.02, 95% CI [-0.03, 0.06], p = 0.44). It was also unrelated to MADRS scores, percentage change in depression, and suicidal ideation change at either timepoint.

Conclusions: In this TRD sample, dissociative symptoms did not predict ketamine's antidepressant or antisuicidal effects. Clinically, increasing dissociation to enhance efficacy may not be empirically supported. Future research should further examine ketamine's psychoactive effects and their impact on depression and suicidality.

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Title: Variable number tandem repeats (VNTRs) regulate epigenome and transcriptome in human prefrontal cortex

Authors: Christian Dillard, Kiran Girdhar, Biao Zeng, Jaroslav Bendl, John F. Fullard, Paras Garg, Mariya Shadrina, Andrew Sharp, Gabriel E. Hoffman, Panos Roussos

Background: To date, most studies have investigated only the impact of single-nucleotide polymorphisms (SNPs) on molecular phenotypes, such as gene expression generated from human postmortem brain tissue to identify quantitative trait loci (QTLs). Additionally, genome-wide association studies (GWAS) have predominantly focused on SNPs, which do not capture the impact of other, complex structural genetic variants. To address this gap, our research specifically examines the impact of variation in the length of variable number tandem repeats (VNTRs) on gene expression and chromatin accessibility phenotypes generated from the human postmortem brain.

Methods: To identify expression VNTRs (eVNTRs) and chromatin accessibility VNTRs (caVNTRs), we first identify VNTRs (motif size ≥ 10 bp and width ≥ 100 bp) using large-scale whole-genome sequencing data from postmortem brain tissue of 989 donors from the Common Mind Consortium (CMC), resulting in the identification of more than 90,000 VNTRs. We apply a linear regression to identify VNTR-phenotype QTL, and then use a sparse Bayesian multiple linear regression (SuSIE) to identify fine-mapped causal VNTRs for each associated phenotype.

Results: We identify approximately 2,000 eVNTRs using gene expression data from a subset of 648 donors in two cortical regions. Additionally, in our chromatin accessibility dataset we identify approximately 4,000 caVNTRs in neuronal and non-neuronal cells. Our fine-mapping tests report over 200(200) eVNTRs(caVNTRs) as causal variants (pip >0.3) highlighting the relevance of VNTRs over SNPs in these regions.

Conclusions: Our results provide further evidence that VNTR copy number variation has functional and regulatory effects in the genome, specifically in the case of neurological disease.

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Title: Linking Neural Representations to Adaptive Behavior with Computational Cognitive Modeling
Authors: Christina Maher, Salman Quasim, Lizbeth Nunez Martinez, Angela Radulescu, Ignacio Saez

BACKGROUND: Humans efficiently navigate complex learning and decision-making by formingrepresentations of task-relevant information, a process facilitated by selective attention. Although the lateral prefrontal cortex (LPFC) and orbitofrontal cortex (OFC) are linked to attention and value-based decision-making, the neurophysiological processes that coordinate these regions in the maintenance of task-relevant representations remain unclear.

METHODS: To investigate this, we combined intracranial electrophysiology (iEEG) from OFC and LPFC of neurosurgical epilepsy patients (N=21) with cognitive modeling of behavior, providing the spatiotemporal resolution to test local and circuit-level hypotheses about neural representations.

RESULTS: Our findings reveal how shared computational strategies across brain regions and individuals enable the brain to maintain representations critical for adaptive decision-making. This approach offers a novel framework for measuring representational alignment at both neural and subject levels, uncovering the neurocomputational principles that drive real-world behavior.

CONCLUSIONS: By integrating iEEG and computational cognitive modeling, we present an approach for studying representational alignment, revealing how it emerges both across brain regions, reflected in shared spectral and temporal features of neural state representations, and across individuals who adopt similar computational strategies to solve real-world decision-making tasks.

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Title: Mechano-Energetic Regulation by Plexins in Radiation-Induced Stress Responses

Authors: Chrystian Junqueira Alves, Haochen Tao, Sita Sadia, Jesse Fisher, Roland Friedel, Hongyan Zou

Background: Radiation therapy (RT) is pivotal in glioblastoma (GBM) treatment but constrained by tumor resistance and toxicity. While RT induces redox imbalance, DNA damage, and senescence, mechanisms enabling tumor evasion remain unclear. Cell mechanics—cytoskeletal forces, mitochondrial energetics, and membrane dynamics—are emerging as critical regulators of radiation resilience. Plexins, mechanosensitive receptors governing cytoskeletal remodeling and membrane tension, may mediate stress adaptation and mitochondrial function. This study explores Plexins' role in coupling cytoskeletal mechanics to mitochondrial energetics, governing RT resistance and informing therapeutic strategies.

Methods: Plexin-mediated mechano-energetic regulation was investigated in irradiated glioma stem cells (GSCs). Patient-derived and murine GSC models were genetically modified to generate Plexin-B2/D1 double knockout (dKO) and Plexin-B2-overexpressing (OE) lines. DNA repair kinetics were assessed via γH2AX foci resolution post-irradiation (1–3 Gy). Mitochondrial dynamics were analyzed using live-cell imaging, ATP levels via luciferase assays, and ROS. Senescence phenotypes were correlated with ATP levels. Pharmacological agents modulated cytoskeletal dynamics to evaluate impacts on ROS, DNA repair, and senescence. RNA-Seq and lipidomic profiling linked Plexin-B2/D1 dKO and OE to redox gene expression and lipid metabolism.

Results: Plexin-B2 OE increased mitochondrial ROS and cytoskeletal-nuclear stress in irradiated GSCs, delaying DNA repair (persistent γH2AX foci) and accelerating senescence (elevated SA-β-galactosidase). Conversely, Plexin-B2/D1 dKO cells showed reduced ROS, faster γH2AX resolution, and decreased senescence. Pharmacological disruption confirmed this link: Blebbistatin reduced ROS and enhanced repair, while Jasplakinolide worsened ROS and repair defects. Lipidomic and RNA-Seq analyses revealed Plexin dKO upregulated redox genes and lipid profiles favoring ROS scavenging, improving redox balance.

Conclusion: Plexins critically regulate radiation resistance by coupling cytoskeletal mechanics to mitochondrial energetics and redox adaptation in GSCs. Targeting Plexin-mediated mechano-energetic crosstalk could enhance RT efficacy in GBM.

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Mitochondrial Dysregulation: A Link Between Opioid Use Disorder (OUD) and Neurodegenerative Disease Development

Ciara Sanisaca, Kion Winston

Background: The opioid crisis has resulted in approximately 100,000 overdose deaths in 2023, with opioid use disorder (OUD) affecting millions globally. Opioids are a class of drug that is derived from the opium poppy plant which act on opioid receptors, a class of G-protein coupled receptors (GPCRs). Constant exposure to exogenous opioids can facilitate a “need” for the drug, leading to incessant and dysfunctional seeking of the drug or OUD. While research has focused on the behavioral aspects of addiction, there is increasing evidence that OUD may lead to neurodegenerative changes. This study investigates the intersection between opioid addiction and neurodegeneration, with a particular focus on mitochondrial dysfunction.

Methods: Post-mortem tissue from individuals with heroin use disorder was analyzed for differentially expressed genes (DEGs) related to neurodegenerative disease specific pathways. Enrichment analysis was conducted to identify genes involved in mitochondrial function.

Results: Preliminary results show significant overlap between DEGs in heroin use disorder and those associated with neurodegenerative diseases. Further analysis revealed that many of these genes are linked to mitochondrial function. We observed disruptions in various critical mitochondrial pathways.

Conclusions: Our research indicates that heroin exposure has a profound effect on gene expression in the human striatum, a critical brain region involved in addiction and reward processing. Further analysis of these results revealed significant alterations in 126 genes that overlap with mitochondrial functions, suggesting that heroin exposure disrupts mitochondrial pathways. These findings emphasize the importance of further research to understand how mitochondrial dysfunction in addiction could lead to long-term neurological consequences, with potential implications for therapeutic strategies targeting both addiction and neurodegeneration.

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Chronic cocaine exposure alters the sex specific balance of approach/avoidance decision-making

Clementine Blaschke1, Kinneret Rosen1, Angélica Minier-Toribio1, Tiffany Lin1, Tamara Markovic1, Freddyson J. Martínez-Rivera1, Antonio Aubry1, Eric J. Nestler1, 2, 3

BACKGROUND: Approach/avoidance (A/A) conflicts require balancing the pursuit of rewards with the potential for undesirable outcomes, a delicate balance disrupted in neuropsychiatric disorders like drug addiction. Despite the prevalence of these disruptive A/A dynamics in drug addiction, the mechanism underlying the interaction between drug exposure and natural reward-seeking during A/A conflict is poorly understood.

METHODS: We used a platform-mediated avoidance (PMA) paradigm—where we condition mice to avoid tones paired with foot shocks by stepping onto a platform at the cost of losing access to saccharine-water rewards. We then exposed them to chronic cocaine or saline injections (20 mg/kg intraperitoneal) for five days. Following a 5-day drug-free period, we tested their decision-making biases under extinction conditions (tones associated with foot shock are present, but no foot shock occurs).

RESULTS: Results reveal that chronic cocaine exposure selectively modulates A/A dynamics, increasing reward-seeking while decreasing avoidance during tone rather than inter-tone periods. To explore the neurobiology underpinning this heightened natural reward-seeking behavior and facilitation of avoidance extinction, we employed a combination of brain immunolabeling and 3D-volume imaging techniques, including iDISCO+, RNAScope, and viral-mediated gene transfer. Our preliminary iDISCO+ results revealed that chronic cocaine induces widespread ΔFosB expression, a transcription factor implicated in addiction-related outcomes, notably in the nucleus accumbens (NAc) and the prefrontal cortex (PFC).

CONCLUSIONS: Ongoing experiments aim to elucidate whether induction or repression of ΔFosB in the NAc and PFC contributes to the observed increase in reward-seeking approach over avoidance. Additionally, we will more specifically dissect the circuitry by selectively manipulating levels of endogenous ΔFosB in NAc neurons expressing dopamine D1 or D2 receptors, known to signal A-A decision-making differentially.

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Bipolar and schizophrenia risk gene AKAP11 encodes an autophagy receptor coupling the regulation of PKA kinase network homeostasis to synaptic transmission

Cong Xiao1, You-Kyung Lee1, Xiaoting Zhou, Le Wang, Meghan G. McReynolds, Zhiping Wu4,5, Eric Purisic2,6, Henry Kim1,2, Xianting Li1,2, Zhiping Pang3, Jinye Dai, Junmin Peng, Nan Yang, Zhenyu Yue*

BACKGROUND: Human genome-wide association studies (GWAS) have identified AKAP11 protein-truncated variants (PTV) as a significant risk gene for both bipolar disorder (BD) shared with schizophrenia (SCZ). AKAP11, a selective autophagy adaptor, plays a crucial role in the degradation of protein kinase A RI complex subunits (PKA-RI). However, the relationship between autophagy and BD and SCZ remains largely unexplored, particularly how loss-of-function in AKAP11 contributes to the BD and SCZ remains unclear.

METHODS: we employed a comprehensive approach that integrated multi-omics analysis, cell biology, and electrophysiology studies in both mouse models and human-induced neurons.

RESULTS: Our findings revealed that AKAP11 is pivotal for coupling PKA kinase activity to synaptic functions. Conditional knockout of AKAP11 in the mouse brain resulted in the accumulation of PKA subunits, leading to disrupted compartment-specific PKA, GSK3, and AKT1 activities and disordered neuronal functions that overlapped with pathways associated with BD and SCZ. Notably, AKAP11 deficiency also impairs neurotransmission.

CONCLUSIONS: Our data provides an insight into the molecular mechanism linking AKAP11 loss-of-function to psychiatric disorders.

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Sensory processing in a genetic mouse model of intellectual disability

Corinne M. Smith, Khaled Althobaiti, Silvia De Rubeis

BACKGROUND: Mutations in the DDX3X gene are responsible for DDX3X syndrome, which accounts for 2% of intellectual disability in females and carries risk for Autism Spectrum Disorder(ASD). Deficits in olfaction are reported across many neurodevelopmental disorders including ASD. Olfaction, one of the first sensory inputs, is a crucial factor in neural development. In mice, the olfactory system serves as a valuable model for studying sensory-dependent behaviors and neurogenesis during development and adulthood. Previously, we reported the critical role of DDX3X in neurogenesis and cortical development. We hypothesize that mutations in DDX3X impair olfactory bulb(OB) development via disrupted neurogenesis, resulting in circuit-level alterations that underlie deficits in olfaction-reliant behaviors. To test this hypothesis, we are assessing the development of the OB and olfaction-related behaviors in a mouse model of DDX3X syndrome (Ddx3x+/- haploinsufficient female mice).
METHODS: We have developed an olfactory acuity behavioral paradigm composed of 4 tasks: 1) scent habituation/dishabituation; 2) scent discrimination; 3) foraging; and, 4) scent-elicited neural activation. Testing of these behaviors has been conducted on Ddx3x+/- female mice, and their female(Ddx3x+/+) or male(Ddx3x+/y) control littermates at 4 months of age. Additionally, we will use immunohistochemistry to quantify OB cell types across development and adulthood, assessing OB formation and maintenance, in Ddx3x+/- mice.
RESULTS: Our results show no significant genotype-driven effects across behavioral paradigms; however, sex differences were observed in the habituation/dishabituation task during social scents.
CONCLUSION: Our data show that adult Ddx3x+/- female mice do not have overt general olfactory deficits. Next, we are assessing olfactory dependent social behaviors in adults and pups. The exploration of OB development across embryonic and early postnatal time points into adulthood will help us understand DDX3X's function in OB neurogenesis and olfaction-dependent behaviors.

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Clusterin secretion by dormant DTCs drives the formation of pro-survival brain niches through astrocyte remodeling

Cristina Megino-Luque, Alexis Wilder, Aubrey Houser, Cialowicz, Katarzyna, Pam de Valle, Deanna Benson5, Andrew Ji, Jose Javier Bravo-Cordero

Brain metastasis develop in 10-30% of women with metastatic breast cancer (BC) and is one of the major causes of their mortality. Autopsy studies support the idea that BC disseminated tumor cells (DTC) are able to remain in a dormant state in the brain and survive until optimal conditions restart their growth forming metastasis. However, the mechanisms by which brain DTCs can survive in this hostile microenvironment remain largely unknown. High-resolution light-sheet microscopy revealed that dormant DTCs reside in discrete niches in several anatomical regions of the brain, including the cortex, midbrain, hypothalamus, and basal forebrain. Multiplex immunofluorescence of brain niches revealed that dormant DTCs promote neuroprotective microenvironments characterized by increased BDNF and TGF□1 levels as well as suppression of proinflammatory markers such as IL1b, 4-HNE or iNOS. Consistently, multiome single-cell ATAC-seq and RNA-seq analysis revealed that dormant DTCs induce astrocyte and neuron plasticity. Dormant DTCs impose a neuroprotective state in astrocytes characterized by high levels of S100A10 and increased expression of transcription factors that promote neuronal survival and development, like Npas3 or Nrxn3. Proteomics analysis of dormant DTCs secretome identified Clusterin (CLU) as a major regulator of astrocyte plasticity. CLU induces a neuroprotective microenvironment that counteract the stress microenvironment induced by DTC seeding through lipid clearance. Finally, we discovered that CLU depletion in dormant DTC prevents astrocyte remodeling and compromises dormant DTCs survival in the brain. Our findings revealed a new mechanism by which dormant DTCs instruct brain astrocytes to promote their survival through the formation of neuroprotective microenvironments.

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THC and the Developing Brain: Sex-Dependent Changes in Decision-Making
Daniel Garcia and Jacqueline-Marie N. Ferland
BACKGROUND: There is growing concern over cannabis use during development including in adolescence. Growing evidence has repeatedly demonstrated a link between adolescent cannabis use and the development of cannabis use disorder (CUD). What remains unclear from these data is whether cannabis use in adolescence causally increases vulnerability to CUD. In this study, we used a translational animal model to investigate the impact of adolescent THC consumption on the adult decision-making and THC intake, phenotypes associated with CUD.
METHODS: Rats were given access to either control or THC-infused edibles three times per week from post-natal day 28-42. In adulthood, decision making was assessed using the rat gambling task (rGT). After the rGT, to determine if adolescent drug experience impacted intake in adulthood, all rats were given daily access to THC edibles. We also assessed whether THC consumption affected rGT performance either in the drug free period or while under the influence of THC.
RESULTS: Regardless of sex, adolescent rats consumed similar amounts of THC. Despite comparable intake, male THC rats uniquely showed increased risky decision-making in adulthood. In contrast to results from adolescence, stark sex differences were observed in adult THC consumption with males consuming significantly more drug than females. Interestingly, adolescent consumption predicted increased adult intake, but only in male rats. Although rGT performance was not acutely affected by THC consumption, both male and female rats with adolescent drug experience showed increased risky decision making after adult consumption, suggesting cognitive vulnerability to the drug in adulthood.
CONCLUSIONS: These data demonstrate distinct impact of adolescent THC consumption on adult cognition and drug intake in males which likely reflects neurobiological alterations promoting CUD-like phenotypes. Ongoing proteomics studies are assessing potential neurobiological correlates of these phenotypes.

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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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Exploring Functional and Structural Connectivity as Markers of Atherosclerotic Burden in Chronic Stress

David O'Connor, Mandy van Leent, Philip Robson, Audrey Kaufman, Maria Giovanna Trivieri, Lisa Shin, Ahmed Tawakol, Zahi Fayad.

Background: Chronic stress is associated with increased levels of cardiovascular disease (CVD). This is typified in post-traumatic stress disorder (PTSD), where increased atherosclerotic burden has been observed. Prior work has suggested that an imbalance in cortico-limbic brain function, commonly noted in PTSD, results in chronic whole-body inflammation, and higher atherosclerotic burden. Yet the effects of chronic stress are likely to impact the whole brain. We investigated the whole brain effects of chronic stress using functional and structural connectivity, and their association with inflammation and atherosclerosis.

Methods: PET/MR imaging of the brain was performed in 70 participants (19 with PTSD, 35 Trauma-exposed controls, and 16 Healthy controls). Task and resting state fMRI (rs-fMRI), diffusion MRI (dMRI) and T1 images were collected. Systemic inflammation was assessed using hsCRP. Atherosclerotic burden was assessed using black blood vessel wall MRI.

Results: Task based connectivity between the right amygdala and whole brain was able to distinguish individuals with higher and lower atherosclerotic burden (70% Accuracy, p=0.011, ROC-AUC=0.75). Structural connectivity between the left amygdala and whole brain was also successful (72.1% Accuracy, p=0.004, ROC-AUC=0.73). In both modalities increased connectivity with the motor cortex is associated with increased atherosclerosis. Visual cortices shown distinct opposite patterns in each modality due to hemispheric bias. Composite scores for the task and diffusion model were significantly associated with hs-CRP ($p < 0.05$).

Conclusions: We found functional and structural connectivity networks which are sensitive to atherosclerotic plaque burden and systemic inflammation. The results suggests that the motor and visual cortices, and their association with the amygdala, play a role in stress related CVD risk, along with the frontoparietal network.

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The role of the subgenual cortex, insula and amygdala in affective states and arousal

Davide Folloni, Frederic M. Stoll, Peter H. Rudebeck

BACKGROUND: Expectations shape affective states. Recent studies suggest a mechanism linking reward prediction errors (RPEs) to mood changes. However, the brain circuits and activity patterns mediating changes in RPE-induced affective states remain unclear. Unveiling these mechanisms is crucial for understanding the basis of normal mood fluctuations as well as affect-related disorders and developing novel treatments.

METHODS: Macaque monkeys (n=2) performed a probabilistic choice task with transitions across RPE contexts defined by different choice-outcome contingencies. Monkeys learned choice-outcome contingencies in the initial RPE context and then used them to guide their behavior in successive contexts. Single-neuron activity in subgenual cingulate cortex, insula, and amygdala was recorded while animals performed the task. Dysfunctions within this network have been implicated in depression. Autonomic activity (heart-rate) was recorded as a physiological measure of affect. RPE and value estimates were obtained by fitting reinforcement learning models to animals' choices.

RESULTS: Transitioning across different RPE contexts affected the animals' choice reaction times (p-value <<0.001, analysis-of-variance), autonomic state (p-value <<0.005, analysis-of-variance) and experienced RPE (p-value <<0.001, analysis-of-variance). RPE- and value single-unit activity at the time of outcome and choice, respectively, was found across all areas, despite neurons in subgenual cortex firing primarily in response to reward. Outcome-related neuronal activity was modulated by the magnitude of RPE and by the RPE context type in all areas.

CONCLUSIONS: Here, we identified changes in neuronal and concomitant autonomic activity within subgenual cortex, insula, and amygdala in response to fluctuations in RPEs. Thus, our data indicate a relationship between context-induced fluctuations in affect and the neuronal activity in a network of affect-related areas.

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Irritability as a Key Factor in Suicidality: A Comparative Analysis Across Internalizing and Externalizing Psychopathologies

Debora Gonzalez, Avraham Reichenberg, PhD, and Shalaila S. Haas, PhD

BACKGROUND: Suicidal thoughts and behaviors (STBs) have been a key concern in internalizing disorders, but less so in externalizing psychopathologies. Studies have linked irritability, a transdiagnostic construct, to STBs in youth, with mixed findings. This study explored its relationship with STBs across internalizing, externalizing, and comorbid psychopathology groups.

METHODS: We included 5397 children from the Adolescent Brain and Cognitive Development (ABCD) dataset (mean[SD] age = 9.93[0.624]; 51.1% male) absent of psychopathology or with the presence of internalizing, externalizing, or comorbid behaviors. We investigated prevalence across groups and performed ANOVAs to compare the prevalence of irritability in children across groups at baseline. Further, we examined associations between irritability and STBs (including passive and active suicidal ideation, self-injurious behaviors, and suicide attempts) across groups through MANOVA and Between-Subjects Effects tests.

RESULTS: Welch's ANOVA identified significant group differences in irritability scores (externalizing=5.28(1.90), internalizing=3.14(1.99), comorbid=6.78(1.97), absent=0.66(1.08), F=2080.05; P<0.001). MANOVA revealed a significant interaction between group membership and irritability, affecting combined suicidality outcomes (F=32.82 and P<0.001 based on Pillai's Trace test). Between-subjects effects confirmed this interaction for all four suicidality outcomes (P < 0.001), indicating that group differences in suicidality vary with irritability scores (F: NSSI = 59.08; Passive SI = 26.83; Active SI = 36.89; SA = 7.26).

DISCUSSION: This study found higher irritability prevalence and scores in internalizing and externalizing groups compared to individuals absent of psychopathology, with the highest levels in those with comorbid conditions. Suicidality outcomes varied by group and irritability, with the strongest effects for NSSI and active suicidal ideation and the weakest for suicide attempts. Findings suggest irritability is an important factor in certain STBs, offering insights for risk assessment.

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An Approach to the Construction of LAWS of MIND.

Desmond Heath

BACKGROUND: Here I attempt to avoid philosophizing when coming to an understanding of how our minds are constructed and how they work to produce self, personality, character, consciousness and how disturbances in this construction results in psychopathology. To avoid adding to the vast accumulation of artifacts of scholarship, I construct what Isaac Newton described as Laws that are derived from observations of matters of fact as opposed to speculations arranged into workable hypotheses—Aristotelian scholasticism. The star charts that were Newton's data base for constructing an understanding of the actions of the celestial sphere are replaced, in this instance, with physical properties of matter—Bayesian probabilistic prediction and close to criticality at the transition between chaos and stability in complex self-tuning systems.—these physical properties of matter are expressed in our brains and the constraints that each has on the other result in self, personality, character, consciousness.

METHODS: Instead of understanding the interaction of inert physical objects in the celestial sphere, I attempt to understand the interactions of physical properties of matter that, by constraining each other compose the living firmament of mind.

RESULTS: Preliminary tentative Laws of Mind. I aim to find the various regularities that may appear in the complex behavioral expression of these two properties of matter. Then I will try to compress this understanding into succinct Laws of Mind.

CONCLUSIONS: I hypothesize that if succinct Laws of Mind can be defined a “Sane Society Revolution” might follow as did Newton’s Laws of Motion make possible the Industrial Revolution.

Key words: Bayesian probabilistic prediction, close to criticality, physical properties of matter, constraints, construction of mind, self, personality, character, consciousness, Laws of Mind, Sane Society Revolution.

2025 Neuroscience Retreat

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Submit your abstract here:

Aversive Memory Integration Across the Dorsoventral Hippocampal Axis Through Brain States

Destynie Medeiros, Justin Lines, Yosif Zaki, BumJin Ko, Madeline Bacon, Austin Baggetta, Denise Cai

BACKGROUND: Memory integration, the process of linking past experiences with new information, is essential for adaptive decision-making and survival. However, under stressful or traumatic conditions, this process can become maladaptive, leading to inappropriate associations that underlie disorders such as post-traumatic stress disorder and anxiety. A highly aversive experience can link learned fear and dorsal hippocampal ensembles to a previously neutral context experienced days earlier through ensemble reactivation during quiet restful periods of bursting activity. Given the established role of hippocampal oscillations, particularly sharp-wave ripples (SWRs), in ensemble reactivation and memory consolidation, we sought to determine whether SWR-driven reactivation facilitates contextual memory linking. The ventral hippocampus is known for its role in encoding and storage of emotional memories. Thus, we will examine the role of ventral hippocampal ensemble reactivation during SWRs to link distinct contextual memories. In this work, we sought to investigate ensemble co-reactivation across the hippocampal dorsoventral axis to uncover the circuit mechanisms underlying memory integration.

METHODS: We utilize Miniscope calcium imaging and local field potential recordings in dorsal and ventral hippocampus to characterize oscillatory dynamics during ensemble reactivation.

RESULTS: We optimized simultaneous calcium imaging and electrophysiology recordings in dorsal hippocampus and validated SWR detection during offline periods prior to and following neutral and aversive experiences in an established memory linking paradigm. We expect that hippocampal ensemble reactivation preferentially occurs during SWR events and that SWR prevalence increases following learning.

CONCLUSIONS: This work allows us to identify the neurophysiological signature governing memory integration during ensemble reactivation across the hippocampus. In our future work, we plan to combine in vivo electrophysiology with ventral hippocampus calcium imaging to probe the role of SWRs in memory integration.

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Submit your abstract here:

The role of tyrosine hydroxylase neurons in the paraventricular nucleus of the hypothalamus in responses to acute stress

Diego Espinoza, Alexandra Alvarsson, Jamie Carty, Maria Jimenez-Gonzalez, Clint Kinney, Malia McCullum, Sarah Stanley

Background

Psychological stimuli that disrupt homeostasis – stressors – lead to metabolic disturbance but the CNS circuits mediating these effects are largely unknown. The paraventricular nucleus of the hypothalamus (PVH) plays a significant role in behavioral, autonomic and hormonal responses to stress. It contains multiple cell types including neurons expressing tyrosine hydroxylase (TH). We aim to determine the roles of PVHTH neurons and their projections to the ventral lateral septum (vLS) in stress-induced metabolic responses.

Methods

We used PRV-Circuit-TRAP-seq to identify CNS neural populations synaptically projecting to metabolically activated organs. We measured PVHTH activity in response to stress using fiber photometry in TH-cre mice with PVH injection of cre-dependent AAV-GCaMP8s. To identify the functions of PVHTH neurons, we tested the effects of acute modulation using PVH injection of cre-dependent AAV9-mCherry(control), hM3Gq (activating), hM4Gi (silencing) in TH-cre mice. We identified downstream circuits from PVHTH neurons using AAV-synaptophysin-mCherry then tested the roles of PVHTH to vLS circuits using cre-dependent AAVrg-FLPo and flp-dependent AAV-control, AAV-Gq, and AAV-Gi in the vLS and PVH, respectively.

Results

PRV-Circuit-TRAP-seq and retrograde tracing identified PVHTH neurons as synaptically connected to pancreas, liver and adipose tissue. Using fiber photometry, we found increased PVHTH neurons activity with acute stress but differences between fed and fasted states. Chemogenetic PVHTH activation impaired glucose and pyruvate tolerance, potentiated stress-induced hyperglycemia and suppressed feeding, without affecting anxiety-like behavior, while activation of PVHTH to vLS circuits decreased feeding.

Conclusion

These findings suggest stress-activated PVHTH neurons regulate the feeding and stress hyperglycemia, independent of anxiety while PVHTH-vLS circuits contribute to stress-induced hypophagia. Future studies will examine upstream circuits communicating with PVHTH neurons.

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Submit your abstract here:

Brain-wide reductions of intrinsic neural timescales in treatment resistant depression
Elizabeth Alcantara, Kenneth Wengler

Background. Major depressive disorder is a leading cause of disability worldwide and approximately 30% of patients develop treatment resistant depression (TRD). Cognitive deficits in depression extend past remission and affect severity of disability. Ketamine is an effective treatment for TRD that modulates the excitation/inhibition balance (E/I) and improves cognitive symptoms. Intrinsic neural timescales (INT) are a resting-state fMRI measure theoretically (biophysical models) and experimentally (chemogenetic manipulations) linked to E/I. We investigate INT alterations in TRD as a marker of E/I underlying deficits in cognition.

Methods. Resting-state fMRI data were analyzed from 128 TRD patients and 34 controls from the Perturbation of the TRD Connectome by Fast-Acting Therapies Human Connectome Project. INT maps for 188 brain regions (averaged across hemispheres) were estimated 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 and three phenotypes: (1) patient vs control group (diagnosis); (2) depression severity and (3) processing speed.

Results. INT were shorter in TRD (33 significant brain regions), particularly in the striatum ($t=-2.10$, $p < 0.001$), limbic system (all $t<-2.24$, $p<0.023$), insula (all $t<-2.25$, $p<0.037$), and cingulate (all $t<-2.35$, $p<0.019$). Additionally, shorter INT were related to worse depression severity throughout the brain (39 significant brain regions), most notably in the accumbens ($t=-1.99$, $p=0.013$), insula (all $t<-2.40$, $p<0.043$), and cingulate (all $t<-2.51$, $p<0.048$). Lastly, longer INT related to increased processing speed performance (33 significant regions).

Conclusions. We identified shorter INT throughout the brain in TRD with greater INT shortening relating to worse depression severity and longer INT relating to better cognition. E/I alterations offer a target mechanism underlying TRD, potentially explaining the effectiveness of ketamine (a known NMDA-receptor antagonist).

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Foraging for interaction across dimensions of social identity: a neuroeconomic task

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

Operant tasks adapted to study appetitive social interactions have facilitated the integration of behavioral economics with rodent social neuroscience, allowing for the dissociation of computationally distinct decision stages along many value dimensions in social settings. Existing naturalistic, cross-species neuroeconomic paradigms further yield the opportunity to translate findings in pre-clinical social behavior research to studies of humans. Utilizing this interdisciplinary perspective could strengthen our understanding of long-term social memory, familiarity discrimination, hierarchy-dependent choice behavior, and evolutionarily conserved social cognitive processes. To this end, I have adapted the food-based neuroeconomic task, Restaurant Row (RRow), into a social decision-making task in which mice forage for social interactions. Social RRow leverages the availability of four conspecific stimuli that vary in subjective value (identity) and access cost (time delays) over the course of months across a changing economic landscape. Alongside the spatiotemporal segregation of choices and interactions, this environmental structure permits the investigation of multiple decision-making mechanisms that determine long-term relationship development. My pilot data validated the task feasibility under several commonly studied experimental conditions, including social novelty vs. familiarity, social vs. non-social stimuli, and genetic predisposition to autism, as well as different social ranks, isolation lengths, strains, and barrier types. My preliminary findings suggest that the reciprocal nature of interactions may reveal important signatures of social choice that not only depend on contextually dynamic and individual relationships, but could recruit separable neurophysiological processes. I have since launched a large-scale behavioral study to thoroughly characterize social neuroeconomic decision-making, and plan to probe the neural correlates of significant behaviors. Ultimately, I aim to extend these findings across species and within this neuroeconomic framework to better explain neural and behavioral foundations of social decision-making in humans.

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Submit your abstract here:

The Role of GluD1 in Regulating NMDA Receptors and Synaptic Plasticity

Eric Purisic, Jinye Dai

Background: Glutamate delta receptor 1 (GluD1) is an orphan ionotropic glutamate receptor linked to neuropsychiatric disorders such as autism, schizophrenia, and intellectual disability. Importantly, GluD1 does not bind glutamate but forms the postsynaptic component of a transsynaptic complex with presynaptic neurexins and cerebellins. It functions to transduce presynaptic signals to modulate AMPA and NMDA receptor function, altering excitatory synaptic transmission. Notably, GluD1 is crucial for glutamatergic synaptic transmission in the ventral subiculum, a key region for hippocampal output associated with schizophrenia, drug-seeking, sleep disturbances, and stress. Our work examines GluD1's impact on NMDA receptor function and synaptic plasticity in the ventral subiculum to help identify the mechanisms by which GluD1 dysfunction leads to neuropsychiatric risk.

Methods: To investigate GluD1 function, we used CRISPR-Cas9-mediated knockout via sgRNA-containing AAVs in vivo (Cas9 knock-in mice) and in vitro (primary hippocampal cultures). We conducted whole-cell patch-clamp electrophysiology in slices and cultures, along with immunoblotting and immunocytochemistry for NMDA receptor subunits. Behavioral tests included the open-field test and passive avoidance in a shuttle box.

Results: GluD1 KO alters synaptic transmission at CA1→Subiculum synapses, inhibiting LTP induction, reducing NMDA-mediated transmission, and accelerating NMDA receptor kinetics. The faster kinetics suggest decreased N2B-containing NMDA receptors, confirmed via pharmacological blockade. In culture, electrophysiological results were replicated without changes in subunit expression, though immunocytochemistry revealed reduced surface-expressed N2B-containing NMDA receptors. Behaviorally, GluD1 KO animals showed hyperactivity, anxiety-like behavior in the open-field test, and impaired passive avoidance memory.

Conclusions: GluD1 plays a significant role in regulating synaptic plasticity at CA1→-Subiculum synapses through its regulation of the trafficking of N2B-containing NMDA receptors to the synaptic surface. Knockout of GluD1 at these synapses in mice leads to significant behavioral deficits consistent with the observed molecular and electrophysiological changes.

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Submit your abstract here:

Median Raphe Region Vgat neurons projecting to LH regulate NREM sleep

Fang Gao, Kaikai Zang, Xingliang Yang, Xueming Hu, Zili Xie, Hongzhen Hu

Background

Slow-wave sleep (SWS) or stage 3 non-rapid eye movement (NREM) sleep, is characterized by EEG delta waves and is essential for memory consolidation. The median raphe region (MRR) is a critical brainstem structure that regulates various physiological and behavioral processes, including wakefulness, memory, social interaction, mood, and cognitive functions. However, its specific role in sleep regulation remains unknown.

Methods

RNAscope was employed to characterize vesicular GABA transporter (Vgat)-expressing neurons in the MRR. Optogenetic activation of MRR neurons or their downstream targets was performed using 473 nm blue light following viral injections. EEG/EMG recording in free-moving mice was conducted to record mouse brain states during optogenetic stimulation. Heart rate and pupil size were measured in head-fixed mice on a treadmill to monitor physiological changes. Synaptophysin-expressing Cre-dependent AAV was utilized for mapping outputs of MRR Vgat neurons, and retrograde Cre-dependent AAV expressing ChR2 was injected into downstream nuclei to label projection-specific populations of MRR Vgat neurons.

Results

MRR Vgat neurons partially co-localized with somatostatin (SST), not VIP or parvalbumin. Optogenetic activation of MRR Vgat neurons rapidly induced SWS-like EEG patterns and reduced heart rate and pupil size, physiological hallmarks of NREM sleep, and REM-like atonia. Whole-brain mapping revealed extensive projections of MRR Vgat neurons, notably to sleep-regulatory regions such as the lateral preoptic area (LPO) and lateral hypothalamus (LH). Using retrograde labeling, we determined that specifically LH-projecting—but not LPO-projecting—MRR Vgat neurons mediated the promotion of SWS.

Conclusions

Together, these findings suggest that the MRR Vgat neurons act as a sleep control center where the Vgat neurons promote NREM sleep transition through projecting to LH nucleus, as well as an inhibitory brake on movement to stop ongoing behavior.

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Submit your abstract here:

Multi-ancestry genome-wide meta-analysis of neutrophil to lymphocyte ratio in the Million Veteran Program

Fotios Tsetsos, David Burstein, Jamie J. R. Bennett, Marios Anyfantakis, Sanan Venkatesh, Jaroslav Bendl, Georgios Voloudakis*, Panos Roussos*

Background/Aims:

The neutrophil-to-lymphocyte ratio (NLR) is a widely used marker of systemic inflammation associated with various disease outcomes.

Methods:

Here, we conducted the first large-scale multi-ancestry genome-wide association meta-analysis of NLR, leveraging data from the ethnically diverse Million Veteran Program. We performed ancestry-specific analyses in participants of European (n=401,666), African (n=103,336), and Hispanic (n=47,698) ancestry.

Results:

In the European ancestry cohort the strongest association mapped to the chr17q21 locus. In the African ancestry cohort, we observed a Mendelian-like dominating effect of the Duffy-null variant, which was strongly associated with neutrophil count. Stratification by this variant further elucidated the genetic architecture of NLR in the African genetic background. In the Hispanic ancestry cohort, both loci contributed jointly. We also identified shared heritability between NLR and several obesity-related traits, including type 2 diabetes mellitus and binge-eating disorder, and implicated spleen and whole-blood tissues in our findings.

Conclusions:

Overall, this study provides insights into the genetic underpinnings of this important inflammatory marker across diverse ancestries and suggests a potential link between obesity-related phenotypes and systemic inflammation.

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Submit your abstract here:

Decreased expression of Alzheimer's gene SPI1 impacts efferocytosis in iPS-derived microglia.

Francesca Garretti, Marcelina Ryszawiec, Brian Fulton-Howard, Edoardo Marcora, Alison Goate

Background: Alzheimer's disease (AD) risk genes converge on endocytosis/phagocytosis, cholesterol metabolism, and immune response pathways, all of which are critical for efferocytic function of microglia. A novel haplotype in SPI1 is associated with delayed age of AD onset, as well as decreased SPI1 expression in myeloid cells and reduced Aβ42 levels in cerebrospinal fluid. SPI1 encodes for PU1, a transcription factor essential for microglial differentiation. However, the effect of decreased SPI1 expression in human microglia on efferocytosis and cell function remain unknow.

Methods: PU1 is essential for microglial differentiation and its modulation impacts microglial development. To circumvent this issue, we developed a strategy for targeting SPI1 by employing RNAi at the final stage of microglial differentiation. Using this approach, we investigated how decreased PU1 levels affect iPS-derived microglial function and confer protection against AD.

Results: We found that PU1-low microglia are positively enriched for DAM and AD gene sets. Functionally, reduced PU1 expression led to increased lipid droplet formation, enhanced cholesterol and APOE efflux. PU1low microglia exhibited increased levels of zymosan-pHrodo but not of indigestible latex beads. These findings suggest that the increased pHrodo signal in PU1-low microglia is due to differences in digestion rather than phagocytic uptake. Indeed, PU1-low microglia displayed a significant reduction in lysosomal mass and acidification. Finally, we observed that PU1 low microglia were more sensitive to cell death stimuli.

Conclusions: These findings demonstrate how AD-associated genes influence lipid homeostasis and the endolysosomal system, underscoring the importance of the efferocytic pathway in microglial cell function and its role in modulating AD risk. Future directions are focused on evaluating the effects of the DAM phenotypes of PU1-low microglia in 3D cultures containing neurons and astrocyte.

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Submit your abstract here:

Neural Circuit Mechanisms of Top-Down Influences on Reward Learning

Frederic M. Stoll and Peter H. Rudebeck

BACKGROUND: Our internal goals and knowledge of the environment shape how we learn stimulus-reward contingencies. While it has been appreciated that knowledge can be used in a top-down processes to enhance learning, the precise neural representations and pathways involved remain unclear.

METHODS: To investigate the patterns of activity supporting top-down enhancement of learning, we trained two rhesus macaques to perform a probabilistic reward-learning task in which animals learned the probabilities of receiving a juice reward associated with 3 unique stimuli. Reward probabilities were systematically reversed over the course of a session and these changes in contingency were occasionally signaled using a salient stimulus, indicating that the probability changed without providing information on the new stimulus-probability contingencies.

RESULTS: Computational modeling of macaques' choices using reinforcement learning models revealed faster behavioral change following signaled compared to unsignaled switches, highlighting that their learning could be enhanced in a top-down manner. While performing the task, we recorded the activity of 3,887 neurons in orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), amygdala and striatum using semi-chronic microdrives. We found that neurons in vlPFC/amygdala were more likely to represent the expected value of choosing the individual stimuli while OFC/amygdala neurons were more likely to encode the stimulus identity. Importantly, amygdala neurons were the first to represent the strategy that monkeys employed to perform the task, while vlPFC neurons were the first to represent monkeys' change in strategy. Furthermore, changes in population activity within vlPFC and amygdala could be observed on the trial immediately following signaled compared to unsignaled switches, leading changes in representations within OFC and striatum.

CONCLUSION: vlPFC and amygdala encode top-down signals to adaptively guide learning.

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Submit your abstract here:

Generating a brain-wide atlas of neuronal activity during myocardial infarction recovery

Gabriel Caumartin, Alexander Leunig, Ziche Chen, Matteo Gianeselli, Abbey Glick, Ana Oliveira Coelho, Jeffrey Downey, Katarzyna Cialowicz, Filip Swirski

Introduction: The role of the brain in post-myocardial infarction (MI) healing and recovery has recently been increasingly appreciated (PMID 35477759, 34102426, 39180327). However, identifying brain region-specific patterns of activity following MI has been challenging due to limitations in imaging techniques. Here, we develop a fast and reliable method to map brain-wide neuronal activation during MI healing.

Methods: We optimized a Fast3D tissue-clearing method (PMID 34966901) to clear and prepare whole mouse brains for imaging in under 3 days. Using this method, we can sequentially image three brains in just one hour using a light-sheet microscope. We employed this method to image mice with activity-dependent genetic labeling of neurons using Trap2-Ai14. We induced MI by ligating the left anterior descending coronary artery and “trapped” neuronal activity at day 3 post-MI, a key time point when systemic and neural responses to cardiac injury are active. Cleared brains were imaged and analyzed with a ClearMap2 pipeline, allowing us to map activation across the entire brain.

Results: Our optimized Fast3D clearing method reliably produced clear, intact brains, enabling rapid imaging with high resolution (~4μm). In mice with MI, we can catalog and quantify activated neurons throughout the brain. This allows us to probe which regions are differentially activated in MI compared to sham.

Conclusion: Our method provides a fast and scalable approach to map brain activity after MI as well as other challenges. This method allows us to generate an atlas of key brain regions activated in response to heart injury. This study will offer insights into how the brain coordinates recovery, and it highlights potential neurocardiac pathways for therapeutic targeting in the future.

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Submit your abstract here:

Neural Correlates of Mentalizing Altered in Childhood Trauma and Cocaine Use Disorder

Gabrielle Zbären, Philip Kalimar-Britt, Vyoma Sahani, Yasmin Hurd, Keren Bachi

BACKGROUND: Childhood trauma is prevalent in individuals with cocaine use disorder (iCUD), and both are associated with social cognition deficits, including impaired mentalizing (social inference). However, the circuitry underlying mentalizing in iCUD remains uncharacterized. We hypothesized that childhood trauma and iCUD would show altered activation of the mentalizing network, which would be associated with deficits in real-world social capacities.

METHODS: Participants (45 iCUD and 34 healthy controls (HC), with high/low childhood trauma) performed the validated Why/How fMRI task, which probes Why versus How photographed naturalistic behaviors are being performed. We performed whole-brain analyses using a Why > How contrast at the first-level, followed by a second-level analysis to characterize group differences on the mentalizing network, with cluster-level family-wise error correction for multiple comparisons (pFWE < .05).

RESULTS: iCUD performed worse than HC on the mentalizing task ($F(1,75) = 4.45$, $p < .05$), with no effect of trauma severity on accuracy. fMRI results showed an interaction in the precuneus, with greater BOLD responses in iCUD-low than HC-low, and lower responses in iCUD-high than HC-high. Precuneus activity negatively correlated with the social closeness personality trait ($r(79) = -.22$, $p < .05$). High-trauma individuals showed increased responses in frontal regions, positively correlated with accuracy ($r(39) = .47$, $p < .01$).

CONCLUSION: Our results suggest that during mentalizing, high trauma is associated with greater frontal activation to achieve similar accuracy as low-trauma individuals, and trauma severity affects the link between precuneus activity and CUD, offering neural insights into how trauma history may influence social functioning in CUD.

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Submit your abstract here:

Gamified Approach to Maximizing Biobehavioral Inhibition in Trauma-Related Disorders (GAMBIT): A Digital Tool to Measure Distinct Inhibitory Control Mechanisms

Dirupo, Khaikin, Federer, Delgado, Morris, DePierro, Murrough

BACKGROUND: PTSD patients exhibit deficits in inhibition, including fear inhibition, memory suppression, and behavioral and emotional dyscontrol. Inhibitory control is linked to symptom improvement, yet deficits in reactive and proactive inhibitory control persist after psychotherapy, suggesting an underlying vulnerability not addressed by standard treatment. This study aims to investigate three different types of inhibitory control mechanisms: preemptive, proactive, and reactive, using a novel fully online task.

METHODS: 212 participants passed a minimum accuracy test (n=300 recruited) and were included in the final analyses. They completed questionnaires assessing demographics, mood and anxiety, and our task (GAMBIT), designed to adapt to individual performance throughout and included different trials for each type of inhibition.

RESULTS: Results showed differences in accuracy across trial types ($F(3, 633) = 1632.32$, $p < .001$), with the highest performance observed in trials measuring preemptive inhibitory control, followed by reactive and finally proactive. The results show also a negative correlation between accuracy in preemptive inhibitory trials and sadness ($r = -0.14$, $p = .041$). Greater self-reported depressive ($r = -0.15$, $p = .026$), anxiety ($r = -0.17$, $p = .013$), and anger management symptoms ($r = -0.15$, $p = .032$) were associated to lower improvement in proactive inhibitory control trials throughout the task. Finally, the improvement in reactive inhibitory control trials throughout the task was higher in participants reporting lower anxiety ($r = -0.14$, $p = .038$).

CONCLUSIONS: These findings confirm the presence of distinct inhibitory control processes that the GAMBIT task can detect. Additionally, they suggest that different types of inhibitory control are associated with specific mood and anxiety symptoms, providing new insight for potential treatments. This study provides an ecologically valid and engaging method for assessing inhibitory control online.

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Submit your abstract here:

Title: Representational Drift Preserves Geometry

Authors: Hajar Zaid, Evan Schaffer

BACKGROUND: Neural representations in many brain regions drift over weeks despite stable short-term tuning, a phenomenon known as representational drift. This raises a paradox: how can the brain reliably retrieve memories if neural representations change? In the piriform cortex, neurons responding to a given odor show no correlation with those activated by the same odor weeks later. Yet, decoding studies reveal that stable readout from drifting representations is possible. While computational models have demonstrated this, the underlying mathematical principles remain unclear.

METHODS: We develop a mathematical framework to explain stable decoding from drifting representations using a two-layer network model. Leveraging random matrix theory, we analyze how the downstream layer processes drifting inputs from the upstream layer. We prove that, under minimal assumptions, the downstream layer naturally forms a tight frame, a structure that preserves geometric relationships between input patterns similarly to an orthogonal basis. This guarantees stable decoding as long as the geometry of the drifting representations remains intact. Additionally, we examine how the number of recorded neurons affects empirical measurements of representational stability.

RESULTS: Our analysis shows that stable decoding from drifting representations is not only possible but inevitable under realistic conditions. The tight frame property ensures that the downstream layer maintains stable input relationships despite drift. We further demonstrate that empirical studies suggesting unstable geometry arise due to limitations in the number of recorded neurons rather than a fundamental breakdown of representational stability.

CONCLUSIONS: Our results provide a general mathematical explanation for stable decoding from drifting representations. By showing that the downstream layer acts as a tight frame, we establish that stable decoding follows naturally from geometric preservation. This resolves the paradox of representational drift and suggests that memory retrieval remains robust despite ongoing neural changes.

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Submit your abstract here:

Vagal sensory neurons promote anaphylactic hypothermia

Hisato Iriki, Lydia Zamidar, Brian S. Kim

Anaphylaxis is a potentially life-threatening allergic reaction to dietary antigens resulting in systemic symptoms including hives, hypotensive shock, and hypothermia. While the activation of mast cells via crosslinking of cell surface IgE is a central mechanism of anaphylaxis, the precise pathophysiology remains unclear. Given the close relationship between mast cells and sensory neurons in tissues, we sought to investigate the potential role of the vagus nerve in mediating anaphylactic physiology. We employed a model of dietary antigen-induced anaphylaxis, wherein mice were epicutaneously sensitized to ovalbumin (OVA) under MC903-induced dermatitis. In mast cell-deficient mice, the anaphylactic hypothermia observed in control mice was absent. And under MC903-induced dermatitis, an accumulation of mast cells near the TRPV1+ sensory neurons in the stomach was observed. When the effects of various agonists on receptors that play a role in the known mast cell-sensory neuron axis were examined, administering an antagonist against PAR1, a receptor widely expressed on vagal TRPV1+ nerves and activated by mast cell-derived chymase, significantly attenuated anaphylactic hypothermia.Noting the significant vagal innervation of the stomach, we then employed compartment-specific chemical denervation using resiniferatoxin (RTX) to selectively impair somatosensory neurons of the dorsal root ganglia or vagal TRPV1+ sensory neurons of the jugular/nodose ganglia in mice. Remarkably, vagal sensory denervation resulted in protection from hypothermia that was not observed in with somatosensory denervation. These findings reveal a previously unrecognized role for mast cell-vagal sensory neuron axis in the stomach in regulating rapid and systemic anaphylactic symptom.

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Submit your abstract here:

Title: Lifespan cellular dynamics and disease associations in the human dorsolateral prefrontal cortex

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1Center for Disease Neurogenomics, 2Friedman Brain Institute, 3Department of Psychiatry, 4Department of Genetics and Genomic Science, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Background: The human dorsolateral prefrontal cortex (DLPFC) undergoes dynamic cellular changes across the lifespan, yet the trajectories of glial and neuronal lineages and their disease relevance remain poorly understood. To investigate this, we mapped cellular maturation, aging, and disease associations using single-nucleus RNA sequencing (snRNA-seq) data spanning the human lifespan.

Methods: We integrated our neurotypical snRNA-seq dataset from PsychAD (0–97 years) with published fetal-to-adult data, yielding 1,454,617 nuclei from 311 individuals. We applied the Uniform Manifold Approximation and Projection of MATuration and Monocle3 for pseudotime inference in key cell types. We analyzed gene expression dynamics and assessed disease associations via single-cell disease relevance scores and genetic enrichment analyses.

Results: Astrocytes followed two trajectories: fibrous astrocytes matured earlier in white matter, while protoplasmic astrocytes matured later in gray matter and were linked to migraines and schizophrenia. Microglia displayed stable enrichment in neuroimmune traits, including Alzheimer's disease (AD) and multiple sclerosis, with aging genes linked to immune regulation. Oligodendrocyte precursor cells to oligodendrocyte transitions revealed enrichment shifts from psychiatric disorders to AD during maturation. Excitatory neurons followed an inside-out developmental gradient, with early enrichment in psychiatric disorders, while inhibitory neurons exhibited subtype-specific temporal variability, with disease associations emerging early in life.

Conclusions: Our findings reveal cell-type-specific developmental and aging patterns in the DLPFC, linking lifespan trajectories to neurological and psychiatric traits. These insights provide a reference framework for understanding neurodevelopmental and neurodegenerative processes.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Submit your abstract here:

Remapping social stress with empathy-driven social buffering

Hyoseon Oh, Romain Durand-de Cuttoli, Lyonna F. Parise, Kenny L. Chan, Rachel L. Fisher-Foye, Scott J. Russo

Background: Social traumas, such as workplace bullying or school violence, are leading causes of many neuropsychiatric disorders including major depressive disorder (MDD). Although MDD is one of the leading global health issues, current medication-based treatments often provide only temporary relief and come with side effects, highlighting the need for innovative therapeutic approaches. Here, we study the impact of "empathy-driven social buffering," where positive interactions between individuals of similar stress status mitigating depression-like
phenotypes, with the overarching goal to uncover new therapeutic avenues. In Dr. Russo's lab, I will study the mechanisms by which empathy-driven social buffering reverses behavioral deficits following exposure to chronic social defeat stress, a mouse model for depression. We will further validate our findings in our clinical cohorts.

Methods: Specific aims and methods include: 1) establishing an empathy-driven social buffering paradigm in male and female mice, 2) identifying brain regions involved in social buffering using tissue clearing and whole brain imaging, and 3) determining specific cell types and circuits through virus tracing, neuronal manipulations, ex vivo electrophysiology and in vivo fiber photometry.

Results and Conclusions: Our preliminary data demonstrate that social buffering between similarly stressed mice restores impaired sociability, highlighting the role of empathy-driven interactions in recovery. This study will identify the neural circuits underlying empathy-driven social buffering, offering novel insights into therapeutic strategies for MDD.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Submit your abstract here:

“Alternative fuels to restore brain integrity amidst mitochondrial deficits”

Background: Mitochondrial defects commonly underlie both neurodevelopmental and degenerative disorders of the brain, often resulting in severe, progressive, and frequently lethal neurological conditions. Nutrient-based interventions are emerging as a promising strategy to mitigate, slow, or even prevent neurological deficits in such diseases. Pyruvate dehydrogenase deficiency (PDHD)—one of the most prevalent mitochondrial disorders—exemplifies this scenario by manifesting both neurodevelopmental and neurodegenerative features, frequently culminating in early mortality. Yet, it remains particularly amenable to dietary therapies due to its direct link with nutrient metabolism. Using multimodal imaging, we identified two metabolic pathways in this condition that—when supported by specific nutrients—preserve neuronal viability, promote brain growth, and extend lifespan.

Method: We used conditional knockdown Pdha1hGFAP mice as a model of human PDHD. Neurodevelopmental deficits and pathological progression were assessed through histological analyses. Metabolic deficits were characterized using MRI, MRS, hyperpolarized MRI, FDG-PET, and 13C tracing, both before and after dietary interventions. We subsequently evaluated survival, neuropathology, and motor performance to determine the therapeutic impact of these interventions.

Results: Pdha1hGFAP mice exhibited microencephaly, ataxia, and shortened lifespan. Multi-modal imaging revealed impaired glucose oxidation and the activation of two pathways that sustain Krebs cycle activity: acetyl-CoA synthesis and the propionate–succinyl-CoA axis. We administered a modified ketogenic diet supplemented with propionate to enhance acetyl-CoA and succinyl-CoA production, respectively. This regimen, for the first time, mitigated neuronal loss and reactive astrocytosis, improved motor function, and extended survival in PDHD mice.

Conclusions: Comprehensive metabolic analysis in a mouse model of PDHD highlights the therapeutic potential of harnessing alternative metabolic pathways to combat mitochondrial dysfunction and the resulting neurological phenotype. Similar strategies may benefit other neurological diseases rooted in mitochondrial defects, underscoring the potential of targeted dietary interventions to improve clinical outcomes.

2025 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Submit your abstract here:

Assessing the Activation Patterns of D1- and D2-Receptor Expressing Neurons In the Ventral Hippocampus Regarding Stress and Learning

Jacob Abroon, Veronika Kondev, Brian Kipp, Adam Ripp, and Eric J. Nestler

Background: Understanding the role and function of dopamine within the central nervous system (CNS) can provide greater insight into the overall influence of this neurotransmitter within the brain as the functions of several brain regions. It has been well established that dopamine exhibits functions related to emotion, learning, and reward-seeking within the CNS, and the type of dopamine neuron, specifically dopamine receptor type-1 (D1) and type-2 (D2), regulates the function of dopamine within the specific cell. Although the roles of these receptors have been studied extensively within the striatum, where they are densely located, the roles of the D1 and D2 receptors within the ventral hippocampus (vHPC), a region responsible for emotion-related memory and anxiety, have been relatively unexplored.

Methods: This study aims to uncover the activation patterns of D1 and D2 receptor expressing neurons within the vHPC by subjecting experimental mice to situations of stress, fear, and learning. The study uses a multitude of different procedures, namely conditioned place preference (CPP), footshock, and optogenetics, in order to gain a holistic understanding of the roles of D1 and D2 receptors.

Results: Our findings shed further light on the role of D1 neurons in the vHPC. In spatial-awareness protocols such as CPP, D1 neuron inhibition may be involved in establishing this visual understanding, and in fear-inducing environments such as footshock, D1 neuron activation may be utilized in establishing the neural relationship between a tone and footshock.

Conclusion: This study encourages further examination into the role of these specific neurons and how they might behave differently. Afterwards, we will seek to understand the activity patterns of different sub-types of dopamine receptor neurons.

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Submit your abstract here:

TITLE: Investigating the Neural Encoding of Reward Prediction Errors and Anhedonia using 7-Tesla MRI

Jacqueline M. Beltrán, Marishka M. Mehta, Grace Butler, James W. Murrough, Angela Radulescu, Laurel S. Morris

BACKGROUND: Anhedonia, a core symptom of Major Depressive Disorder (MDD), is associated with treatment resistance and mediated in part by dopaminergic projections from the ventral tegmental area (VTA). VTA dopamine neurons encode reward prediction errors (RPEs) that guide learning and behavior via projections to the prefrontal cortex (PFC), nucleus accumbens (NAc) and basolateral amygdala.

METHODS: N=74 (37 Healthy, 37 MDD) participants completed a probabilistic instrumental learning task during ultra-high field 7T functional MRI, an image resolution that previously demonstrated VTA network changes in MDD undetectable at 3T. During the task, participants chose between pairs of stimuli to maximize rewards and minimize losses. Behavioral data was fitted to a Q-learning algorithm within a hierarchical Bayesian framework to explore RPE encoding in relation to anhedonia.

RESULTS: There was a significant reduction in learning rates during reward trials ($W=910$, $p=0.0281$), but not loss trials, in MDD participants compared to controls. RPE encoding was reduced in the NAc ($W = 882$, $p= 0.033$) and ventromedial PFC (vmPFC) ($t(72) = 3.0265$, $p = 0.003$), in MDD compared to controls. Reduced NAc activity during learning was associated with anticipatory ($\rho = 0.260$, $p = 0.0253$) and consummatory anhedonia ($\rho = 0.257$, $p = 0.0274$). A separate model revealed that reduced RPE encoding in vmPFC was specific to loss trials in MDD ($t(72) = 2.07$, $p = 0.0418$) suggesting disrupted learning from a negative context is mediated by vmPFC.

CONCLUSIONS: The present findings suggest MDD participants exhibit impaired learning and worse anhedonia with reduced RPE encoding in the NAc.

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Submit your abstract here:

Bi-modal control of the stress response by the medial amygdala

Jamie R.E. Carty, Richard O'Connor, Paul J. Kenny, Sarah A. Stanley

BACKGROUND

Response to environmental stressors is evolutionarily necessary for survival. This response includes and essential bimodal and rapid mobilization of glucose and initiation of escape behavior. Sensory stress signaling converges on the medial amygdala (MeA), which sends stress-relevant input to the ventromedial hypothalamus (VMH), responsible for the regulation of metabolic processes, and to the bed nucleus of the stria terminalis (BNST), an anxiolytic-behavior related center. Taken together, we hypothesize that threat exposure activates the MeA to initiate stress-induced hyperglycemia via circuits involving the VMH and escape-related behavior via circuits involving the BNST. Lastly, these circuits and corresponding behaviors involving the MeA projections are encoded in the ventral hippocampus and can be re-initiated when exposed to the same context.

METHODS

Using fiber photometry in the MeA-VMH and MeA-BNST projections, we exposed mice to sensory stressors to measured changes in population activity. Using optogenetics, we activated the MeA-VMH neurons to examine the effect on glucose and activated the MeA-BNST neurons to examine the effect on escape behaviors. Using contextual fear learning, we observed changes in neural activity, changes in glucose, and escape behavior.

RESULTS

MeA neuronal projections are activated by stress. MeA-VMH activation increases circulating blood glucose. MeA-BNST activation increases escape-like behavior. When re-exposed to a stress environment, a ventral hippocampus-MeA-VMH/BNST projection is re-initialed, resulting in a glucose and escape response.

CONCLUSION

MeA-VMH neural activity drives glucose mobilization and MeA-BNST neural activity spikes in drives escape-like behavior in response to stress. These circuits are reinitiated in the same stress environments, as encoded by a ventral hippocampus-MeA projection. These data suggest that the MeA is a hub for the processing of, the response to, and the encoding of environmental stressors.

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Submit your abstract here:

Title: GiGA1, a Selective GIRK1 Potassium Channel Activator, Reduces Ethanol-dependent Behaviors in Mice

Authors: Jaume Taura, Arianna Marrazzo, Candice Contet, Max Kreifeld, Paul Slesinger

Background: Alcohol use disorder (AUD) is a significant public health issue with limited pharmacological treatment options. Ethanol directly modulates multiple ion channels, including G-protein-activated inwardly rectifying potassium (GIRK) channels. Activation of GIRK channels reduces neuronal excitability, suggesting a potential role in modulating alcohol-related behaviors. However, no FDA-approved treatments specifically target GIRK channels. Here, we investigate GiGA1, a selective GIRK1-containing channel activator, as a potential therapeutic agent for treating AUD.

Methods: To assess the effects of GiGA1 on ethanol-related behaviors, we used two preclinical models: conditioned place preference (CPP) and voluntary ethanol consumption in a drinking-in-the-dark (DID) two-bottle choice paradigm (2BC-DID). Locomotor activity was measured during ethanol-CPP conditioning sessions, and ethanol intake, preference, and blood alcohol concentration (BAC) were analyzed in the 2BC-DID paradigm. Additionally, we compared GiGA1's effects with Baclofen, a GABAB receptor agonist used off-label for treating AUD. Finally, brain-wide cFos mapping was conducted to examine GiGA1's impact on neuronal circuits involved in ethanol's stimulatory effects on neuronal activity.

Results: GiGA1 pre-treatment prevented ethanol-CPP in both male and female mice and mitigated ethanol-induced locomotor stimulation in females. In the 2BC-DID paradigm, GiGA1 significantly reduced voluntary ethanol intake and BAC without affecting water consumption. Compared to Baclofen, which reduced ethanol intake but did not block ethanol-CPP, GiGA1 exhibited a broader impact on ethanol-related behaviors. cFos analysis revealed that GiGA1 reversed ethanol-induced activation in key brain regions associated with AUD, including the central amygdala (CeA), paraventricular thalamus (PVT), and Edinger-Westphal nucleus (EW). Together, these results show for the first time that targeting GIRK1 channels could form the basis of a new treatment for AUD.

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Submit your abstract here:

Chronic social defeat stress

Jaylen Hernandez, Rachel L. Fisher-Foye, Romain Durand-de Cuttoli, Scott J. Russo

Background: One in eight people around the world live with a psychological disorder with the most major ones being Anxiety and Depressive disorders. Chronic stress is a significant risk factor for developing psychiatric disorders. In order to effectively study these disorders we use the Chronic Social Defeat Stress (CSDS) paradigm as a model for psychosocial stress in mice and the Social Interaction test (SI Test) to determine if the mice are socially avoidant.

Methods: CSDS consists of an aggressive and aggressive non-aggressive mouse of different breeds. Every day over the course of 10 days the mice are placed in the same section of a large mouse cage for 10 minutes where the aggressor brawls with the non-aggressor, inducing stress within the non-aggressor. After the 10 days of CSDS, the SI test is done where the non-aggressor is placed within a large arena, threatened by the presence of an imprisoned non-aggressor. Using a computer software we track the behavior and movements of the chronically stressed mouse and classify them as either susceptible or resilient depending on their social interactions or the lack thereof.

Results: 65% of our stressed mice spent less time in the interaction zone of their arena meaning they were termed as our susceptible mice. The other 45% of our stressed mice who showed no signs of social avoidance were termed resilient.

Conclusions: The majority of our stressed mice consistently revealed social avoidance behaviors during the SI test. The analysis of social deficits caused by chronic stress enables us to dig deeper into the molecular and cellular processes of the effects of chronic stress.

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Submit your abstract here:

Title: Mother-Infant Bonding and Maternal Depression: Impacts on Child Behavioral and Neurodevelopmental Outcomes

Authors: Jazmine Chavez, Aisha Said, Rushna Tubassum, Marco Rizzo, Veerle Bergink, Anna-Sophie Rommel

Background: The COVID-19 pandemic disrupted daily life, including the child-rearing experience and mental health. While mother-infant bonding is known to influence a child's emotional and behavioral outcomes, it is unclear whether maternal postpartum depressive symptoms impact this relationship. Behavioral development is linked to future physical and mental health. Understanding these associations is essential for informing public health policies and identifying children who could benefit from early targeted interventions.

Methods: Our study focused on children aged 2-4 years old to investigate the relationship between mother-infant bonding, maternal postpartum depressive symptoms and child behavioral outcomes. We used the following validated tools: the Mother-to-Infant Bonding Questionnaire (MIBQ), Edinburgh Postnatal Depression Scale (EPDS), the Child Behavior Checklist (CBCL), and the Social Responsiveness Scale (SRS). Participants (n=255) were drawn from the Generation C Study, a prospective pregnancy cohort in NYC. Linear regression models were employed to examine the relationships between MIBQ and CBCL as well as MIBQ and SRS. EPDS was included as a moderator. We controlled for maternal age, maternal education, race/ethnicity, and history of mental illness.

Results: Our findings revealed significant associations between mother-infant bonding, internalizing (β=0.11, p=0.05), externalizing (β=0.12, p=0.05) and social impairment (β=0.03, p=0.03). Depressive symptoms did not significantly moderate the associations between MIB score and predicting CBCL (p=0.6) or SRS (p=0.8).

Conclusions: We found that weaker mother-infant bonds were associated with poorer neurodevelopment, but that this association was not impacted by maternal depressive symptoms postpartum. While maternal mental health should be addressed for the wellbeing of both the mother and the child, our results suggest that a strong mother-infant bond may be beneficial even in the presence of maternal depressive symptoms.

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Submit your abstract here:

Diminished intrinsic neural timescales in anterior cingulate cortex is a convergent marker of anxiety and depression in adolescents

Jenna Jubeir, Kenneth Wengler

Background

Preclinical models of depression and anxiety have shown reduced dendritic arborization in the anterior cingulate cortex (ACC) and hippocampus, suggesting reduced recurrent excitation. Intrinsic neural timescales (INT) have been theoretically linked to recurrent excitation and can be measured using resting-state fMRI. Shorter INT have been observed in treatment-naïve adolescent depression. However, INT in adolescent or adult anxiety, and comorbid anxiety and depression, have not been explored.

Methods

Resting-state fMRI data were analyzed from 136 adolescent patients with depression and/or anxiety and 62 controls from the BANDA Project. INT maps for 379 brain regions (HCP-MMP1.0) were estimated using guidelines by Goldberg et al. (Imaging Neuroscience, 2024). Depression and anxiety symptom severities were assessed using the RCADS. Linear regressions were used to investigate relationships between regional INT and three phenotypes: (1) patient vs control group (diagnosis); (2) depression severity; and (3) anxiety severity. Results were analyzed for convergent effects across the three phenotypes and permutation testing was used to minimize risk of false positives.

Results

After Bonferroni correction, no individual regions had significant effects of diagnosis, anxiety severity, or depression severity. The right ACC was the only region with convergent effects: shorter INT related to diagnosis, depression severity, and anxiety severity (all $t < -2.00$, $p(\text{uncorrected}) < .05$; set-level $p(\text{permutation}) = 0.0026$).

Conclusions

We identified that shorter right ACC INT convergently related to diagnosis, anxiety severity, and depression severity in adolescents. Reduced recurrent excitation in the ACC may serve as a neural substrate underlying both anxiety and depression, potentially explaining high levels of comorbidity and overlapping symptoms.

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Submit your abstract here:

Novel experience-driven cortical activity and transcriptomic alterations in a mouse model of autism

Lukin, Muñoz-Castañeda, Iatrou, Garcia-Forn, Dierdorff, Wang, Daskalakis, Wu, De Rubeis

Altered cortical circuits have been strongly linked to autism spectrum disorders (ASD). Mutations in DDX3X cause DDX3X syndrome, a neurodevelopmental condition often co-morbid with ASD. Ddx3x+/- female mice have abnormal neocortical development and present abnormal behavior in open field exploration (OF). Using this validated genetic mouse model of autism, I investigated the gene activity-dependent changes underlying ASD-related alterations and the potential for specific circuit manipulations to ameliorate maladaptive behaviors.

We 3D-mapped brain neural activity after a 10min Open Field (OF) exploration task in Ddx3x+/- female mice, combining iDISCO technique, Fos immunostaining and light-sheet microscopy to identify affected regions influencing abnormal behaviors. Ddx3x+/- mice exhibit a distinct pattern of neuronal activation upon OF experience compared to a Ddx3x+/+ control mice with specific network interactions. Notably, enhanced neural activation is observed in different regions of the cortex including the retrosplenial cortex (RSC), a structure involved in spatial information processing. To elucidate the role of this region and to explore the potential benefits of manipulating this circuits in the Ddx3x+/- mice, I employed chemogenetics using stereotaxic injections of inhibitory DREADDs in this region before OF. In addition, I am approaching dendritic spines changes after behavior in both genotypes, and I am conducting transcriptomics analysis to identify the molecular signature altered in Ddx3x+/- mice in response to experience, with the goal of identifying potential molecular targets that can help to elucidate the cellular mechanisms underlying this behavior.

Our research reveals critical cortical regions involved in the aberrant OF spatial exploration in Ddx3x+/- female mice, shedding light on the complex interplay between genetics, neuronal activity and brain function. Notably, these findings identified promising targets for malleable interventions, offering avenues for therapeutic development.

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Submit your abstract here:

Stress promotes peripheral immune interactions at the brain endothelium.

Johana Alvarez, Flurin Cathomas, Hsiao-Yun Lin, Lyonna F. Parise, Kenny L. Chan, Aarthi Ramakrishnan, Molly Estill, Rachel L. Fisher-Foye, Scott J. Russo

BACKGROUND: Chronic psychosocial stress is a significant risk factor for the development of stress-associated psychiatric disorders, which have increasing worldwide prevalence. Pre-clinical and clinical studies link peripheral immune system alterations to stress-related disorders, demonstrating elevated levels of proinflammatory immune cells and cytokines in circulation. Critically, blood-brain barrier (BBB) endothelial cells interface directly with immune cells and their released factors. Current research highlights region-specific differences in brain endothelial permeability and immune cell migration following chronic psychosocial stress. A causal mechanistic understanding of how these changes occur in stress-responsive brain regions, including the nucleus accumbens (NAc), is not fully demonstrated.

METHODS: We collected endothelial cell mRNA from the NAc of male mice following chronic social defeat stress (CSDS) using translating ribosome affinity purification. Differential gene expression analysis between stress-susceptible, resilient, and control animals was completed in R using DESeq2, while gene set enrichment analysis was completed using Enrichr and Ingenuity Pathway Analysis. We validated genes associated with immune cell migration and permeability via RNAscope and quantitative PCR following endothelial cell magnetic-activated cell sorting.

RESULTS: CSDS strongly affects NAc endothelial cells of stress-susceptible mice, displaying greater differentially expressed genes than 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. We determine that the inflammation-associated adhesion molecule, junctional adhesion molecule 3, is upregulated in stress-susceptible mice.

CONCLUSIONS: Current work aims to virally manipulate the expression of genes related to immune cell recruitment to the endothelium and BBB permeability. This work will uncover unknown regional differences in endothelial cell communication with the immune system following chronic stress.

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Submit your abstract here:

Aggressive cancer cells induce DRD4 expression in neurons increasing neuronal hyperactivity and synaptic remodeling

Jonathan Barra, Natalie Suhy, Cristina Megino-Luque, Ruiqi Hu, Diogo Ribeiro, William Janssen, Allison Sowa, Daniela Di Martino, Martin Kampmann, Anne Schaeffer, Deanna Benson, Samuele G. Marro, Joel W. Blanchard and Jose Javier Bravo-Cordero.

Background: The neuronal microenvironment influences tumor progression and dormancy. We investigated how proliferative versus dormant cancer cells modulate neuronal activity and identified dopamine receptor D4 (DRD4) as a key regulator.
Methods: Human-derived iPSC neurons (iNeurons) and multi-integrated brain organoids (miBrains) were co-cultured with proliferative (T-HEp3) and dormant (D-HEp3) as well as reawakened (R-HEp3) squamous cell carcinoma cells. Neuronal activity was assessed via multi-electrode array (MEA) recordings, synapsin puncta quantification, PSD95/VGLUT1 clustering, and electron microscopy. Primary mouse neurons were co-cultured with proliferative (D2A1) and dormant (D2.0R) mammary carcinoma cells, and human iNeurons were exposed to conditioned media (CM) from proliferative and dormant triple-negative breast cancer models. RNA sequencing of iNeurons treated with HEp3 CM identified potential regulatory pathways and DRD4 inhibition was tested pharmacologically.
Results: Proliferative and reawakened HEp3 cells, but not dormant cells, increased neuronal activity, inducing synaptic changes in miBrains and iNeurons. MEA recordings confirmed this in primary mouse neurons co-cultured with proliferative versus dormant mammary carcinoma cells. RNA sequencing revealed DRD4 upregulation in iNeurons treated with CM from proliferative and reawakened HEp3 cells but not dormant cells. DRD4 inhibition reduced neuronal activity and prevented cancer-induced neuronal hyperexcitability.
Conclusions: Proliferative cancer cells enhance neuronal activity via DRD4 signaling, a phenomenon observed across multiple tumor models. DRD4 upregulation correlates with neuronal hyperactivity, suggesting a role in metastatic progression. Targeting DRD4 may offer a strategy to disrupt tumor-induced neuronal remodelling and prevent metastatic reawakening.

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Submit your abstract here:

Title: A role of juvenile social touch on social behavior development in mice

Authors: J. Saez*, A. Kawatake-Kuno*, J. Riceberg, H. Morishita

Background: Social experience during one's development plays a significant role in the shaping of social functioning. Numerous studies have demonstrated that early social isolation has a detrimental impact on social development. In mice, we have found that juvenile social isolation (JSI) between p21-35 induces social withdrawal in males—characterized by a continued avoidance of stimulus mouse investigation. In contrast, adult isolation shows a limited effect—suggesting that there is a sensitive period for social development. However, it remains unknown which specific aspects of social experience during this window causes excessive social withdrawal. In this study, we test the hypothesis that the absence of affiliative tactile interactions during the sensitive window is a significant factor that triggers social withdrawal.

Methods: To assess the impact of the deprivation of affiliative touch during JSI on social processing, we took pair-housed mice and inserted a clear partition that allowed for all sensory modalities, with the exception of physical touch, from ages p21-35. To test if an affiliative touch-like intervention could rescue social withdrawal, we performed a gentle-stroking interaction to isolated mice during JSI and then assessed their social behavior.

Results: We found that the partition housing was enough to induce social withdrawal behavior in subject mice on a level similar to typical JSI models. We also found that gentle stroking between p28-35 significantly reduced social withdrawal in JSI mice.

Conclusions: These experiments both indicate that lack of tactile interactions during the juvenile period is causally linked to excessive social withdrawal in JSI mice. In the future, we aim to examine the impact of affiliative touch more specifically by manipulating the peripheral neurons that process the sensation of social touch.

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Submit your abstract here:

Intra-arterial Deoxyribonuclease therapy improves stroke outcomes in aged mice with acute ischemic stroke

Junxiang Yin, Michael Wu, Jennifer White, Ellie StClair, Michael F. Waters

Background: Stroke is the third-leading cause of mortality and disability in the world. More than 30% of acute ischemic strokes (AIS) are large vessel occlusion (LVO), contributing to 95% of mortalities and 62% of long-term disability in stroke patients. Endovascular thrombectomy (EVT) is the standard of care for LVOs. Despite there being high rates of recanalization with EVT, more than half of patients still suffer poor outcomes and low micro-perfusion, a phenomenon coined futile recanalization. Neutrophil extracellular traps (NETs) are a major factor of microvascular hypoperfusion after stroke. Deoxyribonuclease I (DNase) targeting NETs exhibited a neuroprotective effect in young mice with AIS. This study explored a novel direct intra-arterial administration of DNase therapy and its effect in aged mice with AIS.

Method: AIS was induced in aged C57BL/6 mice (20±1 months old) followed by reperfusion and immediate, intra-arterial DNase administration via the internal carotid artery. Cerebral blood flow, neurological function, cerebral infarct volume, and NET markers were examined.

Results: Direct intra-arterial DNase therapy significantly increased cerebral blood flow, reduced neurological deficit scores, increased the latency to fall in wire hang test, reduced cerebral infarct volume, and decreased neutrophil and NET count in both the parenchyma and micro vessels in aged mice with AIS compared with age-matched, vehicle controls.

Conclusion: Our data is the first to demonstrate that successful, direct intra-arterial DNase therapy provides more efficient cerebral reperfusion and better outcomes after recanalization during the treatment of large vessel occlusion in aged mice. This study provides evidence for the potential clinical application of catheter delivered intra-arterial DNase therapy post-recanalization.

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Submit your abstract here:

Using Distance-Scaled Imprecision to Moderate the Pace of Belief Updating in Reversal Learning

Justice Simonetti, Alexa Krugel, Laura Berner, Vincenzo Fiore

Background: Human beings must make decisions in uncertain and dynamic environments. In behavioral research, probabilistic reversal-learning tasks are employed alongside belief-updating algorithms to uncover hidden variability within the decision-making process and to infer the computational mechanisms that underlie adaptive behavior. Standard formulas, such as the Rescorla-Wagner equation or Bayes' Theorem, provide an excellent starting point but fail to dynamically adjust the pace of belief updating. As a result, they often produce over- or under-precise predictions, particularly in contexts where incoming data is transient and should not commensurately affect predictions. Here, we demonstrate that by introducing an element of noise—scaled by the distance between the prior and the posterior within a Bayesian framework—we can greatly improve model performance on a probabilistic reversal-learning task. Additionally, the Bayesian Noise model enjoys a level of computational tractability unrivaled by more dynamic models, such as those that track volatility (e.g., the Kalman filter).

Methods: A total of 112 participants completed an online version of a three-armed bandit task lacking an explicitly quantifiable reward structure and featuring an average of one reversal per block. Choice data were analyzed using various models, including Rescorla-Wagner, a Bayesian observer, a Kalman filter, and the Bayesian Noise model, which was adapted from Findling et al.'s Weber-Imprecision model (2020). Model performance was evaluated by comparing total error and Bayesian Information Criterion (BIC) scores.

Results: The Bayesian Noise model unambiguously accounted for human behavior better than the other models described here.

Conclusion: The success of the Bayesian Noise model provides an informative heuristic for how human beings might moderate the pace of belief updating in dynamic environments—suggesting that predictive noise scales with the distance between priors and posteriors.

2025 Neuroscience Retreat

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Submit your abstract here:

Offline cortical activity is representative of task elements from spatial tasks in freely moving animals

Justin Lines, Ann Pierre Louis, 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. Understanding the role of the retrosplenial cortex may lead to elucidating the consolidation of spatial memories as well as identify a novel therapeutic target in the treatment of neurodegenerative disease.

Methods

Here, we image calcium activity from neurons in layers 2/3 of the retrosplenial cortex using Miniscopes in freely behaving animals performing various spatial learning and memory tasks such as linear track and circle track. To test the causal role of retrosplenial cortex on spatial learning and memory we use inhibitory metabotropic Designer Receptors Exclusively Activated by Designer Drugs (DREADDs; AAV8-hSyn-HM4Di-mCherry) to limit the activity of the retrosplenial cortex during spatial learning and memory.

Results

From the recordings of calcium activity, we found neuronal activity in the retrosplenial cortex corresponding to elements of behavior. Further, the inhibition of the retrosplenial cortex via pharmacogenetics, whether during task or offline following the task, we observed a trend of reduction in task performance on the circle track.

Conclusions

Retrosplenial cortex is involved in the encoding of spatial learning and memory tasks, and inhibition of the retrosplenial cortex may influence spatial learning and memory.

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Submit your abstract here:

Deciphering nociceptor neuron and NK cell crosstalk in metastatic dormant breast cancer

Kanishka Tiwary

Breast cancer is a leading cause of cancer-related deaths, often due to recurrence at distant sites like the lungs or brain. This is linked to the awakening of dormant metastatic cells, but how these cells evade immune surveillance remains unclear. An understudied factor in metastasis is the peripheral nervous system, which plays a role in sensing pathogenic infiltration to drive immune responses. However, its influence on regulating breast cancer dormant cells is not well understood.

In this study, we utilized in-vitro co-culture and in vivo dormancy models together with advanced imaging, denervation and flow cytometry, to study sensory neurons and NK cells interactions with dormant cancer cells in the metastatic lung niche. We also employed siRNA knockdown system, sensory neurite projections and ELISA to identify molecules that mediate sensory neuron – dormant cancer cell communication.

Our data reveals a bidirectional interaction between sensory neurons and dormant tumor cells in the lung. Neurite sprouting in sensory neurons increased when co-cultured with dormant disseminated tumor cells (DTCs). In mice, dormant DTCs recruited TRPV1+ sensory neurons in the metastatic niche. Mice denervated with RTX (TRPV1 agonist) reduced sensory neuron projections and CGRP levels, leading to a significant decrease in dormant DTCs and an increase in cleaved-caspase 3 positive DTCs. Additionally, mice without sensory neurons exhibited higher infiltration of natural killer cells, which showed enhanced cytotoxicity against dormant cancer cells.

We believe interaction between dormant DTCs and TRPV1+ sensory neurons support dormant cell survival in the lung by inhibiting the cytotoxic activity of NK cells. Our study provides a novel understanding of how sensory neurons influence the role of the body’s immune system. This could lead to innovative treatments that reduce the risk of metastatic recurrences by eliminating dormant DTCs.

2025 Neuroscience Retreat

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Submit your abstract here:

TITLE: Molecular Underpinnings of Cannabidiol's Anti-Anxiety Effects

AUTHORS: Katie Lynch, Jacquie Marie-Ferland, Alex Chisholm, Yasmin Hurd

BACKGROUND: The first-line treatment for generalized anxiety disorder is SSRI's, but these are not recommended for those recovering from opioid use disorder (OUD), a population that is highly susceptible to developing anxiety. A clinical research trial led by the Hurd lab previously determined that cannabidiol (CBD) significantly decreased both drug cue-induced anxiety and cravings in people with OUD. This cue-induced anxiety reduction with CBD was replicated in rodents. The molecular mechanisms underlying the effects of CBD on this phenotype are unknown.

METHODS: 48 adult male Long Evans rats (12/group) were exposed to three days of foot shocks. Half were exposed to a cue with the shock. Rats were injected with CBD or vehicle (10 mg/kg, IP) one hour before behavioral assessment in both the light/dark paradigm and open field with cue present. RNA-sequencing was carried out on the nucleus accumbens.

RESULTS: The cue significantly increased latency to enter lighted areas ($p=0.007$) and decreased entries into the center of the open field ($p=0.0026$), reflective of an anxiety-like phenotype. CBD instead increased the amount of time spent in the light ($p=0.0162$), an anxiolytic response. Z-score comparison of all group measures indicated a significant reduction of cue-induced anxiety-like behaviors in animals given CBD ($p=0.0028$). Analysis of RNA transcripts in cued-vehicle animals most significantly enriched for abnormal wound healing ($p=0.00006673$, adjusted $p=0.02359$), which CBD reversed. CBD additionally normalized cue-induced increases in transcripts relating to mitochondrial respiration and oxidation that correlated with behavior.

CONCLUSIONS: CBD significantly reduces cue-induced anxiety-like behaviors, additionally preventing the upregulation of transcripts linked to cellular stress. These experiments provide the foundation for further investigation into CBD's protection against anxiety-induced damage.

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Submit your abstract here:

Title: The Role of Immature Oligodendrocytes in BMP4-Mediated Neural Stem Cell Quiescence

Authors: Kavya Harish, Michelle Lu, Ally Salinas, Victoria Fertig, Kristina Sheludencko, Eric Parise, Eric Nestler, Allison Bond

Background: Neural stem cells (NSCs) in the adult hippocampus are essential for neurogenesis, maintaining the capacity for brain plasticity throughout life. During early postnatal development, NSCs enter a quiescent state, ensuring the long-term maintenance of the neural stem cell pool. The mechanisms regulating this transition from active proliferation to quiescence remain incompletely understood. Bone morphogenetic protein (BMP) signaling plays a role in maintaining neural stem cell quiescence in the adult hippocampus, but its role in the developmental transition to quiescence and its cellular source require further investigation.

Methods: Immunostaining combined with RNAscope to determine the source of BMP4 ligand in the developing and adult hippocampus. Primary NSC cultures of early postnatal hippocampal NSCs to test the effects of BMP treatment. Chronic social defeat stress paradigm to assess changes in the amount and source of BMP4 ligand in the hippocampus in the context of reduced neurogenesis.

Results: We hypothesize that developmental and experience-induced changes in BMP4 ligand expression regulate NSC quiescence in the hippocampus. Single-cell RNA-sequencing and in situ hybridization revealed that BMP4 is expressed in immature oligodendrocytes in the hippocampus. BMP4 treatment of primary NSC cultures from early postnatal hippocampus induced quiescence, indicating that BMP signaling can drive quiescence during development. Chronic social defeat stress, known to reduce neurogenesis, causes an increase in immature oligodendrocytes in the hippocampus.

Conclusions: We found that immature oligodendrocytes are the source of BMP4 ligand in the hippocampus during early postnatal development and adulthood, and that the immature oligodendrocyte population changes in size during developmental and stress-induced changes in neurogenesis. Future work will explore a direct link between oligodendrocyte-derived BMP4 and NSC quiescence.

2025 Neuroscience Retreat

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Submit your abstract here:

Title: Histamine-4 Receptor in Itch and Inflammation

Authors: Keaton Song, Zhen Wang, Rintaro Shibuya, Hisato Iriki, Xu Li, Xia Meng, Lydia Zamidar, Brian Kim

Background:
Itch is an uncomfortable sensation that triggers the desire or reflex to scratch. The most well-described form of itch is histamine-mediated, or histaminergic, itch. Histamine can activate itch-specific neural pathways to mediate the transmission of itch from the periphery to the brain. Beyond itch, histamine is also a primary mediator of inflammation in type 1 hypersensitivity responses. Antihistamines targeting histamine-1 receptor (H1R) are commonly used for atopic diseases, but they demonstrate limited efficacy in treating pruritic conditions. Recently, histamine-4 receptor (H4R) has been suggested to be involved in these symptoms but its specific mechanisms remain poorly defined. We previously reported that the cytokine IL-33 amplifies histaminergic itch by acting on mast cells. Herein, we explore the precise contributions of H4R in histamine-mediated itch and inflammation.

Methods:
Itch behavior was assessed after histamine administration in the ear skin following pre-treatment with IL-33 and the H4R antagonist JNJ7777120. Inflammation was quantified via cutaneous anaphylaxis after local histamine challenge. Thermal anaphylaxis was measured following percutaneous sensitization with MC903 and ovalbumin (OVA) followed by OVA challenge after 23 days.

Results:
Systemic administration of JNJ7777120 decreased both histaminergic and IL-33-potentiated histaminergic itch but did not affect cutaneous anaphylaxis. H4R KO mice demonstrated exaggerated anaphylactic hypothermia following OVA challenge.

Conclusions:
H4R mediates IL-33 amplification of histaminergic itch and may be protective against thermal anaphylaxis.

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Submit your abstract here:

Title: Modeling Deep Brain Stimulation for Obsessive-Compulsive Disorder in Macaques: Anterior Limb of the Internal Capsule Connectivity Mirrors Human Findings

Authors: Keondre Herbert, Satoka H. Fujimoto, Atsushi Fujimoto, Catherine Elorette, Martijn Figee, Brian E. Russ, Peter H. Rudebeck

Background:
Deep brain stimulation (DBS) is a promising treatment for patients with obsessive-compulsive disorder (OCD) who are resistant to standard pharmacological and behavioral therapies. Recent findings in humans have identified specific white matter tracts predictive of optimal clinical outcomes following DBS. Despite its clinical efficacy, the underlying mechanisms driving symptom relief remain insufficiently understood. As macaques share important neuroanatomical similarities with humans, they provide a key translational model for understanding how DBS influences OCD-relevant circuits. In this study, we use diffusion-weighted tractography in macaques to identify a DBS target that aligns with the optimal fiber pathways observed in human OCD studies, establishing a basis for investigating how DBS drives symptom relief.

Methods:
In two male macaques, we performed diffusion-weighted imaging and probabilistic tractography from seed regions implicated in human OCD DBS. We then qualitatively compared the resulting white matter pathways to the OCD response tract identified from clinical trials.

Results:
Macaque diffusion tractography seeded from the anterior limb of the internal capsule (ALIC) revealed a trajectory of fibers similar to the best target for DBS treatment of OCD. Within the prefrontal cortex, tracts projected to the ventrolateral and medial prefrontal cortex, as well as the dorsal anterior cingulate cortex. Subcortical connections included the subthalamic nucleus, and zona incerta.

Conclusions:
Our findings suggest that projections through the ALIC in macaques parallel the connectivity of the identified DBS target in humans for OCD. These results lay the groundwork for subsequent DBS experiments in macaques, following human clinical protocols, to assess the brain-wide effects of DBS, using translationally relevant neuroimaging, invasive electrophysiology, and postmortem histology.

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Submit your abstract here:

Title: Regulation of nicotine intake by peripheral sensory systems

Authors: Kevin M. Braunscheidel, Rohan Ghoshal, Mohammad Ishmam, Masago Ishikawa, and Paul J. Kenny

Background: Adverse health outcomes resulting from tobacco use disorder are a leading cause of premature death in the United States. Recent evidence from our lab implicates peripheral systems in nicotine addiction. For instance, nicotine drastically alters the transcriptome of the nodose ganglia (NG) and elevates postprandial cholecystokinin (CCK) levels in mice, similar to smokers. Here, we test the hypothesis that CCK receptors (CCKRs) in gut-innervating NG (vagal) neurons potentiates aversion signal transmittance centrally to regulate nicotine intake in mice.

Methods: Conditioned place aversion (CPA) to a periphery-restricted nicotine receptor agonist, methylnicotinium, was performed. Next, PHP.S-DIO-HM4Di was injected into TRAP2 animals that express Cre in an activity-dependent, temporally-restricted manner yielding inhibitory chemogenetic access to peripheral nervous tissue prior to nicotine CPA. We then recorded GCaMP activity ex vivo in CCKR+ NG in response to nicotine in CCKR-ai96 mice. Next, we measured nicotine intravenous self-administration (IVSA) in mice following stimulation of peripheral CCKRs with CCK-8 or inhibition with dexamethonium. In a separate cohort, CCKR+ NG were ablated via intra-NG injection of CCK-saporin prior to nicotine IVSA. Finally, mice were generated that express the diphtheria toxin (DT) receptor in CCK+ cells. These mice were injected with a custom ‘PEGylated’ DT, to ablate only peripheral CCK+ cells during nicotine IVSA.

Results: Methylnicotinium induced CPA and activated CCKR+ NG similar to a high, equimolar dose of nicotine. Increased nicotine intake resulted from systemic CCKR blockade, CCKR+ NG ablation, and CCK-producing enteroendocrine cell ablation. Conversely, stimulating peripheral CCKR signaling with CCK-8 decreased nicotine intake.

Conclusions: Peripheral actions of nicotine regulate nicotine intake due in part to their influence on CCK-releasing enteroendocrine cells and CCKR-expressing vagal sensory afferents.

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Submit your abstract here:

The impact of the young systemic environment on oligodendrocytes and OPCs in mouse models of aging and Alzheimer's pathology

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

Background: Aging results in reduced overall brain function characterized by molecular, cellular, and cognitive changes. Since aging is a major risk factor for many conditions, including Alzheimer's Disease (AD), its study offers valuable insights into AD pathobiology. One strategy for studying brain aging involves leveraging the systemic environment, which has shown that aged mice exposed to the young peripheral environment exhibit improved synaptic plasticity, reduced neuroinflammation, and improved hippocampus-dependent cognitive performance. Systemic treatment with specific youth-associated proteins has revealed similar rejuvenating potential in aged mice. While these studies have characterized such rejuvenating effects in immature and mature neurons, as well as in microglia, changes in the oligodendrocyte (OLG) lineage remain unexplored. The OLG lineage appears to be among the most responsive CNS cells to the systemic environment, but a thorough functional assessment has not been undertaken. Moreover, while recent AD studies have shown a connection between the OLG 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 immunofluorescence of brain tissue from young plasma injected mice, we studied the OLG lineage in the contexts of aging and AD pathology.

Results: Our single cell analyses show that the aged OLG lineage exposed to young blood exhibit changes in differentiation, oxidative stress pathways, growth, and migration. Additionally, in the APPNL-G-F mouse model of amyloid pathology, OLG lineage numbers increase with age, with significant changes in myelination.

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

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Submit your abstract here:

The organization of single-neuron projections from basolateral amygdala neurons to temporal lobe, frontal lobe, and subcortical structures in macaque

K. Crawford, Z. R. Zeisler, M. A. Eldridge, E. A. Murray, P. H. Rudebeck

Background: The amygdala plays a crucial role in cognition, particularly in processing emotionally salient stimuli like faces. The basolateral amygdala (BLA) projects strongly to temporal lobe structures, likely influencing this process. However, the organization of these connections at the single-neuron level remains unclear. One possibility is that individual BLA neurons branch to multiple regions within the temporal cortex, enabling synchronous and coordinated information processing along the ventral visual stream.

Methods: The recent application of multiplexed analysis of projections by sequencing (MAPseq) in macaques provides a scalable method to study single-neuron projections using barcoded mRNA. Barcoded Sindbis virus was injected into the BLA, and temporal cortex regions were dissected for analysis. We mapped single-neuron projections to the temporal cortex and explored whether these connections also branched to frontal and subcortical areas.

Results: We observed strong connectivity as well as extensive single neuron branching to anterior medial temporal regions, including the temporal polar periallocortex (TPPal), entorhinal cortex, and perirhinal cortex. Most barcoded neurons projecting to the frontal lobe or hypothalamus also branched to the temporal lobe. However, frontal and hypothalamic projections remained largely separate.

Conclusions: Our findings reveal that individual neurons in the BLA branch and project to multiple areas in the brain. The strong projections to anterior medial temporal areas, including TPPal, entorhinal, and perirhinal cortex, possibly highlight a key pathway for amygdala modulation. Branching to both frontal and temporal cortices, as well as the hypothalamus, could indicate a broader role in coordinating emotional and cognitive processes. By applying MAPseq at scale, this study provides new insights into amygdala circuitry and its functional implications in emotion and cognition.

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Submit your abstract here:

Title: How is proprioceptive activity encoded in the somatosensory cortex?

Authors: Khojasteh Z Mirza, Evan S Schaffer

Background: The dysgranular region of the primary somatosensory cortex (S1DZ) responds to proprioceptive stimulation, such as joint movements and muscle stretching. The function of S1DZ remains poorly understood, despite its crucial role in a variety of neural functions, including social behavior and gaze-independent representation of position.

Methods: Our collaborators recorded neural activity in mice performing a joystick task. After mice learned to pull the joystick for reward, joystick resistance was increased to make the reward impossible. To facilitate our interpretation of neural activity in this task, we modeled a biomechanical arm to infer joint angles, muscle stretch, and force through simulations of the task.
We hypothesize that S1DZ may encode features of arm movements. To test this, we built regression models to assess how much variance in neural activity is explained by features such as joint angles, muscle kinematics, and velocity. Because regression models assume linearity, we also train an ANN to perform the same task as S1DZ.
An alternative hypothesis is that S1DZ neurons compute movement prediction errors. To test this, we developed feedback control models and trained ANNs to perform the underlying computations, then compared calcium imaging data with ANN activations.

Results: In simple regression, movement metrics explained only ~3% of S1DZ activity, consistent with prior studies and our expectation for a more complex model. Although the best ANNs outperformed ridge regression, none explained over 8% of the variance. Our Procrustes analysis of the ANN's control loop estimation activity reveals significant promise, laying a strong foundation for further work as we refine the model.

Conclusion:
While our understanding of S1DZ encoding is evolving, our evidence so far suggests it may distinctly capture the crucial difference between estimated and actual states.

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Submit your abstract here:

Heroin Induces Marked Perturbations of the Mitochondria within the Dorsal Striatum

Kion Winston, Jeremy Sherman, Randy Ellis, Joseph Landry, James Callens, Jacqueline Ferland, Alex Chisholm, Konrad Dabrowski, Yasmin L. Hurd

Opioid abuse has continued to be a major public health crisis within the United States, contributing to the growing overdose deaths of ~100,000 people yearly. While current treatments available for opioid use disorder (OUD) have primarily focused on mitigating the maladaptive behavior associated with reward and craving, other complex phenotypes of OUD remain poorly understood. Recent studies have linked long-term heroin exposure to the accelerated proliferation of hyperphosphorylated Tau, the abnormal state of the tau protein that is a hallmark feature of disease such as Alzheimer and Huntington disease. Potential mechanisms that might facilitate the relationship between opioid use and neurodegenerative disease risk remains unclear.

To investigate this relationship, we conducted bulk RNA-sequencing on the dorsal striatum of postmortem human heroin users and matched controls. Bioinformatic analysis identified significant alterations in multiple neurodegenerative pathways which coincided with biological pathways specific for oxidative phosphorylation. Dysregulation in this mitochondrial system has been associated with the proliferation of reactive oxygen species, a decrease in ATP production, as well as the progression of neurodegenerative disease. However, the causal role opioids play in the perturbation of mitochondrial functioning remains unclear.

To further interrogate this dynamic, I utilized a well-established heroin self-administration model alongside techniques to measure expression of nuclear encoded mitochondrial gene expression as well as protein levels. Furthermore, an in-vitro cortico-striatal cell culture could model was used to assess opioid agonist effects on mitochondrial localization and overall organelle health. These approaches aim to clarify the impact on opioid exposure on mitochondrial function and its potential contribution to neurodegenerative disease progression, providing insight into the long-term neurological consequences of opioid use.

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Submit your abstract here:

Title: Chromatin accessibility patterns in peripheral blood cells as predictors of opioid dependence and recovery.

Authors: Konrad Dabrowski, Xianxiao Zhou, Joseph Landry, Keren Bachi, Yuval Itan, Bin Zhang, Yasmin Hurd

In North America, opioid use disorder (OUD) is a critical public health crisis, linked to over 80,000 opioid-associated deaths annually and an estimated $1 trillion in costs over the past decade. Chronic opioid use is associated with transcriptomic and epigenetic brain changes that drive craving and relapse, perpetuating OUD. Currently, no technique can longitudinally monitor brain epigenetic mechanisms across drug addiction phases or treatment responses in humans. However, evidence suggests a connection between blood-based epigenetic mechanisms and brain changes. Epigenetic modifications in blood have been found to mirror alterations in the central nervous system including those seen in neuropsychiatric disorders, suggesting the potential of blood-based epigenetic markers as indicators of brain-related conditions. To investigate this, we conducted an assay for transposase-accessible chromatin with sequencing (ATAC-seq) and RNA sequencing (RNA-seq) on peripheral blood mononuclear cells (PBMCs). We analyzed PBMCs from 106 controls and 170 opioid-dependent individuals, identified per DSM-IV, with subjects on either buprenorphine or methadone maintenance therapy, sourced from the NIDA Center for Genetic Studies. We report changes in chromatin and transcriptomic profiles linked to immune system dysregulation and assess the correlation with clinical measures of opioid use. The reported differentially expressed genes and accessible genomic regions could serve as potential biomarkers of opioid dependence, use, and recovery. These data provide a foundation for developing future scalable, cost-effective blood-based biomarkers to refine OUD diagnosis and support patient monitoring through recovery.

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Submit your abstract here:

Background: Adolescence is hallmarked by heightened risk-taking behavior. The neural circuitry subserving adolescent risk-taking is vulnerable to neurotoxic metals, yet few studies have examined the impact of metal mixtures on these mechanisms. We aimed to identify early-life critical windows when metal mixture exposure is associated with neurocognitive correlates of reward-based risky decision-making in adolescence.

Methods: We analyzed data from adolescents (8-14 years; 45% females) enrolled in the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) cohort in Mexico City. Weekly concentrations (21st gestational week – 43rd postnatal week) of nine metals (Mn, Pb, Cu, Li, Mg, Sn, Sr, Zn) were measured in deciduous teeth using laser ablation-inductively coupled plasma-mass spectrometry. Brain activation and behavior were assessed using a functional magnetic resonance imaging (fMRI) gambling paradigm. A generalized mixed-effects model was used to estimate risk and reward sensitivity. Functional regions of interest were defined for two contrasts: 1) High risk > Low risk decisions: right angular gyrus/inferior parietal lobule (AG/IPL); 2) Gain > No gain outcomes: left insula/rolandic operculum (INS/ROL). Time-varying associations between the metal mixture and neurocognitive correlates were assessed using lagged weighted quantile sum regression (LWQS), adjusting for age, sex, and socioeconomic status.

Results: Postnatal metal mixture exposure was associated with increased risk sensitivity ((β = 0.18 [95% CI 0.042, 0.321]). Prenatal and postnatal exposure was associated with increased reward sensitivity (β = 0.21 [95% CI 0.004, 0.408]). Postnatal metal mixture exposure was associated with reduced right AG/IPL activation during risky decision-making (β = -0.24 [95% CI -0.408, -0.067]) and increased left INS/ROL activation during reward processing (β = 0.28 [95% CI 0.094, 0.469]).

Conclusion: Early-life metal exposure influences neurocognitive mechanisms underlying adolescent risk-taking, emphasizing the importance of exposure timing in shaping neurodevelopmental outcomes.

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Submit your abstract here:

In vivo characterization of a new genetically-encoded fluorescent oxytocin peptide sensor for social behavior

L. Nahar, H. LaCourse, C. Chen, P. A. Slesinger

Oxytocin (OT) is a neuropeptide crucial for cognitive, behavioral, and social functions. Dysregulated OT signaling is implicated in psychiatric disorders such as autism, mood disorders, and substance abuse. A new genetically-encoded GFP-based GPCR sensor MTRIA-OT (Ino et al., PMID: 36138174) has been reported to detect OT in vivo. However, its ability to monitor OT dynamics in key brain regions like the VTA remains unexplored. Here, we test the hypothesis that OT may mediate temporal kinetics of brain neuronal activity as well as behavioral responses using fiber photometry measurements of MTRIA-OT fluorescence phase-locked to behavior. AAV2/8-Syn.MTRIA-OT was stereotaxically injected into the VTA of C57BL6 mice (males,1-2 month-old) and mice were used after 2-4 weeks to allow for viral expression. An optofluidic cannula was stereotaxically implanted to apply different concentrations of OT locally in the VTA while simultaneously measuring the fluorescence of MTRIA-OT. We further characterized MTRIA-OT response using OT antagonists and protease inhibitors. Exogenous OT into the VTA increased MTRIA-OT fluorescence in a dose-dependent manner, confirming expression and function of the sensor. Fiber photometry combined with social behavioral tests in freely moving mice revealed real-time endogenous OT release. Although endogenous OT release during behavior is variable, we observed that fast MTRIA-OT transients were phase-locked with climbing. To assess OT's effects on dopaminergic cells, we injected AAV9-Syn-FLEX-GCaMP7s into the VTA of TH-Cre mice. VTA DA neuronal activity increased with local OT infusion, suggesting OT either directly activates VTA DA neurons or inhibits VTA GABAergic neurons. The combined use of MTRIA-OT, optofluidic fiber photometry, and exogenous OT applications provides a powerful tool to study OT dynamics in the VTA, advancing our understanding of OT's molecular mechanisms and real-time behavioral effects.

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Submit your abstract here:

Single-Nucleus Analysis of Adult Human Olfactory Epithelium Uncovers Shared Neurogenesis Programs with the Brain

Liting Song, Claire Coleman, Clara Casey, Evelyn Hennigan , Alfred Marc Iloreta, Samuel DeMaria , Jaroslav Bendl, John F. Fullard, Pengfei Dong, Panos Roussos

Background: Neurogenesis, a critical process implicated in diverse brain disorders, is greatly diminished in the adult human brain, complicating direct investigations into its mechanistic role in disease. In the olfactory epithelium (OE), olfactory sensory neurons (OSNs) maintain homeostasis via continual neurogenesis throughout life, providing a niche to investigate neurogenesis in vivo. However, the molecular mechanisms underlying this process and its similarities to brain neurogenesis remain largely unknown.

Methods: Here, we performed single-nucleus RNA-seq (snRNA-seq) on 147,008 cells from the human olfactory epithelium of 6 adult donors. After combining with an OE dataset with 28,726 cells in 4 adults, different developmental stages of OSNs were identified, including neural precursor cells (globose basal cells, GBCs) and immature and mature OSNs. We inferred developmental trajectories and assessed the transcriptional and regulatory dynamics of OSN development.

Results: Genes and transcription factors (TFs) involved in regulating neuronal differentiation and neurogenesis were highly expressed in GBCs and early immature OSNs, but were downregulated in mature neurons. Comparative analyses of OSNs and cortical excitatory neurons showed convergence during early developmental stages, including dynamically expressed genes, biological processes, TFs, and polygenic enrichment for psychiatric disorders. In addition, highly matched expression dynamics of risk genes between OSNs and excitatory neurons further validated their convergence.

Conclusions: Overall, OSNs could act as a proxy to study the gene programs critical to neurogenesis in the human brain, providing an accessible model for investigating neurodevelopmental dysfunction in psychiatric disorders.

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Submit your abstract here:

Title: Investigating ubiquitination patterns in an optogenetic tau aggregation system

Author: Lyucheng Zou, Marcos Schaan Profes, Kurt Farrell, John F. Crary

Background: Tauopathies, a group of neurodegenerative diseases characterized by abnormally aggregated tau proteins in the brain, are poorly understood. To investigate the molecular mechanisms of tau aggregation and its downstream pathological effects, we developed a cell-based model overexpressing tau fused with light-reactive CRY2 protein (CRY2-Tau). Blue light stimulation induces CRY2 oligomerization, bringing tau proteins into proximity and promoting tau aggregation.

Objective: We aim to investigate whether our cellular model recapitulates disrupted proteostatic pathways, such as ubiquitination, commonly observed in autopsy studies of tauopathy patients.

Methods: HEK293 cells overexpressing each individual tau isoform (0N4R, 0N3R, and 0N4R P301L) with the CRY2-Tau construct were used. Following blue light activation, Western blot analysis was performed to detect tau aggregates and ubiquitin modifications.

Results: Western blot results revealed light-induced aggregation increased high molecular weight tau species across all isoforms, representing detergent-resistant aggregates. Elevated K63 polyubiquitin chain signal was also detected under aggregating conditions for all tau isoforms. A noticeable difference in the K48 polyubiquitin chain signal can be found in 0N3R tau isoforms under stimulating conditions. The P301L consistently exhibited high K48 signals regardless of aggregating treatment. Given that K63 polyubiquitination is associated with autophagic pathways and K48 polyubiquitination targets proteins for proteasomal degradation, these findings suggest a differential engagement of protein clearance pathways in response to tau aggregation.

Conclusion: Our model recapitulates human tau pathobiological markers, including tau cleavage, tau aggregation, tau phosphorylation and altered ubiquitination patterns. Notably, isoform-dependent differences in ubiquitination suggest distinct clearance mechanisms. These findings support the potential of this system for studying tau aggregation and related clearance pathways, providing insights for future drug development targeting tau aggregation.

2025 Neuroscience Retreat

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Submit your abstract here:

Title: Exploring Relationships Between Chronic Pain and Psychiatric Symptomatology in Individuals Seeking Participation in Depression Research

Authors: Mackenzie B. Hargrove, Andrew Delgado, James W. Murrough, Rachel Fremont

Background: Chronic pain (CP) and mental health disorders (MHD) are common in the general population. There is evidence supporting a bidirectional relationship between these disorders and some clinicians have conceptualized pain as also fitting within the biopsychosocial model commonly used for MHD. In this model, it has been hypothesized that early childhood traumas (ECT) may increase inflammation and sensitize pain pathways that could contribute to CP and MHD. Despite this, pain is rarely evaluated during routine psychiatric care or in psychiatric research settings. We hypothesize that individuals with CP will report elevated psychiatric symptomatology across multiple domains and that individuals with CP and mixed MHD may represent a unique population amongst individuals seeking Depression Research. We will explore whether self-reported diagnosis of CP increases the risk for depression, anxiety, or PTSD, and determine if this represents a unique phenotype for individuals with CP in a diverse sample of participants seeking out Depression Research.

Methods: Convenience sample self-report survey data, adjusted for age, sex, race, ethnicity, and household income, from the Depression and Anxiety Center Screening pilot study (n=1,168; collected between 2016 and 2024) were used to explore interactions between chronic pain and Psychiatric Symptomatology.

Results: On average, patients with CP scored 9.51 points ($p<0.001$), 10.20 points ($p<0.001$), and 8.08 points ($p<0.01$) higher on measures of depression (BDI), anxiety (STICSA), and PTSD (PCL), respectively, compared to patients without CP.

Discussion: Observable and significant differences in self-report responses between patients with CP versus patients without CP exist in this population. These findings could support that there exists a unique phenotype of CP patients with MHD that present for Depression Research.

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Submit your abstract here:

Madeline Bacon, Yosif Zaki, Denise Cai

After trauma, individuals often experience flashbacks, nightmares, and intrusive thoughts. However, the neural mechanisms that drive traumatic memories to persistently resurface remain unclear. Neuronal reactivation—the reemergence of neural activity after an initial experience—is essential for memory consolidation. While studies have examined offline neural dynamics in the hours after learning, little is known about how long reactivation continues beyond that period. This project explores the duration of reactivation after an experience and whether aversiveness alters its patterns.

We use the v4 miniature microscope to record calcium dynamics from a stable population of cells in dorsal CA1 of the hippocampus across one week. Mice were exposed to either a neutral or aversive context (foot shock). Immediately after, they were returned to their home cage for an hour of calcium and behavioral recording. The home cage recording was repeated for another four days after. On day six, mice were placed back in the original context before a final home cage recording. On day seven, all mice explored a novel context for five minutes.

Across both groups, cells that were highly active during encoding remained highly active in the initial home cage recording, with a strong correlation that weakened over days, consistent with neuronal drift and excitability changes. Both groups showed a gradual decay in reactivation across days. This is consistent with fluctuating neuronal excitabilities across a days-long timescale, where excitable neurons decrease their excitability, giving way for the lowly excitable neurons to come up in excitability. All aversive-exposed mice froze equally during recall. However, individual differences in reactivation correlated with freezing in the novel context, suggesting that greater reactivation contributes to fear generalization, while context-specific fear expression appears independent. These findings highlight reactivation as a potential mechanism underlying persistent, maladaptive fear responses following trauma.

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Submit your abstract here:

Identification of circuit involving the paraventricular hypothalamus to stress-related organs

Malia McCollum, Diego Espinoza, Jamie Carty, Sarah Stanley

Background: Stress exposure results in activation of the sympathetic nervous system releasing epinephrine and the hypothalamic-Pituitary-Adrenal (HPA) axis releasing corticosterone. These hormones increase blood glucose and modulate the immune system. The paraventricular nucleus of the hypothalamus (PVH) has been linked to regulation of stress, energy balance, and immune responses. A subpopulation of PVH neurons express tyrosine hydroxylase (TH), a rate-limiting enzyme in the catecholamine biosynthesis pathway, but their contribution to stress-induced metabolic and immune responses is unknown. We aim to examine how the PVH-TH neurons are connected to stress-related glucose and immune responses.

Methods: C57B16 mice [10-15 weeks, male and female] were stressed (30 min restraint) then perfused 60 minutes later using 10% formalin. Brains were fixed overnight. C57B16 mice [10-15 weeks, male and female] were injected with pseudorabies virus (PRV-GFP, 1-5ul) into the pancreas, spleen, liver, or epididymal white adipose tissue (eWAT) and perfused 5 days later. Brains from stressed and PRV-injected mice were sectioned using a vibratome [50µm] and immunostained for Fos [1:250], GFP [1:500] or TH [1:500]. Brain sections were imaged by confocal microscopy then analyzed using ImageJ (stress) or Imaris (PRV-injected).

Results: PVH neurons and PVH-TH neurons have increased Fos with restraint stress. Stress increased the number of TH+ neurons within the PVH. In the PVH, PRV-GFP expression overlaps with a subset of TH+ neurons showing a synaptically connected circuit to the liver, pancreas, spleen, and eWAT.

Conclusion: PVH-TH neurons are activated by stress. Stress increases TH+ neurons within the PVH, possibly through an increased expression of TH in neurons that were previously undetectable. The activated PVH-TH neurons could regulate peripheral organs to control blood glucose (pancreas, liver, eWAT) and immune function (spleen).

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Submit your abstract here:

Affective Traits as Risk Factors for Cannabis Use

Manasa Kumar & Jacqueline-Marie Ferland

Background: Despite debates around the addiction liability of cannabis, approximately 10-30% of regular users meet the criteria for Cannabis Use Disorder (CUD). CUD is highly comorbid with multiple psychiatric conditions including depression and anxiety. What is unclear from clinical data is whether these phenotypes precede or are the result of cannabis use. We leveraged a rodent model to study affective behavior including anxiety, sociability, and anhedonia-like behavior, and whether these behaviors predicted or were produced by volitional consumption of Δ9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis.

Methods: Rats were tested in open field, three-chamber sociability, and the sucrose preference tests before and after access to edibles to determine pre- and post-drug effects. After the initial behavioral screen, rats were assigned into control and THC groups. Rats were introduced first to a low-dose (0.13mg/kg) THC gelatin, and later progressed to high-dose THC (0.27mg/kg) to determine preference for a higher concentration edible.

Results We observed staggering sex differences in the consumption of both low- and high-dose THC gelatin, where male rats consumed a significantly higher amount of THC gelatin compared to female rats. There were also clear individual differences in THC consumption, with a subgroup of animals exhibiting high levels of THC consumption even after doubling the concentration of THC. High THC intake was predicted by increased exploration in the open field and social avoidance, but these behaviors were not significantly changed by drug consumption. In contrast, high consumer rats exhibited reduced sucrose preference after drug experience.

Conclusions: Our study suggests that intake is predated by novelty-seeking and social avoidance but may induce depressive-like behavior, phenotypes known to be associated with CUD. Ongoing metabolomics studies examining the molecular correlates of these phenotypes are underway.

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Neurometabolomics core application note: Energy metabolism dynamics of the developing brain

Background: The developing brain has exceptionally high energy demands and is notably vulnerable to metabolic disturbances. The cerebellum, in particular, is a highly heterogeneous region requiring robust carbon metabolism. By using isotopic tracer strategies, we can elucidate how and when different substrates fuel central metabolic pathways during early cerebellar development. Here, we describe a method for studying cerebellar development in mice and highlight key observations about energy metabolism during this critical period.

Methods: C57BL/6J mice aged from postnatal day P0 to P21 were administered one of three isotopic tracers: [U-13C]-glucose, [U-13C]-propionate, or [3,4-13C]-glucose. Cerebellum and forebrain samples were analyzed by gas chromatography–mass spectrometry (GC–MS) to quantify isotopologue distributions in glycolytic and TCA cycle intermediates.

Results: In P7 mice, [U-13C]-glucose labeling revealed high 13C enrichment in glycolytic intermediates but reduced labeling in TCA intermediates relative to P21, with TCA intermediate enrichment increasing notably by P15 and indicating a developmental shift from glycolysis toward oxidative phosphorylation. Meanwhile, [U-13C]-propionate labeling confirmed an anaplerotic role for propionate in early cerebellar development, demonstrating significantly higher 13C enrichment in succinate, fumarate, and malate in younger mice compared with older mice and the forebrain. Furthermore, [3,4-13C]-glucose labeling revealed elevated pyruvate carboxylase activity as the cerebellum matured, underscoring the growing importance of TCA cycle flux over time, particularly relative to the forebrain.

Conclusions: These findings show that the developing brain’s energy metabolism transitions from predominantly glycolytic pathways to oxidative phosphorylation around P15, with the cerebellum exhibiting greater reliance on oxidative metabolism than the forebrain. Early cerebellar development also appears to depend on alternative carbon sources to maintain TCA cycle function. Overall, these insights could pave the way for more precise therapeutic strategies targeting neurological and mitochondrial disorders in early life.

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Submit your abstract here:

Effects of ECT vs. Ketamine on Reported Quality of Life and Cognitive Functioning

Esha Talati*, Marcella Corwin*, Shely Khaikin, Andrew Delgado, Mackenzie B. Hargrove, Amit Anand, Sanjay Matthew, James W. Murrough, Rachel Fremont (*equal contribution)

BACKGROUND: Though electroconvulsive therapy [ECT] is currently regarded as the standard neuromodulatory intervention for patients with treatment resistant depression [TRD], recent studies have suggested that IV ketamine may be a non-inferior treatment option. However, ECT is correlated with greater frequency of memory impairment measured by cognitive assessment. It remains unclear how these impairments may affect subjective well-being. We aim to examine differences in end of treatment responses on quality-of-life measures [QOLS] alongside self-reported cognitive and physical functioning [CPFQ] between arms.

METHODS: Using data from the ELEKT-D trial, Mount Sinai and Baylor study sites, we obtained a sample size of 52 (n=28 ketamine, n=24 ECT) individuals who completed all study procedures. Participants were randomized 1:1 to ketamine or ECT, enduring a 3-week treatment phase and up to 6-month follow-up. We compared mean total and sub-scores from domains on the QOLS between arms, performing ANCOVA analyses adjusting for baseline values. Similarly, we compared mean total CPFQ scores using ANCOVA analyses, performing an additional comparison of modified summary scores isolating memory recall and word-finding items.

RESULTS: There was no significant difference of mean total score or sub-scores on the QOLS, mean total CPFQ scores, or modified CPFQ summary scores between arms.

CONCLUSIONS: ECT and IV ketamine are similarly efficacious in treating TRD. We found that despite objective cognitive concerns reported in ECT patients, this does not seem to be reflected in self-reported measures of quality of life and functioning. Investigating perceived side-effects can improve the ability of physicians to accurately describe expected risks and benefits of these TRD treatments.

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Submit your abstract here:

The relationship between neurophysiological responses and neuropsychological questionnaires in children aged 2-4 years: a preliminary EEG study from the Generation C cohort

Authors: 1Rizzo M, 1Tubassum R, 1Milazzo F, 1Schmitt Y, 1Rommel A-S
1Icahn School of Medicine at Mount Sinai, Psychiatry Department, New York, NY

BACKGROUND: Identifying neural and cognitive mechanisms underlying neurodevelopmental difficulties, such as externalizing, internalizing and autistic traits, is crucial for early and targeted intervention. The event-related potentials (ERPs) N2 and N170 reflect inhibitory control and face-processing, respectively, two cognitive processes that have been linked to neurodevelopment. Here, we investigate whether these ERPs are related to externalizing, internalizing and autistic traits in 2-4-year-old children.
METHODS: Electroencephalographic (EEG) recordings were obtained from 20 children (mean age±SD 41±3.0, 14 females) during a Go/No-Go task, eliciting the N2, and a face-processing task, eliciting the N170. We ran linear regression models to assess the associations between frontal N2 and parietal N170 amplitudes and parent-reported internalizing and externalizing behaviors (using the Child Behavior Checklist; CBCL), as well as autistic traits (using the Social Responsiveness Scale; SRS), adjusting for child age and sex.
RESULTS: While the frontal N2 and parietal N170 were successfully elicited in response to their stimuli, no significant associations were observed between N2 amplitude and CBCL scores (mean±SD = 6.6±6.4) ($p>0.05$), or between N170 amplitude and SRS scores (mean±SD = 28.3±22.0) ($p>0.05$). Data collection is ongoing, and an expanded analysis will be presented at the retreat.
CONCLUSIONS: In this sample, the neural markers for inhibitory control and face-processing were not linked with adverse child neurodevelopment. We will evaluate longer-term effects and expand the sample size to further assess the validity and utility of these neurodevelopmental markers.

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Characterizing JADE1-mediated modulation of tau proteostasis through optogenetics

Marcos Schaan Profes, Lyucheng Zou, SoongHo Kim, Kurt Farrell, John F. Crary

BACKGROUND: Tauopathies are neurodegenerative disorders marked by toxic tau accumulation, with no disease-modifying treatments. Understanding tau toxicity, particularly of four microtubule-binding domain repeat isoforms (4R), is crucial for therapeutic progress. Recently, we identified JADE1 as a potentially neuroprotective factor, warranting further investigation into its role in tauopathy. Recent studies have explored the use of CRY2, a protein that oligomerizes following light induction, linked to tau to study tau pathobiology. OBJECTIVE: To characterize JADE1's ability to modulate tau proteostasis leveraging a CRY2-based system for controlled tau aggregation. METHODS: We used cell free protein interaction assays to determine whether JADE1 could block tau aggregation induced by arachidonic acid. Additionally, we developed a cellular model using the light-activated CRY2 protein enabling spatiotemporal control over tau aggregation to assess aggregation kinetics and burden due to imbalances in tau isoforms and mutations. JADE1 levels were assayed with biochemistry and optogenetic tau aggregation was challenged by its overexpression. RESULTS: JADE1 blocked 4R tau aggregation in cell free assays. Prolonged light stimulation (12h) in CRY2-tau cells produced tau inclusions, confirmed to be phosphorylated and aggregated by western-blotting and immunocytochemistry. Co-overexpression of JADE1 with 4R tau reduced 4R levels but not 3R tau. Immunoblotting revealed depletion of p62, an autophagic protein that targets protein for degradation. CONCLUSIONS: This study demonstrates the feasibility of generating tau aggregates using a CRY2-tau model and highlights JADE1's significant role in tau proteostasis. These findings deepen understanding of JADE1's involvement in tau pathobiology and support its potential as a biomarker and therapeutic target.

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Submit your abstract here:

Precision Medicine's Future: Polygenic Risk Scores on the Rise

Cristian Ortega[1], Marvin Nitsem[1], Judit Garcia-Gonzalez[2], Fenley Theluscar[2], Paul O'Reilly[2]

BACKGROUND: Polygenic Risk Scores (PRS) estimate an individual's genetic predisposition to disease by combining risk alleles from genome-wide association studies (GWAS). PRS has potential applications in precision medicine by predicting disease susceptibility, guiding early interventions, and informing treatment decisions. However, a key limitation is that most PRS studies are based on European ancestry, potentially affecting health disparities.

METHODS: PRS is calculated by summing risk alleles weighted by their effect sizes from GWAS datasets. This study visualizes PRS accuracy through bar plots and high-resolution threshold comparisons. By testing various SNP thresholds, we determine which model fit best predicts disease risk.

RESULTS: The PRS bar plot highlights the most accurate prediction threshold, aligning closely with the model fit. The high-resolution PRS plot further refines accuracy by assessing multiple thresholds. Our analysis demonstrates PRS's predictive power but also underscores the need for diverse genetic datasets to improve applicability across populations.

CONCLUSIONS: PRS represents a promising tool in disease risk prediction and drug development. By identifying genetic risk factors, precision medicine can offer targeted prevention strategies. Future advancements should focus on diversifying genomic data to ensure equitable healthcare benefits.

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Submit your abstract here:

EEG-Guided Neuromodulation to Enhance Deep Sleep in Parkinson's Disease

Mason Dallegge, Sanjana Murthy, Emmanuel During, Joohi Jimenez-Shahed, Allison C. Waters

Background: Despite the overwhelmingly high prevalence of sleep disorders in Parkinson's Disease (PD), current treatment approaches fail to address the underlying neurological dysfunction driving this pathology. Disrupted sleep physiology often leads to insomnia and daytime sleepiness, which contribute to reduced quality of life and worsened prognosis, emphasizing the need for alternative treatment approaches.
Transcranial alternating current stimulation (t-ACS), a non-invasive approach to sleep neuromodulation, has shown promise in treating disordered sleep. Previous studies have demonstrated the ability of t-ACS to improve both objective and subjective sleep quality. However, this approach has not yet been explored in PD, despite the clear relevance to disease pathology.

Methods: Patients diagnosed with PD are recruited for participation in a one-week experimental design. They are provided with an at-home sleep t-ACS apparatus (Sleep WISP) consisting of a bedside nanocomputer and EEG/t-ACS capable headband. The technology detects precursors to deep sleep and then administers alternating current to entrain slow wave oscillations. The study design includes two nights of acclimatization, two nights randomized between sham-TES and experimental intervention, and two final nights of applied TES.

Results: Our preliminary steps of testing an at-home, EEG guided t-ACS system further demonstrate feasibility of application. Furthermore, we reported on objective sleep indices, such as total sleep time and N3 sleep duration, and subjective sleep indices, such as perceived sleep quality and subjective daytime sleepiness.

Conclusion: Sleep dysfunction is a driving factor in the disease progression and symptomatology of PD. The treatment of these disorders stands to benefit from continued research into novel and innovative approaches towards their resolution. Our ongoing research seeks to further investigate the feasibility and efficacy of EEG-guided t-ACS to enhance deep sleep in PD.

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Submit your abstract here:

A Locus Coeruleus to bone marrow circuit modulates hematopoiesis

Authors:

Matteo Gianeselli, Alexander Leunig, Jeffrey Downey, Abigail Glick, Ana Coelho, Gabriel Caumartin, Ziche Chen, Filip K. Swirski

Background:

Hematopoiesis, the process of blood cell production, is tightly regulated to meet physiological demands. While peripheral nerves are known to influence the bone marrow niche, the role of higher brain circuits in regulating hematopoiesis remains unclear. The Locus Coeruleus (LC) is a key noradrenergic brain region involved in autonomic and stress responses, but its potential role in hematopoiesis has not been fully explored.

Methods:

To investigate brain-to-bone marrow communication, we used polysynaptic pseudorabies viral tracing from the femur to map neural circuits projecting to the bone marrow. We specifically examined the involvement of the LC and other nuclei within the Central Autonomic Network (CAN). Additionally, we selectively ablated noradrenergic neurons in the LC with chemical and viral methods and analyzed changes in peripheral blood leukocytes and hematopoietic progenitor proliferation in the bone marrow by spectral flow cytometry.

Results:

Viral tracing revealed direct projections from the LC and several CAN nuclei to the bone marrow.
Ablation of noradrenergic neurons in the LC resulted in leukocytosis of the lymphoid and myeloid lineage in the peripheral blood.
There was increased proliferation of both committed and multipotent hematopoietic progenitors in the bone marrow.

Conclusions:

Our findings suggest that the LC acts as a central regulator of hematopoiesis. Disrupting LC noradrenergic signaling leads to heightened leukocyte production and hematopoietic stem and progenitor cell activity in the bone marrow, highlighting a potential brain-to-bone marrow regulatory axis. Understanding this neural

control of hematopoiesis could have implications for conditions involving immune system dysregulation, such as cardiovascular disorders and inflammatory diseases.

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Submit your abstract here:

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, Sunrae Taloma, Anagha Menon, Scott Nanda, Vijay Ramani, Robert Sebra, and Georgia Panagiotakos

Background: Calcium signaling is a key regulatory node linking developmental cues and intracellular responses during neural stem and progenitor cell proliferation and differentiation, and its deregulation is associated with neuropsychiatric conditions of developmental origin. During neurogenesis, numerous calcium channels undergo alternative splicing to maintain calcium homeostasis. In the embryonic cortex, we and others have described temporally regulated inclusion of disease-relevant exons of Cacna1c, encoding the voltage-gated calcium channel Cav1.2. In other tissues, coordinated alternative splicing of Cacna1c transcripts produce cell- and tissue-specific channels with distinct biophysical properties. It remains unclear, however, how full-length Cacna1c and other ion channel-encoding transcripts are spliced at a cell type-specific level during corticogenesis and how differential isoform utilization contributes to neuronal development.

Method: To elucidate ion channel splicing patterns during cortical development, we used an in utero labeling technique (“FlashTag”) to isolate RNA from enriched isochronic populations of newborn mouse cortical cells, spanning radial glia stem cells to neurons. We then performed single molecule long-read sequencing (incorporating enrichment for 62 ion channels or calcium signaling-related transcripts) in parallel with short-read RNAseq to discover the developmental trajectory of Cacna1c splicing.

Results: Our preliminary analyses reveal potential radial glia- and neuron-specific Cacna1c transcripts that we are validating by performing in situ hybridization on embryonic brain tissue using BaseScope. We will then assess electrophysiological properties and biological functions of these isoforms during cortical development.

Conclusion: Defining cell-type specific isoforms of Cacna1c and other ion channel transcripts across neurodevelopmental time will provide insights into calcium-dependent cellular processes underlying normal and dysfunctional brain development.

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A Novel Early Onset Spinocerebellar Ataxia 13 BAC Mouse Model with Cerebellar atrophy, Tremor, and Ataxic Gait

Junxiang Yin, Jerelyn A. Nick, Swati Khare, Heidi E. Kloefkorn, Michael Wu, Jennifer White, James L. Resnick , Kyle D. Allen, Harry S. Nick, Michael F. Waters

Background: Spinocerebellar ataxia 13 (SCA13) is an autosomal dominant neurological disorder caused by mutations in KCNC3. Our previous studies revealed that KCNC3 (Potassium Voltage-Gated Channel Subfamily C Member 3) mutation R423H results in an early-onset form of SCA13. Previous biological models of SCA13 include zebrafish and Drosophila but no mammalian systems. More recently, mouse models with Kcnc3 mutations presented behavioral abnormalities but without obvious pathological changes in the cerebellum, a hallmark of patients with SCA13.

Method: Here, we present a novel transgenic mouse model by bacterial artificial chromosome (BAC) recombineering to express the full-length mouse Kcnc3 expressing the R424H mutation.

Results: This BAC-R424H mice exhibited behavioral and pathological changes mimicking the clinical phenotype of the disease. The BAC-R424H mice (homologous to R423H in human) developed early onset clinical symptoms with aberrant gait, tremor, and cerebellar atrophy. Histopathological analysis of the cerebellum in BAC-R424H mice showed progressive Purkinje cell loss and thinning of the molecular cell layer. Additionally, Purkinje cells of BAC-R424H mice showed significantly lower spontaneous firing frequency with a corresponding increase in inter-spike interval compared to that of wild-type mice.

Conclusion: Our SCA13 transgenic mice recapitulate both neuropathological and behavioral changes manifested in human SCA13 R423H patients and provide an advantageous approach to understanding the role of voltage-gated potassium channel in cerebellar morphogenesis and function. This mammalian in vivo model will lead to further understanding of the R423H allelic form of SCA13 from the molecular to the behavioral level and serve as a platform for testing potential therapeutic compounds.

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Submit your abstract here:

Alcohol Use Disorder (AUD), otherwise referred to as Alcohol Abuse, is a medical condition during which patients struggle to control alcohol intake levels following previous intoxication or use. AUD is a largely understudied condition within neuroscience, and the neurological mechanisms behind it are not well known. What neurological systems are critical in Alcohol abuse? More specific knowledge on this will be critical in contributing to the development of a treatment. Oral Self-Administration was the primary method for evaluating alcohol drinking behaviors within mice in our study. Every mouse is placed in their own individual chamber which each contains an active lever, providing alcohol, and an inactive lever which does not result in a reward. Lever presses are recorded electronically. Throughout the first twelve days of the study, active lever presses in both males and females increased despite a stagnation in inactive lever presses and infusion trends. Our study reinforces previous knowledge of alcohol drinking behaviors and the addictive properties of alcohol.

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Submit your abstract here:

Title: Investigating transcription factor regulation of neural stem cell quiescence in the hippocampus
Authors: Michelle Lu, Allison Bond.

Background: Neural stem cells (NSCs) in the dentate gyrus (DG) give rise to new neurons throughout development and adulthood and become quiescent during early postnatal development. Quiescence is a hallmark of adult NSCs; however, little is known about the mechanisms underlying the transition of NSCs from proliferation to quiescence. Gene regulatory analysis of single cell RNA sequencing of NSCs during this transition revealed distinct changes in transcriptional regulator activity correlated with two sequential steps, identifying candidate regulators for each step of the transition.

Methods: We will create viral shRNA constructs to knockdown candidate transcriptional regulators (Hopx, Npas3, Nr3c1) and determine their role in developmental NSC transition to quiescence. First, we will validate our shRNA constructs through transfection of HEK293T cells to verify the high knockdown efficiency at the RNA level with qPCR. Next, we will inject shRNA-containing retrovirus directly into the mouse DG at postnatal day 1 (P1). Analysis of NSC maturation with immunofluorescence staining for proliferative markers at distinct developmental timepoints, including P7, P14, and P30, will reveal the role of each transcription factor in regulating DG NSC development and transition to quiescence.

Results: Transfection of Hopx shRNAs in HEK293T cells have shown a 90% knockdown efficiency at the RNA level. Preliminary mouse injections with trypan blue dye have demonstrated that we are able to accurately inject virus directly into the mouse DG at P1. Upon injection of Hopx-shRNA retrovirus into P1 mice, I expect to see knockdown of Hopx at the protein level and delayed neural stem cell development and transition to quiescence.

Conclusions: This project will provide insight into the molecular mechanisms that regulate the developmental NSC transition to quiescence and establishment of the adult NSC state.

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Mitochondrial complex I in cholinergic neurons forms impulsive-like behavior in diabetic mice.
Mohammad Jodeiri Farshbaf, Yacoub Alokam, Kristi Niblo, Jessica L Ables
Background: Cholinergic neurons are susceptible to degeneration in the hippocampus and basal forebrain in animal models of diabetes. Cholinergic neurons, including the sparse cholinergic interneurons (CIN) in the striatum, rely on mitochondria to provide acetyl Co-A not only for energy but also as a necessary building block for acetylcholine (ACh) neurotransmitter synthesis. Diabetes modulates mitochondrial function, physiology and distribution in the brain as well as other organs. Mitochondrial complex I (MCI) is the main hub of reactive oxygen species (ROS) generation and metabolic reprogramming of a cell depending on the type of available carbon source. In support of the premise that altered MCI activity can affect behavior, local injection of the MCI inhibitor rotenone into the nucleus accumbens (NAc) decreases social dominance in rats, while global MCI impairment led to anxiety-like behavior in mice. However, MCI's role in CIN in the NAc and the development of impulsive behavior in diabetes remains unknown.
Methods: We examined different time points after STZ-induced diabetes onset to determine how the brain responded to chronic hyperglycemia, with the limitation that mitochondria were not examined with respect to cell type or intracellular location. We also used TRAP sequencing to find out gene expression changes in the NAc and medial habenula (MHb).
Results: Our results showed that MCI expression changed in cholinergic neuron in the NAc and MHb in a sex-dependent manner in a diabetic mouse model. Studying their behavior showed at the later stage of diabetes, male mice showed impulsive-like behavior which was correlated with their chronic hyperglycemia level.
Conclusion: Diabetes influenced MCI expression in cholinergic neurons which led to impulsive-like behavior formation.

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Submit your abstract here:

Dissecting VTA circuitry with ultra-high field 7T MRI: Relationships with anhedonia and depression

Mu Li, Grace Butler, Yael Jacob, James Murrough, Laurel Morris

Animal models of depression suggest that ventral tegmental area (VTA) hyperactivity underlies depressive symptoms and anhedonia (Chaudhury et al., 2013). However, due to the limited resolution of 3T MRI, the VTA circuitry related to motivation in MDD patients and anhedonia subtypes remains underexplored. Ultra-high field 7T MRI has been proven to be more sensitive and can reveal subtle changes that cannot be detected with 3T MRI (Morris et al., 2019). Therefore, we aimed to use 7T resting-state fMRI to explore the relationship between different subtypes of anhedonia and VTA circuitry functional connectivity in MDD patients and healthy controls. We examined VTA functional connectivity with mesocortical and mesolimbic brain regions in MDD (n=40) and healthy controls (HC, n=38), and assessed the subtypes of anhedonia using the Temporal Experience of Pleasure Scale (Chan et al., 2010). The VTA exhibited hyperconnectivity with the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex, and 17 other areas in MDD compared to HC. Distinct connectivity patterns between consummatory and anticipatory anhedonia were observed. Consummatory anhedonia was associated with hyperconnectivity between VTA and the dorsomedial PFC (dmPFC), while anticipatory anhedonia showed hyperconnectivity between the VTA and mesocortical/mesolimbic regions. Network analysis (Jacob et al., 2016) further revealed that, compared to HC, the VTA in MDD exhibited hyperconnectivity and greater influence on both mesocortical and mesolimbic regions. At higher anticipatory anhedonia levels, the VTA was more influenced by the amygdala, dmPFC, and nucleus accumbens (NAc), while at high consummatory anhedonia levels, it was also affected by the hippocampus and NAc. In conclusion, VTA hyperactivity played a central role in MDD and anhedonia, and distinct connectivity patterns were identified as factors contributing to the heterogeneity of anhedonia subtypes.

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Can Resting-state EEG Predict Cocaine Cue-Reactivity in People with Cocaine Use Disorders?

Zhang Z, Bel-Bahar T, Shaik R, Greenspan H, Alia-Klein N, Goldstein R, Parvaz M

Background
Drug cue-reactivity, a key predictor of relapse in substance use disorders, is assessed via event-related potentials to drug cues, which although clinically significant, is not scalable. Contrastingly, resting EEG can be used to study brain states and is more scalable for clinical translation. Here, we applied machine learning to identify resting-state EEG features that predict cocaine-cue reactivity, and assessed their association with craving and drug use outcomes in individuals with cocaine use disorder (iCUD).

Methods
Resting-state and cue-reactivity data were analyzed from 89 iCUD. EEG sensor space was stratified into frontal, central, and parietal sensor clusters. Resting-state delta, theta, alpha, and beta bands in absolute and relative power were extracted. P3 and LPP measures of cue-reactivity were derived and one-hot encoded to classify between those showing cue-reactivity (amplitude: drug > neutral) and those who did not. Random forest was applied to the resting-state features.

Results
Relative eyes-closed delta and beta power at the frontal medial cluster yielded a classification accuracy of 0.92 for predicting P3 at the frontal cluster. Eyes-open alpha, beta, and delta relative power at the parietal cluster predicted the drug cue-reactivity in both frontal and parietal clusters at an accuracy of 0.80. The eyes-closed frontal absolute alpha power was positively associated with the onset age of cocaine use ($r=0.25$, $p_{corrected}=0.0267$). Eyes-closed delta relative power in the frontal ($r=0.24$, $p_{corrected}=0.0288$) and central ($r=0.27$, $p_{corrected}=0.0128$) cluster was positively correlated with cocaine abstinence.

Conclusions
These results show that resting-state EEG features, which predict drug-cue reactivity, are also associated with severity of and recent abstinence from cocaine use in iCUD.

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Submit your abstract here:

Characterizing the constructs of motivation: externally vs. internally generated motivation
N.Hackman1, M. Li2, P. Neukam2 , J. Beltran2, JW. Murrough2, LS. Morris2
Background: Motivation is a fundamental psychological and neurobiological process that drives goal-directed behavior. While extrinsic motivation has been well-characterized in the context of external rewards, the mechanisms underlying intrinsic motivation remain poorly understood. Deficits in intrinsic motivation are particularly relevant in major depressive disorder (MDD), where anhedonia and volitional impairments are core symptoms. This study investigates the neural correlates of intrinsic and extrinsic motivation in individuals with MDD and healthy controls using the Internal-External Motivation Task (IMT).
Methods: 75 adults (37 healthy individuals, 38 with MDD) completed the IMT during ultra-high field 7T functional MRI scanning. The IMT systematically varied reward and effort levels to assess intrinsic versus extrinsic motivation. Neuroimaging data were preprocessed using AFNI and analyzed using general linear modeling. First- and second-level analyses examined group differences in brain activation during extrinsic and intrinsic motivation conditions, focusing on key reward and effort-processing regions, including the cingulate cortex, orbitofrontal cortex, anterior insula, and sensorimotor networks.
Results: Healthy controls exhibited greater activation in reward-processing regions, such as the cingulate cortex, orbitofrontal cortex, and caudate, and deactivation in sensorimotor areas during motivated decision-making. In contrast, MDD individuals demonstrated reduced sensorimotor and cognitive control engagement but increased activation in visual, self-referential, and associative networks. This shift toward internally focused processing and compensatory cognitive strategies contributed to diminished agency perception and impaired motivation regulation.
Conclusions: These findings suggest that MDD is associated with altered motivation-related neural processing, characterized by reduced sensorimotor engagement and increased reliance on self-referential and visual processing networks. Identifying these neural mechanisms may inform targeted interventions, such as neuromodulation or effort-based training, to restore motivation in MDD and improve goal-directed behavior in psychiatric disorders.

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Submit your abstract here:

Reduced Synchronization of Neural Responses to a Drug-Related Movie in Heroin Use Disorder

Natalie McClain, Greg Kronberg, Nelly Alia-Klein, Rita Goldstein

Background: Cue-reactivity studies that assess drug-biased salience attribution—a core addiction symptom—have traditionally utilized controlled task paradigms with static images of drug and nondrug cues. However, these simplified measures may not fully capture real-world responses that occur in complex, cue-rich environments. Naturalistic stimuli such as movies can circumvent these limitations, as they elicit stronger emotional responses and engagement, and allow for direct competition between cue types within the same context. Shared responses to movie viewing can be measured with inter-subject correlations (ISC) of brain responses, reductions in which have been linked to cognitive dysfunction in psychiatric disorders but has not been studied in addiction.

Methods: Seventy-seven individuals with heroin use disorder (iHUD) and 35 demographically matched healthy controls (HC) passively viewed the first 17 min of a drug-themed movie, 'Trainspotting,' while undergoing fMRI. ISC scores were compared between groups over 450 regions with FDR correction for multiple comparisons.

Results: ISC scores were significantly reduced in iHUD compared to HC spanning many regions, with the strongest effects observed in reward-related subcortical (bilateral nucleus accumbens, p's < 0.03), cognitive control (right cingulate, p's < 0.05), and default mode network (left parahippocampal cortex, p's < 0.05) regions, followed by differences in limbic (p's < 0.05), salience (p's < 0.05), and dorsal attention (p's < 0.01) network regions (all corrected p-values).

Conclusions: We found reduced ISC scores in many canonical addiction-related brain regions during passive viewing of a drug-themed movie, suggesting addiction-related cognitive deficits may produce individualized neural responses to naturalistic stimuli. These findings demonstrate the value of naturalistic fMRI paradigms with drug-specific contexts for examining real-world neural responses to drug cues in addiction.

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Submit your abstract here:

Evaluating Synaptic Morphology in the Medial Habenula of the Diabetic Mouse Model

Authors: Natasha Rice, Samantha Brown, Adriana Mendez, Zainab Oketokoun, Mohammad Jodeiri Farshbaf, Molly Estill, Li Shen, Jessica Ables

Background: 38 million people in the US suffer from diabetes and patients with diabetes are 2-3 times as likely to develop depression compared to the general population. It has been found that habenular knock out of choline-acetyltransferase results in anhedonia like behavior. Anhedonia is characterized by the inability to experience pleasure from activities that would normally be pleasurable and is used to diagnose MDD. TRAP-sequencing data of cholinergic neurons of the medial habenula suggests that there are changes in dendritic spine morphology and the extracellular matrix in hyperglycemic groups. I hypothesize from data presented through TRAP-sequencing, there are changes in dendritic spine morphology.

Methods: ChAT-NuTRAP male mice treated with 50mg/kg STZ or vehicle were collected and utilized for TRAP-sequencing. Habenula were harvested and cholinergic neurons were immunoprecipitated for analysis. ChAT-Cre male mice underwent intracranial Brainbow AAV injections and were treated with 50mg/kg STZ or vehicle. All mice were collected at the 6-week time point.

Results: TRAP-sequencing results displayed that hyperglycemic groups experienced a downregulation of acetylcholine producing, transport and release genes. Genes involved in the regulation of neuronal growth, shape and plasticity were upregulated in hyperglycemic groups while genes involved in neurotransmission and calcium influx were downregulated. Genes associated with dendritic spine development and morphogenesis like D16ERTD472E, ARF6 and RAC1 experienced an upregulation in hyperglycemic groups. The expression of the Brainbow AAV in cholinergic neurons of the medial habenula was confirmed through immunofluorescence staining.

Conclusions: Transcriptomic data displays alterations in genes involved in synaptic plasticity and currently there are studies underway to confirm whether there are synaptic morphological changes in cholinergic neurons of the medial habenula due to hyperglycemia.

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Submit your abstract here:

Age-related loss of goal-directed learning in male mice carrying a Parkinson's gene mutation

Nathaniel H. Westneat, Alexandra R. Magee, Deanna L. Benson, George W. Huntley

Background: Cognitive abnormalities in Parkinson's are common, more prevalent in males, and include a loss of goal-directed (action-outcome) learning while habitual (stimulus-response) learning dominates. To understand the time-course and sex-specificity of these cognitive changes, we addressed goal-directed learning in young and older-aged cohorts of male and female wildtype mice and mice carrying a Lrrk2G2019S Parkinson's-associated gene mutation.

Methods: We subjected male and female Lrrk2WT(WT) and Lrrk2GS (GS) mice at young adult (P90) and older (P160) ages to a 4d, touch screen-based instrumental learning task consisting of one day of continuous reinforcement, followed by three days of random interval reinforcement schedules (RI15, RI30, RI30). Goal-directed vs. habitual responding was assessed based on sensitivity to outcome devaluation following the instrumental learning task.

Results: Young adult and older male WT mice increased their responding across the 4d learning task and were subsequently sensitive to outcome devaluation, demonstrating intact goal-directed learning at both ages. We found no significant differences by age or genotype in instrumental responding compared to GS male mice of either age. However, while the young adult GS males displayed sensitivity to outcome devaluation, the older GS males were insensitive to devaluation, indicating habitual responding. In pilot studies of females, young adult WT females made significantly greater numbers of nose-poke responses during instrumental learning compared to older WT females and GS females of either age.

Conclusion: While age did not affect goal-directed learning in wildtype mice, as male GS mice aged from P90 to P160, they shifted from a goal-directed to habitual responding strategy. This pattern is similar to human Parkinson's, suggesting this is a good model to further interrogate the circuit and mechanistic basis.

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Submit your abstract here:

Decoding neural states from frontal cortex and amygdala during decision making
Neelima Valluru, Frederic M. Stoll and Peter H. Rudebeck

Background:

Every day, we make countless economic decisions, evaluating and updating our choices based on available information. Prefrontal cortex (PFC), striatum and amygdala are thought to play a central role in this process, although how our available options are dynamically represented by neurons within these areas remains unclear. Further it is also unknown whether different regions within PFC exhibit differences in how they dynamically represent choice options.

Methods:

We used activity recorded from 16,780 neurons across PFC and limbic regions of two monkeys choosing between options with different juice reward probabilities. We used Linear Discriminant Analysis (LDA), Support Vector Machines (SVMs), and neural networks to classify the neural activity associated with each choice option, which we refer to as a “state”, on each trial and quantified how often activity was in one of these states.

Results:

We found that SVMs achieved the highest decoding accuracy compared to LDA and neural networks. Following the presentation of the options, neural activity oscillated between states but then quickly moved to represent the value of the option that subjects would choose. Further, we found that neurons from certain areas made a greater contribution to decoder performance compared to others. Subdivisions of ventral PFC and amygdala exhibited the strongest state representations, and removing these areas from the decoders significantly reduced performance.

Conclusions:

Our findings support the idea that decision-making is a dynamic process, with neural states fluctuating as we make decisions. We also show that a core set of areas in ventral PFC and amygdala appear to make a stronger contribution to signaling the choice that will be made during a decision, potentially indicating that these are critically involved in guiding decision-making.

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Submit your abstract here:

Centrosomal Chaos: Kizuna Dysregulation Alters Neuronal Structure in ASD-Linked Model

Joonho Seo, Neha Ahmed, Georgios Voloudakis

Background: The protein Kizuna, encoded by the Kiz gene, is essential for centrosome stability during cell division and cilia-related functions, both crucial for neural and cortical development. Using single-nucleus transcriptome and epigenome-wide analysis, our recent study linked neuronal Kiz overexpression to Autism Spectrum Disorder (ASD). Thus, we hypothesize that Kiz overexpression during neural development and subsequent centrosomal dysfunction increase ASD risk.

Methods: In vitro, Kizuna overexpression construct was created by placing Kiz cDNA or a scramble sequence downstream of a Chicken β-actin hybrid intron (CBh) promoter in a lentiviral backbone. Lentivirus was produced via triple transfection in HEK293T cells and used to infect primary neurons from P0 mice at DIV 1 with either pLV-CBh-Scr or pLV-CBh-Kizuna. Immunofluorescence confirmed significant Kizuna protein elevation. In vivo, P0 mice received intracerebroventricular injections of either pLV-CBh-Scr or pLV-CBh-Kizuna lentivirus. After three weeks, EGFP-positive pyramidal neurons in cortical layers II-III were analyzed electrophysiologically.

Results: Elevated Kizuna expression disrupts neurite development in primary neurons, reducing synaptic branching and extension in pLV-CBh-Kizuna-expressing cells. Moreover, anti-Kizuna fluorescence intensity negatively correlated with neurite length, emphasizing Kizuna's essential role in dendrite formation, synapse development, and cilia establishment through cytoskeletal regulation. Electrophysiological recordings in brain slices showed that neurons with elevated Kizuna expression exhibited over twice the evoked action potentials, indicating hyperexcitability. Our findings point to a simplified dendritic architecture, where reduced membrane integration lowers the threshold for repetitive firing.

Conclusions: Kizuna overexpression disrupts neural development in mice, hindering neurite outgrowth in vitro and causing electrophysiological changes in vivo. The role of centrosomal structures in ASD remains largely unexplored. Understanding how Kizuna dysregulation affects brain development may reveal therapeutic targets for ASD.

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Submit your abstract here:

Decoding Blood-brain Immune Crosstalk at the Single-Cell Level

Nicole Bussola, Isotta Landi, Eric Vornholt, Lora E. Liharska, Ryan C. Thompson, Noam D. Beckmann, Alexander W. Charney

BACKGROUND: The central nervous system has traditionally been considered isolated from the peripheral immune system due to the blood–brain barrier (BBB). However, in conditions affecting BBB permeability, such as Parkinson's (PD) or Alzheimer's (AD) disease, peripheral immune cells can infiltrate the brain, exacerbating pathology or contributing to neuroprotection. Yet, critical questions remain: Which blood cells cross the BBB? Do they undergo phenotypic adaptations in the brain? How do they interact with resident cells?

METHODS: We analyzed single-cell RNA sequencing data from 26 paired blood and brain tissue samples from the Living Brain Project at Mount Sinai. Our analysis included cell composition, differential expression, transcription factor and pathway activities (CollecTRI, PROGENy networks) to investigate adaptations of brain-infiltrating immune cells. We developed Tensor-S2R, an unsupervised pipeline integrating cell-to-cell communication techniques (LIANA), tensor decomposition (Tensor-cell2cell), and downstream analysis of ligand–receptor (LR) pairs to identify interactions between specific brain–blood cell types.

RESULTS: We found that blood-derived immune cells can cross the BBB with distinct infiltration and adaptation capacities. We uncovered a complementary program of monocyte-mediated protection and CD8+ T cell-driven inflammation in the brain, with monocytes modulating T cell activation via the Estrogen pathway. We also identified T cells gene signatures consistently present in blood samples of AD and PD patients across two external cohorts. Additionally, we discovered a dynamic signaling cascade among monocytes, neurons, and microglia that modulates both inflammation and its resolution, along with novel LR candidate pairs. Key findings were experimentally replicated in a mouse model.

CONCLUSIONS: Our study provides direct evidence of bidirectional brain–immune interplay, offering insights into molecular mechanisms that could inform non-invasive biomarker discovery and targeted therapies for neurodegenerative and neuroinflammatory diseases.

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Submit your abstract here:

Single-cell dissection of the genotype to immunophenotype relationship in glioblastoma

Nishant K Soni, Kavita Rawat, Zhihong Chen, Bruno Giotti, Dolores Hambardzumyan, & Alexander M. Tsankov

Background: Glioblastoma (GBM) is an aggressive tumor with inter- and intra-tumoral heterogeneity. The TCGA initiative identified three GBM subtypes—Proneural (PN), Mesenchymal (MES), and Classical (CL)—based on gene expression. Aberrations in genes like EGFRvIII, NF1, and PDGFRA correspond to specific subtypes. We used the RCAS/tv-a gene transfer system to generate murine GBM models (mGBM) with similar cell-of-origin to human GBM. These models resemble human myeloid cell composition and expression profiles. We aim to compare mGBM and hGBM to identify cross-species similarities and validate human target candidates in the tumor microenvironment.

Methods: High-throughput, single-cell RNA sequencing (scRNA-seq) has advanced understanding of tumor heterogeneity in GBM. To determine if there is a causal link between GBM genetic drivers and TME heterogeneity, we performed scRNA-seq, multicolor flow cytometry, and computational analysis on EGFR-, Nf1-, and PDGFB-driven GEMMs to dissect the effect of common GBM genetic drivers on the TME.

Results: PDGFB-driven tumors were more proliferative and enriched for Wnt signaling, while EGFRvIII-driven tumors showed increased interferon signaling. Nf-1 silenced tumors had higher myeloid abundance, immunosuppressive interactions, Treg infiltration, and elevated Ctla4 expression. Our analysis identified distinct tumor microenvironment (TME) cell composition, ligand-receptor interactions, and gene expression linked to GBM genetic drivers, validated by immunohistochemistry and flow analysis. Comparing with human GBM RNA-seq data, we observed similar patterns in tumors with EGFRvIII deletion, NF1 mutation, or PDGFRA amplification.

Conclusions: Our integrative approach shed light on genotype-specific TME crosstalk, cataloged the cross-species similarities/differences in GBM subtype tumor heterogeneity, and built a comprehensive resource and pre-clinical platform for identification and validation of murine- and human-relevant GBM therapeutic targets in the appropriate genetic context.

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Submit your abstract here:

Parkinson’s disease mutation LRRK2-G2019S-induced cilia defects are rescued by rab12 knockout in specific cell types in mouse brain

Authors: Nitika Kamath, Xingjian Li, Hanwen Zhu, Ji Sun, and Zhenyu Yue

Background: Mutations in leucine-rich repeat kinase 2 (LRRK2) are linked to common inherited forms of Parkinson’s disease (PD). Most PD-associated LRRK2 mutations cause an increase of the kinase activity in LRRK2, leading to neuropathologies, including primary cilia deficiency---a pathological hallmark in PD patient brains. Our previous work and others identified RAB12 as both a substrate and an activator of LRRK2 in the brain. Notably, Rab12 knockout (KO) rescues LRRK2 PD-linked G2019S-induced cilia defects in primary astrocytes. Here, we investigate if disrupting the RAB12-LRRK2 interaction alleviates cilia defects in different cell types in vivo.

Methods: LRRK2 G2019S-BAC transgenic mice were crossed with Rab12 KO mice to generate LRRK2 G2019S/Rab12 KO compound mice. Cryo-EM analysis was performed to identify the RAB12-LRRK2 binding interface. Immunofluorescent staining and image analysis was used to examine the ciliogenesis in astrocytes, cholinergic neurons, and parvalbumin (PV) neurons in the mouse dorsal striatum.

Results: LRRK2 G2019S/Rab12 KO compound mice were successfully generated. In LRRK2 G2019S mice, primary cilia were significantly reduced in astrocytes, cholinergic and PV neurons in dorsal striatum, confirming the effect of LRRK2 G2019S mutation on ciliogenesis. Interestingly, in LRRK2 G2019S/Rab12 KO compound mice, cilia reduction caused by LRRK2 G2019S was reversed in astrocytes and PV neurons but not cholinergic neurons, implicating a cell type-specific rescue effect of Rab12 KO.

Conclusions: Rab12 KO mitigates LRRK2 G2019S-mediated cilia defects in astrocytes and PV neurons but not in cholinergic neurons. Targeting Rab12-LRRK2 signaling can be explored as potential therapeutics in LRRK2-linked PD.

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Submit your abstract here:

Deciphering the mechanisms of chronic kidney disease-associated pruritus (CKD-aP)

Nobuya Abe, Zili Xie, Xueming Hu, Fang Gao, Xingliang Yang, Xinqi Guo, Yachen Yang, Hongzhen Hu

BACKGROUND: CKD-aP is a distressing condition characterized by persistent itching in patients with CKD. Despite its profound impact on quality of life, CKD-aP remains underrecognized due to its non-immediate lethality and the lack of effective treatments, leading to inadequate symptom management. While uremic toxins, immune dysregulation, neuropathy, and opioid imbalance are implicated in the CKD-aP development, the underlying mechanisms remain poorly understood. Our objective is to uncover the molecular and cellular basis underlying CKD-aP by exploring the interplay between metabolism and skin neurophysiology, with a particular focus on Merkel cell (MC)–sensory nerve interactions.

METHODS: We employ a 5-week adenine-induced CKD mouse model to assess itch behaviors. Spontaneous scratching is video-recorded, while alloknesis is evaluated using von-Frey filaments. The MC–sensory nerve complex is examined through immunohistochemistry and flow cytometry. Serum and skin metabolomes are analyzed via mass spectrometry, and key metabolites are intradermally injected to assess their role in itch responses.

RESULTS: CKD mice progressively develop mechanically evoked alloknesis without spontaneous itching or increased transepidermal water loss, indicating the absence of dry skin. CKD conditions reduce the number of MCs in skin touch domes, while touch-sensitive fibers remain unaffected. Flow cytometry confirms a decreased frequency of skin MCs in CKD mice. Chemogenetic activation of MCs in Atoh1-CreER;LSL-hM3Dq-DREADD mice rescues CKD-induced alloknesis. Metabolomic analysis reveals a greater accumulation of altered skin metabolites compared to systemic metabolites in the CKD-aP model. Repeated intradermal injections of metabolite "X" is sufficient to induce alloknesis in a dose-dependent manner.

CONCLUSIONS: CKD-derived toxic metabolites drive mechanical itching by disrupting MC-sensory nerve signaling. This study provides mechanistic insights into the role of CKD-associated metabolites in pruritus and identifies potential therapeutic targets for CKD-aP.

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Submit your abstract here:

Neurovascular Coupling and Cerebral Blood Flow Responses in Post-Concussion Syndrome: A Meta-Analysis on the Physiological Basis of Cognitive Fatigue

Padmanayakege Chamithra Rupasinghe, Nadir Abdelrahman, Krystine Ferreira

Background
Neurovascular coupling (NVC) is an important physiological phenomenon in which cerebral blood flow (CBF) supplies the activated neurons in the local region of interest but disturbances in post-concussion syndrome (PCS)/mild Traumatic Brain Injury (mTBI) are increasingly thought to contribute to cognitive fatigue. This meta-analysis collates the available evidence to gain clarity around the association between NVC dysfunction, CBF dysregulation, and cognitive fatigue within a PCS population.

Methods
We systematically reviewed 31 studies (2010-2024) from PubMed, Scopus, and the Cochrane Library. The key terms included neurovascular coupling, cerebral blood flow, cognitive fatigue, and post-concussion syndrome. The studies were included if they provided metrics for NVC/CBF that are quantifiable and included fatigue assessments that have been validated. The data were synthesized with pooled correlation coefficients, standardized mean differences, and subgroup analyses. Heterogeneity was determined using the I^2 statistics and Q statistic.

Results
This meta-analysis revealed a strong negative correlation between impaired NVC-CBF responses and cognitive fatigue severity ($r = -0.68$ [-0.75, -0.59]), with aerobic training showing greater symptom improvement than pharmacotherapy ($g = 0.94$ vs. 0.31) and military personnel exhibiting higher CBF deficits compared to athletes (OR = 1.40 [1.12, 1.75]), highlighting the central role of cerebrovascular dysregulation in PCS-related cognitive fatigue.

Conclusion
Impaired NVC and CBF dysregulation are central to cognitive fatigue in PCS/mTBI. While interventions show partial efficacy, recovery remains heterogeneous. Targeting cerebrovascular regulation (e.g., aerobic training) may improve outcomes. Future research should validate NVC as a biomarker and optimize rehabilitation protocols for at-risk populations.

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Submit your abstract here:

Investigating the Impact of LRRK2 Kinase Activity on Melanoma and Parkinson's

Pamela Del Valle, J. Javier Bravo-Cordero, Deanna L. Benson

In order to identify cellular events that drive a shared risk for melanoma and Parkinson's, we are developing a microscopy-based analysis pipeline based on tissue clearing. We investigate GFP-tagged YUMM1.7 melanoma allografts in wildtype mice and in mice carrying a knockin mutation for one of the most common genetic risk factors for Parkinson's: Lrrk2-G2019S.

In each melanoma allograft, we (1) capture intravital cellular dynamics using 2-photon microscopy, (2) clear and 3D reconstruct the same cellular elements using light sheet microscopy, and (3) immunolabel cell types of interest after reverse-clearing the tumor. Host melanocytes and sympathetic axons are visualized by Cre-dependent tdTomato expression driven by a tyrosine hydroxylase promoter.

Our preliminary data has confirmed the overall strategy works. In melanoma in both wildtype and Lrrk2-G2019S mice, tumor cell motility is modest and host melanocytes are widely recruited. At the same time, innervation patterns are notably distinct and are likely to reflect additional differences in tumor composition, observations that are being pursued.

We believe this strategy will define key events in melanoma progression and reveal how changes in cellular composition or dynamics may drive shared risk between melanoma and Parkinson's.

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Title:
MEC2 stellate cell activity facilitates type 2 dentate spikes and pathological hypersynchronous events in healthy and epileptic mice.

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Paul A. Philipsberg, Emanuel M. Coleman, Zoé Christenson Wick, Yu Feng, Kaylin M. Pimshan, 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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Submit your abstract here:

Title: Impaired early fibrotic process in CADASIL iPSC driven mural cells

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Background: Wound-healing, involves acute inflammatory response, cellular migration, proliferation and remodelling of the extracellular matrix. In health, this necessary process resolves once the wound has healed. However, in pathological states, the process continues or in instances is triggered unnecessarily, leading to fibrotic remodelling of the peri-vascular matrix. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic disorder caused by a mutations in NOTCH3, resulting in a chronic form of small vessel disease with robust fibrosis, dysregulated angiogenesis and hypoxemia. Post-mortem CADASIL brain tissue shows increased fibronectin and fibrillin-1 deposits and thicker arteriolar walls. Mural cells, including pericytes and smooth muscle cells proliferate and degenerate.

Aim: Discover molecular abnormalities in the CADASIL early wound healing process using iPSC-derived mural cells (iMCs)
Methods: Mutation carrying and isogenic iMCs were exposed to a wound healing assay for 24h. Gene expression and protein detection (IHC) were evaluated 24h after wound.
Results: NOTCH3 mutated iMCs present a faster migration in a scratch wound assay when compared to isogenic controls. Fibronectin, N-cadherin and Platelet-derived Growth Factor Receptor Beta (PDGFRb), that are involved in the initiation and effectiveness of wound healing, were increased at 24h after the wound assay in mutated iMCs.
Conclusion: The in vitro wound scratch assay is capturing in a simplified and highly reproducible fashion iMC-driven abnormalities in the wound healing process for CADASIL. Next steps will include drug screening to reverse the in vitro mutation associated molecular and cellular phenotypes observed in CADASIL iMC.

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Spectral quality and localization in MR Spectroscopy data from opioid use disorder patients

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3Johns Hopkins University, Baltimore.

Background: Opioid use disorder (OUD) is associated with neurochemical changes that can be characterized by MR spectroscopy (MRS). In OUD, chronic opioid exposure can alter metabolites such as N-Acetyl Aspartate (NAA), Choline (Cho), Creatine (Cr), and Glutamate/Glutamine complex (Glx). This study examines inter-rater reliability in measuring amygdala metabolites using MRS, aiming to contribute to more consistent and reproducible results in OUD research.

Methods: We performed single-voxel MRS in the amygdala of 16 participants with OUD maintained on methadone. The voxel was placed within the amygdala, and an expert rater assessed the quality of voxel placement on a 5-point scale based on visual inspection. MRS data processing was conducted using jMRUI. Inter-rater (two independent raters) reliability was assessed using the Intraclass Correlation Coefficient (ICC). Bland-Altman analysis was also performed to assess agreement between the two raters.

Results: 15 participants achieved good or excellent VOI localization ratings, while one was rated poorly. The histogram highlights this distribution, showing a predominance of high-quality voxel placements. The ICC analysis showed strong inter-reader reliability for metabolite measurements, with ICC values ranging from 0.662 to 0.950. Bland-Altman plots further confirm agreement between the raters. For all metabolites, mean differences were close to zero, with most data points within the 95% limits of agreement, indicating minimal bias between raters.

Conclusion: Despite minor outliers, high ICC values and minimal inter-rater bias confirmed robust reproducibility across metabolite measurements. These findings strengthen the reliability of MRS for neurochemical research in OUD, promoting standardized protocols to improve future consistency.

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Can the Neuromelanin of the Locus Coeruleus be a Biomarker for Pathological Anxiety?

Philipp T. Neukam, Sarah C. Boukezzi, Yael Jacob, Yolanda Whitaker, Priti Balchandani, Laurel Morris, James Murrough

Background: Mood and anxiety related disorders are among the most prevalent neuropsychiatric conditions in the United States. Research suggests that neuromelanin (NM) within the locus coeruleus (LC), the substantia nigra (SN) and the ventral tegmental area (VTA) is associated with those disorders. We used 7-Tesla imaging of the brainstem with a NM-sensitive contrast to segment the LC and SN/VTA area and investigate the relationship between NM and measures of pathological anxiety.

Methods: The data set consisted of patients with mood and anxiety related disorders (N=88) and healthy controls (N=61). Individual LC and SN/VTA masks were created from a brainstem ROI with 400μm³. The MASQ was used to measure anxious arousal (AA), general distress (GD) and anhedonia (AD). Correlations tested relationships between NM content in the LC, SN/VTA and the MASQ scales. Fisher's Z transformation was used to test whether the correlation coefficients were significantly different from each other.

Results: We found a significant positive correlation between AA and LC-NM ($r = .182$, $p = .033$). This correlation was stronger without HC ($r = .308$, $p = .006$). Furthermore, the correlation coefficient for LC-NM/MASQ-AA was significantly higher than the coefficient for LC-NM/MASQ-GD ($p = .013$) but not significantly different from LC-NM/MASQ-AD ($p = .374$). We didn't find a significant correlation between LC-NM/MASQ-GD, ($p = .786$) and LC-NM/MASQ-AD ($p = .129$). For SN/VTA-NM, we didn't find a significant correlation for any scale (all $p > .10$).

Conclusion: Our findings suggest that NM could serve as a potential biomarker for norepinephrine functioning and potential therapeutic target, as its presence in the LC is strongly and specifically associated with AA, which underscores the significance of LC microstructure in mood and stress-related mental disorders.

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Independent effects of neuropsychiatric/neurodegenerative PGS on brain cell-type-specific gene expression

Rachel Bercovitch,Sanan Venkatesh,Fotios Tsetsos,Deepika Mathur,Marios Anyfantakis,Jaroslav Bendl,John. F. Fullard,Gabriel E. Hoffman,Georgios Voloudakis*,Panos Roussos*

BACKGROUND:Trait-associated transcriptional changes across neuropsychiatric and neurodevelopmental disorders (NPD/NDDs) are well documented, yet the impact of aggregated genetic risk on cell-type-specific gene expression (CTSGE) remains underexplored. We investigated the association between polygenic scores (PGS) for 15 NPD/NDDs and CTSGE in 922 postmortem brain samples of European ancestry, using single-nucleus RNA sequencing (snRNA-seq) data from the PsychAD cohort.
METHODS:PGS were computed and tested against normalized gene expression across 8 cell types. Gene set enrichment analysis (GSEA) identified relevant biological pathways, while cell-cell interaction (CCI) analysis uncovered dysregulated signaling pathways linked to PGS. We evaluated the contribution of complement component 4 (C4) haplotypes—imputed at the top schizophrenia (SCZ) risk locus—to expression changes. We then compared our PGS-based findings to transcriptome-wide association studies (TWAS) and differentially expressed genes (DGE) analyses to assess overlap and specificity.
RESULTS:We detected 30 significant PGS-gene associations (FDR < 0.05) across seven cellular classes, with 70% (n=23) of these genes being downregulated. Most associations occurred in SCZ, particularly within excitatory and inhibitory neurons, highlighting these cell types as major targets of polygenic risk. Further analysis demonstrated that C4 haplotypes partially explained SCZ-related CTSGE changes. GSEA revealed axon development and neurogenesis pathways in SCZ, and receptor tyrosine kinase signaling in bipolar disorder. Notably, CCI analyses pointed to altered neuron–glia interactions. Comparing these results with TWAS and DGE showed that PGS–CTS gene expression associations were largely distinct from transcriptome-wide or differential expression changes.
CONCLUSIONS:NPD/NDD PGS associations with CTSGE are driven by aggregated genetic risk and do not overlap substantially with trait-specific DGE or TWAS findings. These results suggest that polygenic predisposition influences CTSGE through mechanisms independent from those captured by traditional transcriptome-wide or differential expression approaches.

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Submit your abstract here:

Neural Correlates of Obsessive-Compulsive Disorder Symptom Severity Across the Schizophrenia Spectrum

Rachel Brunn & Erin A. Hazlett

Background: Obsessive-compulsive symptoms(OCS) are common in schizophrenia, yet their link to cognitive flexibility remains unclear. No study has compared OCS in schizophrenia and schizotypal personality disorder (SPD). Prior work suggests frontal lobe sparing in SPD compared to schizophrenia. This study examines neurocognitive correlates of OCS in SPD and schizophrenia using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and perseverative errors from the Wisconsin Card Sorting Test (WCST), a measure of cognitive inflexibility and dorsolateral prefrontal cortex (DLPFC) function. Associations between OCS and psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).

Methods: Participants included 45 healthy controls (HC), 30 SPD, and 42 schizophrenia (SZ) patients. HCs and SPD individuals were recruited online. SZ patients were recruited from Mount Sinai Health. All completed SCID-5 interviews; HCs and SPD also underwent SIDP. Psychotic symptoms were assessed with PANSS. Exclusion criteria included substance use disorder, traumatic brain injury, or neurological illness. ANOVAs examined group differences ($p<0.05$), followed by Tukey's HSD. Pearson correlations assessed associations with OCS severity.

Results: SPD participants exhibited OCS severity comparable to SZ but both groups were significantly higher than HC?. Significant group differences were found for WCST performance. SZ patients showed poorer cognitive flexibility than HC and SPD. The SPD group was intermediate but did not significantly differ from either. Across the SPD and SZ groups, greater OCS severity correlated with higher positive symptom severity. In SZ, greater negative symptoms were linked to poorer WCST performance.

Conclusions: This is the first study directly comparing OCS in SPD and schizophrenia. Findings suggest that SPD individuals exhibit severity of OCS comparable to SZ. Greater OCS severity in schizophrenia-spectrum disorders is associated with cognitive inflexibility, reinforcing the role of prefrontal dysfunction in obsessive-compulsive psychopathology.

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Role of anterior cingulate cortex in stress-induced deficits in social behavior

Rachel L. Fisher-Foye, Romain Durand-de Cuttoli, Long Li, Antonio V. Aubry, Carole Morel, Hyoseon Oh, Jaylen Herandez, Teagan Daly, Zoe Otto, Darielle Lewis-Sanders, Lyonna F. Parise, Johana Alvarez, Scott J. Russo

BACKGROUND
Diminished social interaction is a hallmark behavior in numerous psychiatric diseases, including major depressive disorder, and has been linked to increasing suicide rates in recent years. However, the neurobiological mechanisms underlying altered prosocial behavior remain poorly understood.
METHODS
Utilizing a preclinical model of social trauma, the chronic social defeat stress (CSDS) model, we aim to elucidate the brain-wide neurobiological mechanisms contributing to social deficits. We used clearing and whole brain c-Fos mapping to identify alterations in brain reward circuitry following CSDS, highlighting a potential role for the Anterior Cingulate Cortex (ACC) in regulating social behavior. We seek to delineate the role of ACC in social reinforcement and motivation using an operant social self-administration (SSA) task in conjunction with the resident intruder (RI) task. We will identify specific ACC neuronal cell types associated with stress-induced social deficits using immunohistochemistry and in vivo Ca2+ imaging with fiber photometry in both tasks. We will also explore the causal relationship between ACC neuronal dynamics and social behaviors using chemogenetics or optogenetics in both tasks.
RESULTS
Preliminary data indicates reduced social interaction in RI and SSA acquisition in CSDS-exposed mice, indicating that there are broader deficits beyond classical social avoidance. We hypothesize that CSDS-induced alterations in ACC neuronal activity contribute to reduced social reinforcement and motivation.
CONCLUSION
This research will provide novel insights into the neurobiological substrates of social deficits, a prominent transdiagnostic symptom in psychiatric disorders. By elucidating the role of ACC neuronal dynamics in stress-induced social motivation, this study has the potential to inform targeted interventions for social anhedonia.

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Title: Traumatic stress induces fear generalization and enhanced prelimbic cortex activity

Authors: Rasika R Iyer, Anthony F Lacagnina, Leonie F Boesch, Roger L Clem

Post-traumatic stress disorder (PTSD) affects about 6% of people in the United States, and women are more likely to develop PTSD than men. A common symptom of PTSD is the generalization of fear to environments and stimuli that are not associated with the initial trauma. While there are several theories for such nonassociative effects, the underlying mechanisms are largely unknown, which has limited the development of preclinical models of pathological fear. We found that mice exposed to a form of traumatic stress had greater freezing to auditory tones compared to unstressed animals, despite having never been exposed to these stimuli. In addition, using calcium imaging, we found that this behavioral change was accompanied by an increase in activity in the prelimbic cortex (PL). Notably, both the behavioral and neural effects were driven by female animals. Following traumatic stress during early adolescence, analysis of specific cell types in PL revealed that both excitatory projection neurons (PNs) and somatostatin-expressing interneurons (SST-INs) exhibited enhanced auditory- as well as foot shock-elicited responses, which were each associated with increased defensive freezing. Indeed, SST-INs were activated in trauma-exposed mice at stimulus intensities that yielded no activity in unstressed controls. Future work will extend these findings by investigating how trauma influences neural responses to visual and auditory stimuli in an ethological assay of freezing and flight behaviors, where trauma-exposed mice exhibit heightened defensive reactions. Our data suggest a circuit mechanism for generalized fear after intense aversive experiences, in which previously non-threatening stimuli acquire aversive motivational properties.

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Submit your abstract here:

TITLE: Altered maturation of local inhibitory circuits in mPFC of mice carrying a Parkinson's risk gene mutation.

AUTHORS: R Kurian, M Fields, AR Magee, CA Guevara, NH Westneat, DL Benson, GW Huntley.

BACKGROUND: Parkinson's (PD)-associated mild cognitive impairment (PD-MCI) is a prodromal symptom that greatly elevates risk of conversion to dementia. PD-MCI is more common and progresses faster in males for unknown reasons. The maturation of parvalbumin (PV) neurons, which requires formation of perineuronal nets of ECM, is critical for normal cognitive function by regulating a balanced ratio of excitation (E) and inhibition (I) of principal neurons. We showed previously that male mice carrying a LRRK2G2019S Parkinson's mutation have subtle cognitive changes and functional abnormalities in maturation of GABAergic inhibition and E/I balance of mPFC corticostriatal neurons. Here, we hypothesize the basis for such abnormalities is altered maturation of PV neurons.

METHODS: A combination of PV immunofluorescence and WFA (lectin) labeling of PNNs is applied to sections through areas PL/IL of wildtype and LRRK2G2019S male and female mice across several developmental ages and young adulthood. ImageJ is used for quantitative comparisons between genotypes.

RESULTS: In young adult male mice, PV neuron density in mPFC is similar between genotypes. However, the percentage of PV neurons that contain a PNN is significantly lower in mutants compared to wildtypes. This loss of PNN coverage appears specific to PV neurons, since the percentage of non-PV neurons that contain a PNN is similar between genotypes. Ongoing analysis will examine females, other cortical areas to assess regional specificity, and a developmental series to determine when abnormalities in PV/PNN maturation emerge.

CONCLUSIONS: These data suggest that abnormal structural and functional maturation of local inhibitory circuits in mPFC contribute to PD-MCI in humans, and reveal potentially new therapeutic targets to prevent or ameliorate early cognitive decline in PD.

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Submit your abstract here:

Impact of Childhood Trauma and Premorbid Stressors on the Development of Psychotic Symptoms

Renata Gonzalez, Sansara Mahtani, Niamh Mullins

Experiences of childhood trauma and premorbid stressors can increase the risk of developing psychotic symptoms, such as hallucinations and delusions. The Genomic Psychiatry Cohort (GPC) study aims to identify the genetic hallmarks that contribute to the development of neuropsychiatric disorders, such as schizophrenia (SCZ), schizoaffective disorder, bipolar disorder (BD), and obsessive-compulsive disorder (OCD), emphasising diverse populations. The following study draws preliminary conclusions from existing GPC data, evaluating childhood trauma and premorbid stressors, and their impact on psychotic symptoms.

Using the Adverse Childhood Experiences (ACE) questionnaire and the Diagnostic Interview For Psychosis And Affective Disorders (DIPAD), two assessments completed with GPC study participants (n = 172), participants were divided into categories by childhood trauma (ACE score ≥ 4) and presence of premorbid stressor. Chi-square tests were performed to examine categorical associations, while logistic regression estimated odd ratios for psychosis risk.

Psychosis prevalence was highest (95%) in individuals with both childhood trauma and a premorbid stressor. Logistic regression indicated that neither childhood trauma ($p = 0.785$) nor premorbid stressors ($p = 0.446$) significantly predicted psychosis risk. While non-significant, childhood sexual trauma (CST) showed the strongest association with psychosis ($p = 0.113$). A 1-point increase in ACE score was associated with a 15% increase in psychosis risk ($p = 0.099$), but this relationship was also non-significant.

While childhood trauma and premorbid stressors together increase psychosis risk, independently neither is a strong predictor. Further research with the full cohort is needed to confirm these effects. This study highlights the continuing need of examining adverse childhood experiences and premorbid stressors as markers for psychosis. This could aid in the creation of better diagnostic tests and preventive measures, ultimately allowing at-risk individuals to receive care at an earlier stage.

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Impacts of Interpreter Use on Psychiatric Care

Rhyann Clarke, Renata Gonzalez Chong, Isotta Landi, Alexander Charney

BACKGROUND: Communication in a native language is crucial for effective psychiatric care. Due to New York City's large international population, there is a need for effective methods when assessing non-English speaking patients. Currently, the Mount Sinai psychiatric department uses a variety of translation methods, including phone interpreters, family members, and other hospital personnel. In this study, patient charts will be analyzed to determine the impact of translation on patient care.

METHODS: Psychiatric emergency department charts were analyzed using Python's pandas and regex to identify interpreter use and patient language. Interpreter types were categorized (e.g., Native Speaking Provider, Pacific Interpreters, family). SectionSpan notes were processed using spaCy to determine word count and psychiatric-related word usage by comparing words against a predefined psychiatric care keyword list.

RESULTS: The "preferred language" column had 55% accuracy in patient notes. Among patients using Pacific Interpreters, only 54.5% had an interpreter code recorded. Interpreter use was mentioned in 12 areas of the notes. Future analyses will examine total word count and psychiatric word percentage.

CONCLUSIONS: From preliminary data, it is clear the "At A Glance" data points are not always accurate, and interpreter use can impact the ability to fill out charts in completion. In an urban center like New York City, there is a need for in-person psychiatric care in an individuals' native language. In psychiatric care, communication between the patient and doctor is the primary method of diagnosis. With this bridge impacted, patients will continue to struggle with their mental health.

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Background: Prader-Willi syndrome (PWS) is the most common cause of life-threatening childhood obesity. Obesity-related symptoms, including hyperphagia, weight gain, increased fat mass, and reduced voluntary activity, have been specifically linked to the silencing of the Magel2 gene. Magel2 is normally densely expressed within the lateral hypothalamus (LH), a brain region key to regulating motivated behaviors and energy expenditure. However, the impact of Magel2 absence on PWS-associated changes to food-related motivation is still not fully understood. Additionally, chemogenetic stimulation of LH orexin neurons alters homeostatic feeding in wild-type (WT) mice but has no effect in Magel2-null mice. As such, we hypothesized that mice lacking functional expression of Magel2 would show disruptions to motivated behaviors.

Methods: To assess homeostatic feeding, we food-restricted the mice before allowing them to consume standard laboratory chow. To measure food-related hedonic drive, we allowed the same mice to consume calorically dense palatable food items while fully sated. Finally, we gave separate cohorts of mice unlimited access to both chow and palatable food and recorded weight gain and food intake.

Results: Homeostatic feeding was unchanged in Magel2-null mice. Surprisingly, hedonic feeding was impaired. When granted free access to both standard chow and palatable food, Magel2-null mice gained more weight than their WT counterparts despite consuming the same total calories. However, Magel2-null mice obtained a larger portion of their calories from the palatable food source compared to WT mice.

Conclusion: An absence of Magel2 expression leads to complex changes in food-related motivation that depend on the palatability of the food source. Additionally, chemogenetic stimulation of the orexin system produced feeding behavior changes only in WT mice, suggesting that lifelong Magel2 deficiency renders the orexin system therapeutically inert. Further investigation is needed to determine the impact of artificial orexin system manipulation on other Magel2 deficiency-related behaviors.

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Submit your abstract here:

Local neural activation in the skin regulates lung inflammation.

Rintaro Shibuya, Brian S. Kim

Background: Asthma is a common inflammatory lung disease affecting 300 million people worldwide. Despite the well-established role of type 2 immunity in its pathogenesis, it is increasingly appreciated that asthma can be modulated by the nervous system, especially through vagus nerves. We have previously reported that vagal sensory neurons (VSNs) inhibit asthma-like inflammation through the suppressive function of CGRPβ. However, it remains unclear how VSNs can be modulated to regulate lung inflammation. VSNs are unique in that they almost exclusively innervate visceral organs including the lung, but there is one exception: the auricular branch of the vagus nerve that supplies the ear skin. Although the precise function of this nerve branch remains unknown, it represents a potential portal by which VSNs can be modulated. Thus, we hypothesized that manipulating skin-innervating neurons could control lung inflammation.

Methods: Asthma-like lung inflammation was induced by intranasal injection of Alternaria Alternata. Chemogenetic activation/inactivation of skin-innervating nerves was achieved with two approaches: 1) Intradermal injection of CNO into the ear skin of TRPV1-hM3Dq/TRPV1-hM4Di mice and 2) Intradermal injection of AAV9-DIO-DREADD(Gq)/AAV9-DIO-DREADD(Gi) into the ear skin of TRPV1Cre mice followed by intraperitoneal injection of CNO three weeks later.

Results: We performed CTB- or AAV-mediated neural tracing to map direct innervation between the vagal ganglia and the ear skin. These neurons were TRPV1+ and CGRP+ sensory neurons. Next, we found that chemogenetic activation of skin-innervating nerves did not affect lungs at steady state but suppressed asthma-like lung inflammation characterized by decreased accumulation of pathogenic immune cells such as ILC2s and increased CGRPβ protein in the airway. By contrast, chemogenetic inhibition of skin-innervating neurons resulted in augmented allergic lung inflammation with decreased CGRPβ protein in the airway.

Conclusions: Ear skin-innervating TRPV1+ neurons regulate lung inflammation.

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Submit your abstract here:

Heterogeneous regulation of polymorphic transposable elements affects transcriptome in human adult brain

Risa Watanabe, Bicheng Jiang, Travis Dawson, Foramben Patel, Cyril J Peter, Aman Agarwal, Will Lounsbery-Scaife, Maya Fridrihk, Sathiji K. Nageshwaran, Deborah Mash, Nadejda M. Tsankova, Robert P Sebra, Benjamin K Chen, Dan Hasson, Schahram Akbarian

Background: Transposable Elements (TEs) provide inter- and intra-individual heterogeneity. TE copy numbers are variable between subpopulations, and somatic TE retrotranspositions occur in healthy brain. Accumulating evidence suggests TEs function as cis regulatory element in brain, but due to its repetitive nature, studying the loci-specific genetic and epigenetic profile of TEs have been difficult, limiting our knowledge on TE heterogeneity, epigenetic landscape, and their effect on brain function.
Methods: To sorted and homogenate postmortem samples from multiple regions in brain (N=48), we applied fiber-seq, an adenine-methylation based long-read single-molecule chromatin accessibility assay, and single cell long-read RNA-seq.
Results: We identified >4 million structural variant (SV)-TEs, of which >6,000 were sample-specific. Long interspersed nuclear element 1 retrotoransposons (L1s), especially the evolutionally young subfamilies, were highly repressed, while long terminal repeat retrotransposons (LTRs) showed loci-specific increase/decrease in accessibility. Of unique isoforms in brain, 12-18% overlapped TEs, including the sample-specific SV-TE. Although 1.7-4.8 thousand unique isoforms overlapped full-length L1s, no isoforms were confidently annotated as L1-promoter driven, as suggested by epigenetic results.
Conclusions: Human brain accommodates diverse TE distribution, which is regulated heterogeneously and is reflected in transcriptomic diversity.

Supported by NIDA DP1 DA056018.

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USING DIFFUSION TENSOR IMAGING ALONG THE PERIVASCULAR SPACE (DTI-ALPS) TO EXAMINE RELATIONSHIPS BETWEEN GLYMPHATIC FUNCTION, AMYLOID, AND COGNITION IN OLDER ADULTS

Ryan Wales, Anna Marin, Ziwei Xu, Cody Ruais, Jasmin Richard, and Trey Hedden

BACKGROUND: Recent evidence has suggested that glymphatic system dysfunction is a key component of Alzheimer's disease (AD) pathogenesis. This may result in improper clearance of amyloid-beta, leading to accumulation of neuritic plaques. Glymphatic function can be estimated using diffusion tensor imaging along the perivascular space (DTI-ALPS). In this study, we investigate how DTI-ALPS is related to AD pathology and cognition.

METHODS: 132 participants (103 cognitively normal, 29 MCI) underwent diffusion imaging, amyloid (florbetaben) PET, tau (PI-2620) PET, and a neuropsychological battery. Spherical ROIs were manually placed bilaterally in the association and projection fibers at the level of the lateral ventricles. The ALPS index was calculated as the ratio of flow perpendicular to the perivascular space (x-axis) compared to flow in the association (y-axis) and projection fibers (z-axis), where an index of 1 indicates healthy/typical clearance. Regressions examined whether ALPS was related to amyloid, tau, or cognition, controlling for age and sex.

RESULTS: We found a significant relationship between reduced ALPS in the left hemisphere and increased whole-brain amyloid, even after controlling for tau. Reduced left-ALPS was also associated with worse performance on the Preclinical Alzheimer's Cognitive Composite. Participants with MCI showed a significant relationship between reduced left-ALPS and episodic memory, but cognitively normal participants did not.

CONCLUSIONS: These results suggest that impaired clearance may contribute to greater amyloid burden, especially among those with MCI. Individuals with poor or worsening clearance may show more rapid amyloid accumulation, highlighting the need for longitudinal investigation. Critically, amyloid therapies may be less effective in removing plaques from individuals with impaired glymphatic systems that cannot clear the amyloid before it reaccumulates.

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Submit your abstract here:

Title: Global and Localized Computational Metrics to Identify Biomarkers and Morphometric Changes Accompanying Alzheimer's Disease

Authors: Sam Edwards, Muhammad Parvaz*, Shalaila S. Haas*

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a substantial decline in hippocampal and amygdalar volume as well as entorhinal cortical thickness. Through state-of-the-art computational methods, we produced a global metric of brain health with a biological brain-age model and localized morphometric deviations through a pre-trained normative model. Together, these tools provide valuable biomarkers and an enhanced understanding of onset and progression of AD.

Methods: T1w images from 494 individuals in the ADNI dataset were analyzed. 179 individuals with AD (mean[SD] age: 74.6[8.4]; 46.37% female) and 315 cognitively-unimpaired (CU) individuals (mean[SD] age: 73.5[6.96]; 55.24% female) were included. Images were processed with FreeSurfer to extract 68 cortical thickness (CT), 68 surface area (SA), and 14 subcortical volume (SV) measures. BrainAGE (global) and regional morphometric deviation scores were computed via the age-and-sex-specific models on the CentileBrain platform. Localized Z-scores were clustered as infranormal (≤-1.96), supranormal (≥1.96), or normal (>-1.96<1.96). BrainAGE was compared using independent-samples t-test and the proportion of infra/supranormal scores were compared using a 2-proportions-Z-test.

Results: Mean brainAGE was significantly higher in AD (4.77[5.26]) as opposed to CU (−0.72[4.5]), ($T = 12.2$, $P = 3.36e-30$, $ES = 1.14$). Infranormal deviation proportion was significantly higher in AD for both hippocampal (ADprop: 51.68%, CUprop: 5.88%, $P<0.001$) and amygdalar (ADprop: 27.1%, CUprop: 1.75%, $P<0.001$) volumes. Infranormal deviation proportion was also significantly higher in AD for entorhinal CT (ADprop: 31.56%, CU: 4.13%, $P<0.001$).

Discussion: AD individuals exhibit significantly higher brainAGE and substantial reductions in the hippocampus and amygdala and entorhinal CT, indicating accelerated aging and degeneration. These results highlight the potential of pairing brainAGE with normative models to yield valuable biomarkers and localized information on morphometric changes accompanying AD.

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Neuroeconomically dissociable decision-making computations are altered by Shank3 haploinsufficiency

Pedersen S.M.B., Jahan N., Yakubov B., Kasparov S., Sushil S., Cai J., Granzino K., Hussain Z., Abid A., Ramirez A., Andraka E., Hara E., Li Y., Durand-de Cuttoli R., Buxbaum J., Sweis B.M.

The mechanisms underlying decision-making encompass distinct information processing computations, which can be differentially perturbed within psychiatric conditions. Autism spectrum disorders (ASDs) are characterized by intellectual impairments, altered communication and social interactions, and repetitive behaviors or restricted interests. Phelan-McDermid Syndrome is a rare ASD caused by deletions in the SHANK3 gene, which is critical for maintaining functional synapses. Rodent studies have been limited in their ability to model cognition of these patients, often relying on full knockout-mice to yield stronger behavioral phenotypes. This reduces the translational potential of animal studies, as homozygous SHANK3 deletions are extremely rare or non-viable in humans. We aimed to fill this knowledge gap by robustly characterizing complex decision-making behavior of haploinsufficient mice by leveraging the neuroeconomic foraging paradigm, “Restaurant Row,” which has been translated across species. We longitudinally tested 48 C57BL/6J mice (SHANK3+/+ vs SHANK3+/-, male and female) across a changing economic landscape. Mice had 30-min daily to forage for their primary source of food by navigating a maze, weighing opportunities to earn food rewards of varying costs (tone-indicated delays) and subjective value (flavors). We found robust SHANK3+/- phenotypes typified by altered deliberation behaviors during cost-informed decisions that were not explained by overt differences in feeding behavior, motivation, or other types of choices. Fitting our data to a drift-diffusion model revealed striking changes in drift rates, but not decision boundary or bias parameters. These findings highlight variations to evidence accumulation processes during value-based judgements and provide a translational computational framework to understand decision-making mechanisms underlying altered behavior in neurodevelopmental disorders.

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Establishing a 3D patient-derived midbrain organoid model to investigate the pathogenesis of sporadic tauopathy

Samin Hassan, Kristen Whitney, Grace Selecky, Margaret Krassner, Claudia De Sanctis, Victoria Flores Almazan, SoongHo Kim, Kurt Farrell, Megan Iida, Ruth Walker, Melissa Nirenberg, Sally Temple, John Crary

Background: Tauopathies are characterized by the accumulation of abnormal tau protein in neurons and glia in the brain. Progressive supranuclear palsy (PSP) is a tauopathy involving selective vulnerability of dopaminergic neurons and glia in the midbrain resulting in a clinical movement disorder. Human induced pluripotent stem cell (hiPSC)-derived organoid models are a tool that can better recapitulate disease mechanisms in the human brain.

Methods: Fibroblasts cultured from sporadic PSP patients were reprogrammed into hiPSCs and paired with control lines from existing collections. HiPSCs were maintained with StemCultures FGF2-Discs, seeded into spinner flasks to generate pluripotent spheres, patterned into midbrain organoids using pharmacological-directed differentiation, and maintained for up to one year. Reliable patterning was confirmed with qRT-PCR, immunohistochemistry, and immunoblot using cell-type specific markers. Bulk-RNA sequencing was performed across multiple time points.

Results: Organoids displayed a cytoarchitecture compatible with the developing midbrain. Neural progenitor and dopaminergic markers were positive in a time-dependent manner, with mature dopaminergic neurons detected by one month. GFAP-positive astrocytes appeared before four months. Cells positive for oligodendrocyte precursor cell (OPC)-markers were observed at six months and Luxol fast blue (LFB)-positive myelin fibers by ten months. On the transcriptomic level, organoids expressed developmental pathways consistent with maturation.

Conclusions: Sporadic PSP patient hiPSCs reliably differentiate into midbrain organoids, resulting in a model containing key cell-types affected in PSP. Critically, this protocol intrinsically generates oligodendrocyte-lineage cells starting by six months without the addition of oligo-specific patterning compounds. This powerful model is a valuable resource to investigate disease mechanisms and provide insight into cell-type specific drivers.

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Submit your abstract here:

Dysregulated frontal-visual cortical communication during cognitive control in a mouse model of Fragile X syndrome.

Samuel Allen*, Alesia Singh*, Tadaaki Nishioka, Justin Riceberg, April Serratelli, Yury Garkun, Hirofumi Morishita
(*equal contribution)

BACKGROUND: Previously, frontal-visual projection activity before stimulus presentation was found to be essential for attention function, specifically following error trials. Moreover, we recently demonstrated that frontal-visual projection neurons display increased glutamatergic input in adult Fmr1KO mice: a consequence of aberrant adolescent maturation. Here, we aimed to understand how altered circuit development promotes attention deficits in Fmr1KO mice,

METHODS: We utilized fiber photometry recording of calcium and glutamate signaling in frontal-visual projections to evaluate circuit function and LFP recording in the ACA and V1 to assess network dynamics in adult Fmr1KO mice during 5 Choice Serial Reaction Time Task (5CSRTT).

RESULTS: In the 3 seconds before stimulus presentation, calcium activity in the wildtype (WT) circuit was highest in correct trials preceded by errors. Conversely, Fmr1KO mice did not show error-biased recruitment. Glutamate input dynamics showed post-correct preference in both groups, but linear regression analysis determined only Fmr1KO glutamate input dynamics significantly contributed to output calcium activity. At the network level, Fmr1KO mice showed increased coherence between ACA and V1 at both the theta and gamma frequencies.

CONCLUSIONS: These findings demonstrate that frontal-visual projection activity is altered in adult Fmr1KO in the context of aberrant adolescent maturation. Moreover, the output calcium activity of projections in Fmr1KO is shifted closer to the glutamatergic input dynamic which may be a consequence of retained connectivity. This altered activity and function may precipitate network differences between the ACA and V1 in Fmr1KO mice, and future studies will aim to understand the impact frontal-visual projection neurons have on network dynamics.

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TIMP2 modulates the effects of cognitive enrichment on synaptic plasticity

Samuele Petridis, Emily Paolillo, Ana Ferreira, Hanxiao Liu, Jeffrey Zhu, Kaitlin Casaletto, Joseph Castellano

Background: TIMP2 is a youth-associated systemic factor crucial for hippocampal function and necessary for adult neurogenesis and synaptic plasticity. Previous studies suggest that exercise and environmental enrichment enhance neurogenesis, partly through blood-borne factors, but whether TIMP2 mediates these effects remains unknown.

Methods: In order to assess the effect of differing pools of TIMP2, we applied a longitudinal enrichment paradigm to evaluate whether enrichment increases plasma TIMP2 levels in WT mice exposed to social and exercise enrichment. Immunoblotting and immunohistochemistry were applied to detect TIMP2 changes and perturbations in neurogenic cells. Neurogenesis was assessed via DCX and other neuroblast markers. To address the relationship between activity levels, cognition, and plasma protein levels, we analyzed thousands of plasma proteins using SomaScan from human subjects fitted with actigraphy monitoring, integrating this data with cognitive assessments.

Results: We find that human subjects with higher overall activity levels have significantly higher TIMP2 levels and cognition. To study the mechanism in vivo, we examined neurogenesis in WT and KO mice . WT mice exposed to the enriched activity paradigm exhibit increased levels of adult neurogenesis, as assessed by DCX+ cell number in the dentate gyrus and deleting TIMP2 results in reduced adult neurogenesis regardless of standard or enriched housing conditions. TIMP2 KO mice showed no difference in DCX+ cell numbers between enriched and standard housing conditions, indicating that TIMP2 is necessary for enrichment-induced neurogenesis.

Conclusions: These results highlight TIMP2 as a key factor in hippocampal plasticity, underscoring its potential as a novel target for age-related cognitive decline and neurodegenerative diseases. Future studies will explore how TIMP2 mediates adult neurogenesis enhancements in enrichment models and in the setting of mouse models of neurodegeneration.

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Single-nucleus transcriptome-wide association study of human brain disorders

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Background: Brain disorders exhibit cell-type-specific characteristics, yet most transcriptome-wide association studies (TWAS) have been constrained by the use of homogenate tissue, limiting their resolution. We present a single-nucleus (sn) TWAS leveraging snRNA-sequencing of over 6 million nuclei from the dorsolateral prefrontal cortex of 1,494 donors across three ancestries—European, African, and Admixed American.

Methods: We constructed 94 ancestry-specific sn transcriptomic imputation models (TIMs) across 27 non-overlapping cell-types, enhancing the resolution of genetically-regulated gene expression (GReX) and uncovering novel gene-trait-associations (GTAs) across 12 brain disorders. We utilize Million Veteran Program (MVP) and GWAS summary statistics for downstream analyses establishing cell-type specificity and cross-ancestry concordance.

Results: We can reliably impute 20,189 (59.9%), 18,742 (55.6%) and 13,923 (41.3%) of 33,688 assayed genes within the PsychAD dataset in Europeans, Africans, and Admixed Americans, respectively. Our snTWAS revealed cell-type-specific GReX dysregulation, identifying over 4,000 novel GTAs not detected by homogenate approaches. Furthermore, fine-mapping retained 64.7% of GTAs. By applying these snTIMs to the MVP, we validated major findings and explored the pleiotropy of GReX, revealing cross-ancestry concordance and utilizing multiple ancestries to fine-map causal genes.

Conclusions: This approach enhances the discovery of biologically relevant pathways and gene targets, highlighting the importance of cell-type resolution and ancestry-specific models in understanding the genetic architecture of brain disorders.

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Submit your abstract here:

Impaired Regulation of the Breathing Center Worsens Fear Responses and Disrupts Metabolic Balance

Sanutha Shetty, Pamela Toh, Samuel J Duesman, Diego Espinoza, Sarah Stanley, Prashant Rajbhandari, Abha Karki Rajbhandari

Background: Breathing is essential for cellular and whole-body metabolism and is closely linked to emotional states under stress. Unsurprisingly, individuals with stress-related disorders such as PTSD often exhibit irregular respiration and comorbidity with metabolic syndromes such as obesity and diabetes, deeming the need for further exploration. The preBötzinger complex (preBötC) is a brainstem region that is critical for generating breathing rhythms and expresses PAC1 receptors that bind to PACAP, a neuropeptide vital for regulating both respiration and stress-related behaviors. However, the role of PAC1 signaling in the preBötC in integrating stress and metabolism remains unclear.

Methods: To investigate this breathing-stress-metabolism link, we examined the loss-of-function effects of PAC1-expressing neurons in the preBötC by injecting AAV2-GFP-Cre/AAV2-GFP virus in the preBötC of PAC1-floxed mice for Cre-mediated selective deletion of PAC1 receptors. After three weeks, mice underwent stress-enhanced fear learning (SEFL), a mouse model of PTSD-like fear. We also concurrently measured cardiorespiratory outcomes using a telemetry device during SEFL. Lastly, we measured changes in metabolism using indirect calorimetry and glucose tolerance test.

Results: First, SEFL increased cFos expression in the preBötC, indicating heightened neuronal activity. Second, preBötC-PAC1 ablation worsened fear generalization, increasing freezing on SEFL Day 2. Third, PAC1 ablation alone heightened fear responses to mild stress on Day 3. Fourth, PAC1-ablated SEFL mice showed greater heart rate deviation, glucose intolerance, reduced CO_2, and lower energy expenditure. Finally, we identified a novel preBötC projection to brown adipose tissue and the liver, linking respiratory control to metabolism.

Conclusion: In conclusion, our findings highlight the role of preBötC neuropeptide signaling in regulating stress and metabolism, offering potential for therapies targeting psychological and physiological stress effects.

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Beyond the direct and indirect pathways: single-cell connectomic profiling of the nucleus accumbens

Sarah Claypool, Lauren Wills, and Paul Kenny

Background
The striatum mediates reward learning and decision making through distinct networks of projection neurons. Dorsal striatum forms two distinct pathways: direct containing dopamine receptor 1 (D1)-expressing neurons projecting to substantia nigra pars reticulata (SNr) and ventral tegmental area (VTA); indirect containing dopamine receptor 2 (D2)-expressing neurons which modulate SNr and VTA through projections to the globus pallidus (GP). However, little is known about nucleus accumbens (NAc) projection networks. The NAc medial shell (msNAc) is a hedonic hotspot, where mu opioid receptor stimulation in msNAc increases “wanting” and “liking” for food rewards (Pecina and Berridge, 2005). Our study uses MAPseq to identify msNAc connectomics at a single-cell resolution.

Methods
Mice were injected with oxycodone (5 mg/kg, s.c.) or saline for 10 days, followed by Sindbis virus injection into msNAc on day 11. 40-44h later, brains were removed and flash frozen. Injection site and target regions were dissected using a cryostat, barcodes were sequenced, and a connectivity matrix was built based on identification of unique barcodes in one or more target regions.

Results
Robust barcode expression was found in ventral pallidum (VP), lateral septal nucleus (LSn), lateral hypothalamus (LH), and bed nucleus of the stria terminalis (BNST). No barcodes were detected in GP or SNr, supporting a different projection architecture from dorsal striatum. Principal component analysis showed that LH, BNST, and LSn clustered together, while VP clustered separately.

Conclusions
The mNAcSh contains at least two unique populations of medium spiny neurons (MSNs). Whether these two populations represent novel segregations of D1 vs D2 MSNs remains unclear. Follow up experiments will use viral tracing to verify that mNAcSh neurons projecting to VP and LSn are indeed separate populations as predicted by MAPseq.

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Submit your abstract here:

APOE4-associated changes in the systemic environment regulate hippocampal phenotypes

Sarah Philippi, Brittany Hemmer, Hanxiao Liu, Monika Jain, Yihang Wang, Manav Kapoor, Joseph Castellano

Background: The APOE-ε4 allele is the strongest genetic risk factor for Alzheimer's disease (AD), increasing risk 3-12-fold relative to APOE-ε3. Work investigating aging as a risk factor identified perturbations in blood-CNS communication, and administration of aging-associated blood-borne proteins modifies brain function. Characterizing plasma proteomic changes across systemic states may thus be critical for development of novel CNS therapies. We hypothesized that the plasma proteome varies between APOE4 and APOE3 subjects, and that these systemic changes account for differences in brain function according to APOE genotype.

Methods: We applied aptamer-based SOMAscan proteomics to examine plasma proteome differences by APOE genotype in human subjects and in APOE-knockin (KI) mice. Molecular processes regulated by systemic apoE were characterized via hippocampal bulk RNAseq following blood-sharing between APOE4-KI and APOE3-KI mice. Pathways were further investigated using confocal imaging in hippocampi of parabionts.

Results: We identified APOE isoform-dependent differences in plasma protein levels and CNS-associated pathways in humans and APOE-KI mice. Ontology-based analyses on differentially expressed genes from hippocampi of mice exposed to opposing APOE genotypes highlighted altered neuroinflammation, oligodendrocyte differentiation, and myelination pathways, phenotypes that were confirmed by confocal imaging experiments. Specifically, exposure to APOE4-KI blood increased microglia activation and decreased myelination in APOE3-KI mice, whereas exposing APOE4-KI mice to APOE3-KI blood yielded converse effects on both microglial state and oligodendrocyte differentiation. Baseline differences were further validated in naive APOE-KI mice. Conclusions: These findings suggest APOE4-associated brain phenotypes are, in part, mediated by how APOE4 alters the systemic compartment. Communication between CNS cells mediating these effects will be investigated using snRNAseq. Ongoing experiments will investigate protective effects of the APOE3 systemic compartment on APOE4 hippocampi, potentially opening new therapeutic avenues for AD.

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Investigating non-coding autism de novo variants in human stem cell-derived neurons

Sarah E. Williams, Justin Koesterich, Linda L. Boshans, Kayla Townsley, Anat Kreimer, Kristen Brennand, Nan Yang

BACKGROUND: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with a complex genetic architecture. Thousands of non-coding de novo variants (DNVs) have been identified, but the functional contribution of these to ASD etiology remains uncertain. Regulatory activity is highly context-dependent, so to determine whether non-coding DNVs may impact gene regulation in a cell type relevant to ASD, our lab annotated the enhancers present in human stem cell-derived excitatory and inhibitory neurons at baseline and depolarized states and intersected these results with the 255,106 ASD DNVs.

METHODS: Using a massively parallel reporter assay (MPRA), we tested whether the non-coding DNVs found in neuronal enhancers alter cis-regulatory activity in glutamatergic or GABAergic human neurons in baseline or activated states, as well as a pilot experiment in neural progenitor cells (NPCs). Further, we performed activity-by-contact modelling to identify the genes regulated by DNV-containing enhancers. To validate cis-regulatory activity and to compare trans-effects on downstream gene networks, a CRISPR inhibition screen will be performed targeting a subset of ASD DNV-containing enhancers and their predicted gene targets.

RESULTS: We identified 2,495 ASD DNVs within neuronal enhancers, hundreds being cell-type specific or activity-dependent. 105 of these DNVs significantly altered enhancer activity in NPCs, with a similar number coming from probands and unaffected siblings. Gene-enhancer mapping revealed that a subset of DNV-containing enhancers is predicted to regulate high-confidence ASD genes.

CONCLUSIONS: I hypothesize that ASD DNVs will have context-specific effects on enhancer activity and subsequent gene expression in human neurons, with a modulatory impact on genes and gene networks associated with ASD. These results would indicate a functional role for non-coding de novo variation in autism etiology.

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Association of Psychological Resilience with Decelerated Brain Aging in Cognitively Healthy World Trade Center Responders

Saren H. Seeley, Rachel Fremont, Zoe Schreiber, Laurel S. Morris, Leah Cahn, James W. Murrough, Daniela Schiller, Dennis S. Charney, Robert H. Pietrzak, M. Mercedes Perez-Rodriguez & Adriana Feder

Background. Despite their exposure to potentially traumatic stressors, the majority of World Trade Center (WTC) responders – those who worked on rescue, recovery, and cleanup efforts on or following September 11th, 2001 – have shown psychological resilience, never developing long-term psychopathology. Psychological resilience may be protective against the earlier age-related cognitive changes associated with posttraumatic stress disorder (PTSD) in this cohort. The current study estimated the difference between estimated brain age from structural MRI data and chronological age in WTC responders who participated in a parent fMRI study of resilience (N=97). We hypothesized that highly resilient responders would show the least brain aging, and explored associations between brain aging and psychological and cognitive measures.

Methods. WTC responders screened for absence of cognitive impairment were classified into three groups: WTC-related PTSD group (n=32), Highly Resilient (n=34) group without lifetime psychopathology despite high WTC-related exposure, and Lower WTC-Exposed (n=31) control group also without lifetime psychopathology. We used BrainStructuresAge, a deep learning algorithm-based pipeline that estimates voxelwise age from T1-weighted MRI data, to calculate decelerated (or accelerated) brain aging relative to chronological age (“BSAGE gap”).

Results. Globally, brain aging was decelerated in the Highly Resilient group and accelerated in PTSD, with a significant group difference (p=.021, Cohen’s d=0.58); the Lower WTC-Exposed control group exhibited no significant brain age gap or group difference. Lesser brain aging was associated with resilience-linked factors including lower emotional suppression, greater optimism, and better verbal learning.

Conclusions. Cognitively healthy WTC responders show differences in brain aging related to resilience and PTSD.

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Behavioral and functional neuroimaging assessment of subcallosal anterior cingulate cortex overactivation in non-human primates

Satoka H. Fujimoto, Atsushi Fujimoto, Catherine Elorette, Keondre Herbert, Adela Seltzer, Lazar Fleysher, Ki Sueng Choi, Helen S. Mayberg, Brian E. Russ, Peter H. Rudebeck

BACKGROUND: Hyperactivity of the subcallosal anterior cingulate cortex (scACC) has been found in individuals with depression and people experiencing normal sadness. Whether experimentally induced hyperactivity in scACC is sufficient to induce depressive-like behaviors and alter brain-wide patterns of functional connectivity remains unclear.
METHODS: Excitatory DREADD receptors (hM3Dq) were surgically introduced bilaterally into the scACC of two female rhesus macaques. Subjects were then behaviorally tested in a Pavlovian conditioning task, human intruder test, and natural activity in their home cage as well as undergoing resting-state functional MRI when the DREADD receptors were acutely activated by systemic injection of deschloroclozapine. Neuroimaging data were analyzed to investigate changes in functional connectivity with scACC.
RESULTS: ScACC overactivation reduced animals' affiliative vocalizations and engagement with the environment in their home cage and increased anxious pacing behavior during the human intruder test. In the Pavlovian task, scACC overactivation decreased reward-anticipatory licking and a change in heart rate, a phenomenon associated with reduced reward-guided motivation. During fMRI, scACC overactivation increased scACC functional connectivity with the limbic network (hippocampus and amygdala), and decreased connectivity with the dorsolateral prefrontal cortex.
CONCLUSIONS: Our results demonstrate that acute overactivation of the scACC in macaques is sufficient to alter reward-guided motivation and trigger depressive and anxiety-like behaviors. These behavioral effects were mirrored by changes in functional connectivity between scACC and limbic areas, mirroring changes seen in acute negative mood induction in humans.

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Network-BrainAGE: A New Metric to Assess Network-Based Brain Aging

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Background
Extensive research has established the difference between neuroimaging-predicted and actual chronological age (brainAGE), as a robust and biologically meaningful measure of brain health. We have previously released brainAGE models in development and across the lifespan. However, brainAGE is generally computed as a global index of age-related brain changes, disregarding information about spatial variation. In this study, we expand on our previous work to develop large-scale brainAGE models for specialized brain networks in healthy individuals across the lifespan.

Methods
The T1w structural images will be processed using standard pipelines in 9473 healthy individuals (aged 3-92 years; N[%] female = 5126[54.11%]) across 9 datasets. The Schaefer atlas was used to generate parcels (200, 400, 600, 800, 1000) of cortical thickness and cortical surface area, each assigned to one of 7 Yeo networks. Sex-specific pooled datasets were split into 80% training/20% testing subsets. Model performance was assessed by mean-absolute-error and the correlation between predicted and chronological age.

Results
For all networks except the visual network, the mean-absolute-error reduced with increasing number of parcels (ranges across all: visual=6.00-6.70; somatomotor=5.00-5.67; dorsal-attention=6.91-7.32; salience=5.31-5.92; limbic=5.82-6.65; control=5.46-6.20; default=4.89-5.51). For all networks, the mean-absolute-error reduced with increasing number of parcels (ranges across all: visual=8.03-9.32; somatomotor=6.71-7.97; dorsal-attention=9.22-9.86; salience=7.43-8.41; limbic=8.00-9.27; control=7.63-8.68; default=6.73-7.83). Correlation between predicted and chronological age was high across all networks (mean correlation across networks = 0.93) and varied by maximally 0.02 with increasing parcels. Correspondence between males and females for mean-absolute-error across networks was high (>0.97).

Conclusions
This study introduces novel network-specific brainAGE models, indicating variability in model performance across specialized networks. These models offer potential applications in clinical samples that might demonstrate stronger associations with cognitive deficits, psychopathology, and risk factors.

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Title: Aging-Related Brain Structural Changes in Mood and Anxiety Patients

Authors: Shely Khaikin, Laurel Morris, Priti Balchandani, James Murrough, Yael Jacob

Background: Normal aging is known to alter brain structure in multiple ways detectable through neuroimaging, such as enlarged ventricles, cerebro-spinal fluid (CSF) volume, and white matter hypointensities (WHM). Accelerated biological aging has been hypothesized as a mechanism underlying the clinical and cognitive deterioration of brain pathologies such as depression. Therefore, there is a need to identify brain aging patterns in patients with brain pathologies to determine whether and how they differ from healthy normal patterns of aging. We aimed to explore whether we can quantify imaging accelerated biomarkers in psychiatric patients.

Methods: The sample (N=199) included HC (N=89) and patients (N=110), who met DSM-5 criteria for mood and anxiety-related disorders as assessed through a diagnostic interview. All participants were recruited for neuroimaging studies conducted at the Depression and Anxiety Center and underwent an ultrahigh field 7-Tesla MRI T1-weighted anatomical scan with a resolution of 0.7^3 mm voxel size. Automatic segmentation was performed using FreeSurfer software. Linear regressions were conducted to analyze associations between brain structures volumes in HC and patients while controlling for estimated total intracranial volume (eTIV), age, and sex.

Results: No statistically significant differences between groups were found in the following brain structures' volumes: left lateral ventricle, left inferior lateral ventricle, third ventricle, fourth ventricle, CSF, right lateral ventricle, right inferior lateral ventricle, and WHM. HC (mean age = 33.8 years, min = 18 years, max = 64 years); patients (mean age = 31.83 years, min = 18 years, max = 63 years).

Conclusions: Further longitudinal research is needed to explore whether other factors, such as disorder duration and severity, age at disorder onset, and medication effects, influence brain volumetric changes.

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Dietary Polyphenol Consumption: A Demographic Analysis

Sibilla Masieri*, Alexia Lizzano*, Camille Dupiton*, James Murrough

Demographic factors influence diet quality and polyphenol intake, which varies based on food accessibility, cultural preferences, and socioeconomic factors. This study examines polyphenol consumption across gender and racial groups. Participants (N=102) completed the Diet History Questionnaire (DHQ-3) to assess dietary intake over the past month. Polyphenol intake was analyzed across six sources: wine, beer, tea, coffee, whole grains, and fruit. A t-test found no significant difference in polyphenol intake between genders ($p = 0.829$). A one-way ANOVA indicated significant differences among racial groups ($p = 0.0067$), though post-hoc tests did not confirm specific pairwise differences. Fruit was the most common source of polyphenols (36 participants), followed by coffee (31), whole grains (21), and tea (17), while beer (3) and wine (1) contributed minimally. These findings suggest racial differences in polyphenol consumption exist at the group level, though individual disparities remain unclear.

Introduction

Polyphenols, plant-based compounds with anti-inflammatory properties, vary in dietary intake due to demographic factors. Understanding these variations may reveal broader dietary inequities. This study examines polyphenol consumption by gender and race, identifying intake disparities across six dietary sources.

Methods

Polyphenol intake was assessed using the DHQ-3, a web-based food frequency questionnaire. Reported intake was analyzed against a polyphenol database. A t-test compared intake by gender, while a one-way ANOVA examined racial differences.

Results

No significant difference in polyphenol intake was found between genders. Racial differences were significant, though post-hoc tests did not confirm specific disparities. Fruit and coffee were the most common polyphenol sources, while beer and wine were least consumed.

Conclusion

This study highlights racial differences in polyphenol intake but suggests further research is needed to clarify the underlying factors. Investigating socioeconomic and cultural determinants may help address dietary disparities.

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Submit your abstract here:

Data-driven weights for optimizing power in genome-wide association studies

Sonali Gupta, Georgios Voloudakis, Gabriel Hoffman, Panos Roussos, David Burstein

Background

Despite their success, genome-wide association studies (GWAS), have been plagued by a replication crisis, where genome-wide significant SNPs are not replicated across studies. Bonferroni and false discovery rate multiple testing corrections which uniformly downweight all p-values, reducing statistical power. To address this, we developed statistical software to boost power by constructing data-driven weights that incorporate prior information about the SNPs while controlling the false discovery rate.

Methods

We perform simulations leveraging effect sizes and standard errors from discovery cohorts to inform the optimal p-value weighting scheme to maximize power. Building upon recent advances in statistical modelling, we account for effect size heterogeneity and replication bias across large-scale datasets by integrating PheMED to quantify phenotypic misclassification using only summary statistics. We also correct for the winner's curse, acknowledging that random variation significantly influences top SNP rankings when performing millions of statistical tests.

Results

Our methodology increased replication power from 27.9% to 38.5% when applied to binge-eating disorder GWAS data from the Million Veteran Program. The weighted hypothesis testing approach strengthens replication despite phenotypic misclassification and statistical dilution. We will further evaluate using additional Million Veteran Program GWAS data, particularly for neuropsychiatric traits. Our approach also identifies systematic biases, improving GWAS reproducibility and interpretability.

Conclusions

Our tool enhances GWAS replication efforts by integrating prior knowledge and correcting for biases like the winner’s curse, effect size heterogeneity and accounts for the impact of phenotype misclassification and statistical dilution. Preliminary results show that data-driven hypothesis weights increase the power for replication by 10.6%. This tool can serve as a valuable resource in maximizing meaningful discoveries by enhancing study design, refining effect size estimation, and ensuring robust findings across diverse cohorts.

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Submit your abstract here:

Title: LEAP2 as a Potential Modulator of Stress-Induced Metabolic and Behavioral Changes

Authors: Susana Munoz-Lara, Alex Gillespie, Daelah Nicholas, Ki Ann Goosens

Background:
Ghrelin, a stomach-derived peptide hormone, stimulates hunger and is elevated after chronic stress, remaining high in both rodent stress models and trauma-exposed humans (Yousufzai et al., 2018). Chronic stress is linked to weight gain, impaired glucose tolerance, and heightened fear responses—effects likely driven by increased ghrelin signaling. Liver-expressed antimicrobial peptide 2 (LEAP2) is an endogenous antagonist of the ghrelin receptor (Ge et al., 2018). We hypothesize that LEAP2 counters chronic stress-induced ghrelin elevation and propose that LEAP2 overexpression could mitigate stress-related weight gain, glucose intolerance, and fear responses, offering a potential therapeutic target for metabolic and psychiatric disorders.

Methods:
A total of 28 mice (8 females, 20 males) were injected with either an AAV8-LEAP2 virus (n = 13) or an AAV-shmir-LEAP2 virus (n = 15). Mice were weighed on the day of injection and weekly for approximately 6 weeks. Four weeks post-injection, a glucose tolerance test was performed, followed by three days of contextual fear conditioning and testing.

Results:
Mice injected with AAV-shmir-LEAP2 showed greater weight gain compared to baseline. These animals also exhibited reduced glucose tolerance relative to the AAV8-LEAP2 group. AAV8-LEAP2 mice demonstrated lower freezing behavior following shocks and weaker long-term contextual fear memory compared to AAV-shmir-LEAP2 mice, suggesting a reduced fear response.

Conclusions:
AAV-LEAP2 mice demonstrated weight loss, consistent with existing literature linking enhanced LEAP2 to reduced food intake via decreased ghrelin signaling. However, AAV8-LEAP2 mice exhibited impaired glucose clearance, contradicting our hypothesis that LEAP2 elevation would improve glucose tolerance. These findings suggest that elevated LEAP2 may contribute to glucose intolerance, a potential risk for conditions like diabetes. Additionally, reduced freezing behavior in AAV-LEAP2 mice indicates that LEAP2 elevation may enhance stress resilience.

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Cross-Ancestral Gene-Target Prioritization for Opioid Use Disorder

Suzannah De Almeida, David Burstein, Eirini Sparaki, Panos Roussos* and Georgios Voloudakis*

Recent genome-wide association studies (GWAS) have identified genetic regions linked to Opioid Use Disorder (OUD), offering insights into potential treatments. However, variability in disease definitions and population differences across studies weakened genetic associations, a phenomenon known as effect size dilution. This research aims to address this using a novel statistical method, PheMED, to enhance discovery power. Additionally, we aim to integrate cell-type-specific gene expression data to identify causal genetic variants and gene dysregulation driving OUD across ancestries.
PheMED is a cutting-edge statistical methodology designed to enhance the power of GWAS discoveries by correcting for effect size dilution. Preliminary analyses were conducted on publicly available OUD GWAS data for African and European genetic ancestries.
We further incorporated state-of-the-art expression quantitative trait locus (eQTL) reference panels to map gene activity patterns to specific brain cell types. Mendelian randomization, a causal inference statistical framework, was utilized to integrate genetic variants and eQTL data to uncover cell-type-specific genetic risk mechanisms for OUD.

Preliminary analyses using PheMED revealed a 111% increase in discovery power for African genetic ancestry and a 78% increase for European genetic ancestry. Integrating eQTL data under the Mendelian randomization framework identified several novel and previously reported genes with potential drug targets, including African genetic ancestry: RTN4 and EPHX2 in astrocytes and European genetic ancestry: NCAM1 in inhibitory neurons and GABRA2 in excitatory neurons.

Our results demonstrate that correcting for effect size dilution using PheMED significantly enhances gene discovery across populations. By integrating cell-type-specific gene expression data, we reveal novel mechanistic insights into OUD and identify actionable genetic targets for therapeutic development. This research has the potential to advance personalized medicine approaches for OUD treatment and improve reproducibility in genetic studies across ancestries.

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Submit your abstract here:

Title: Deciphering Single-Cell Genomic Landscape of Brain Somatic Mosaicism in Alzheimer's Disease

Authors: Swapnil Tichkule, Pengfei Dong, Gabriel Hoffman, Panos Roussos

Background: Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disorder, characterized by toxic protein accumulation, causing cellular dysfunction and neuronal loss. While genetic factors play a role, germline mutations explain only ~50% of cases, leaving many sporadic cases unexplained. Somatic mutations (SMs)—non-inherited genetic alterations that accumulate with age—are emerging as potential contributors to neurodegeneration, but their role in AD remains unclear.

Methods: We performed joint multi-omic single-nucleus sequencing (snRNA-seq and snATAC-seq) on brain samples from 135 AD cases and 111 unaffected controls. Neuronal and glial brain cell types were identified and annotated across three brain regions (Brodmann areas 22, 36, and 46). De novo SMs were identified, with stringent filtering applied to exclude germline variants and artifacts. We then used linear mixed models to estimate SM accumulation rates, deconvoluted mutagenic processes contributing to SMs, and assessed their pathogenic effects and functional consequences in driving AD pathogenesis.

Results: Our findings reveal that AD exhibits a high SM accumulation rate across all studied brain regions and cell types, primarily due to impaired DNA repair mechanisms. Notably, glial cells displayed a significantly higher SM burden compared to neuronal cells. Moreover, SMs show highly pathogenic effects, being particularly enriched in AD-associated genes, including APP and PSEN1, and implicating critical biological processes such as neuronal growth, development, function, communication, and microtubule instability.

Conclusion: We highlight SMs as a potential yet underrecognized contributor to AD pathology, addressing gaps left by germline studies. The enrichment of SMs in previously unreported genes and pathways highlights their novel role in AD progression. This finding enables patient stratification based on SM burden and supports targeted therapeutic strategies to mitigate DNA repair deficiencies, advancing precision medicine in AD.

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Submit your abstract here:

Impairment in synaptic downscaling in striatal projection neurons expressing Parkinson's linked LRRK2-G2019S mutation

S Gupta, A Tielemans, CA Guevara, P Del Valle, AR Magee, GW Huntley, DL Benson

Background: People with Parkinson's including those carrying LRRK2G2019S mutations show cognitive impairments compared to the non-PD population. The mechanisms driving this are poorly understood. Our recent work shows that corticostriatal synapses in D1R-striatal projection neurons (SPNs) in mice expressing LRRK2-G2019S accumulate an excess of GluA1-containing AMPARs that is permissive for LTD but prevents LTP. We hypothesized that the LRRK2-G2019S mutation disrupts homeostatic scaling, which normally adjusts surface AMPA receptor levels while retaining relative differences in synapse strength, ultimately impairing cognitive function.

Methods: Network activity was modulated in wildtype and LRRK2-G2019S cortico-striatal co-cultures with TTX (to induce upscaling) or bicuculline (downscaling). Surface AMPAR subunit levels were quantified by surface biotinylation and immunolabeling. To assess synaptic scaling in intact circuits, we selectively manipulated D1R-SPN activity using Cre-dependent excitatory or inhibitory DREADDs in Drd1a-Cre and LRRK2-G2019SxDrd1a-Cre mice. Whole-cell patch-clamp recordings of mEPSCs were acquired following JHU mediated DREADD activation, administered through drinking water for 48h.

Results: In wildtype SPNs, GluA1 but not GluA2 surface levels scaled up and down in response to TTX and bicuculline, respectively. However, LRRK2-G2019S SPNs failed to downscale AMPARs while upscaling remained intact. Similarly, by chemogenetic manipulation of intact circuits, wildtype D1R-SPNs exhibited changes in synaptic strength consistent with up- and downscaling, whereas LRRK2-G2019S D1R-SPNs failed to downscale. Notably, mEPSC amplitudes in neighboring non-DREADD-expressing D2R-SPNs remained unchanged upon JHU activation, suggesting that homeostatic scaling may be cell-autonomous in SPNs.

Conclusions: These findings identify a homeostatic synaptic defect in LRRK2-G2019S D1R SPNs, where impaired downscaling may contribute to synaptic saturation and dysfunction. These data suggest that in human Parkinson’s, both Hebbian and homeostatic synaptic plasticity deficits may contribute to cognitive impairments.

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Submit your abstract here:

Does Leap 2 Promote Stress Resilience in Mice?

Tahsina Islam, Alex Gillespie, Daelah Nicholas, Susana Munoz-Lara, & Ki A. Goosens

Background: Ghrelin is a hormone produced in the stomach that activates growth hormone secretagogue receptors (GHS-R). Chronic stress can lead to weight loss, increased blood glucose levels, and heightened fear responses in rodents, effects that are likely driven by enhanced ghrelin signaling. Liver-expressed antimicrobial peptide 2 (LEAP2) is a natural antagonist of ghrelin. It prevents ghrelin from binding to GHS-R, thereby inhibiting GH release, lowering basal glucose levels, and reducing food intake during fasting states.

Methods: Our lab hypothesizes that LEAP2 modulates the impact of chronic stress-induced ghrelin; LEAP2 overexpression will limit stress-induced elevation of blood glucose, fear, and weight loss. 11 mice (8 females and 3 males) were injected either with an AAV8-LEAP2 or an AAV-shmir-LEAP2 virus 4 weeks before behavioral testing. Weights were recorded a week before behavior testing and every week following. A glucose tolerance test was performed the day before the subjects underwent two days of fear conditioning, which was followed by a week of immobilization stress exposure (1hr/day) Blood glucose levels were measured before and after stress.

Analysis/Conclusion:
According to Figure 2, Mice who received the AAV-shmir-LEAP2 virus had a greater percent weight change compared to their body weight before behavior testing, which is consistent with previous studies. Figure 3 shows that the AAV8-LEAP2 virus mice could not clear glucose from their blood as quickly compared to AAV-shmir-LEAP2 mice, which is inconsistent with previous data. We expected that increased levels of LEAP2 would enhance glucose tolerance, instead, our data suggest mice with high LEAP2 levels have glucose intolerance, which can lead to diabetes. Figure 4 indicates, AAV8-LEAP2 animals froze more than the AAV8-shmir-LEAP2 animals, suggesting that higher levels of LEAP2 do promote stress resilience.

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Submit your abstract here:

Lysosomal Proteins in Cerebrospinal Fluid as Biomarkers for Parkinson's Disease

Takahiro Shimizu, Cong Xiao, Henry Kim, Xianting Li, Zhenyu Yue

Background
Parkinson's disease (PD) is the second most common neurodegenerative disorder in the United States, characterized by intracellular α-synuclein accumulation and dopaminergic neuron degeneration in the substantia nigra pars compacta. While advancements in diagnostic tools, such as neuroimaging, have facilitated PD diagnosis, biomarkers for ultra-early detection and those reflecting PD pathophysiology remain unavailable. Many PD-associated risk genes function within the autophagy-lysosome pathway, implicating lysosomal dysfunction in PD pathogenesis. Recent studies indicate that dysfunctional lysosomes are actively secreted; LRRK2, a well-known PD-associated gene, plays a central role in this process. This study investigates lysosomal proteins in cerebrospinal fluid (CSF) as potential PD biomarkers.

Method
We analyzed CSF proteomics data from the publicly available Parkinson's Progression Markers Initiative (PPMI) database. Furthermore, we used a mouse model carrying the LRRK2 G2019S mutation, a well-known disease-associated mutation, to investigate the effects of LRRK2 mutations on lysosomal secretion.

Results
PPMI CSF proteomics data revealed enrichment of lysosomal proteins in PD patients carrying the LRRK2 pathogenic variant (LRRK2 PD). In primary astrocytes from LRRK2 G2019S mutant mice, lysosomal overload stress increased lysosomal secretion compared with WT primary astrocytes. Furthermore, α-synuclein preformed fibrils (PFFs), which accumulate in PD brains, induced similar lysosomal overload stress and activated LRRK2.

Conclusions
Elevated lysosomal proteins in CSF may serve as a biomarker for LRRK2 PD. Primary culture experiments indicate that this increase may reflect lysosomal overload stress in the brain, with α-synuclein PFFs possibly contributing to this stress in PD.

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Cross-Species Proteomics Reveal Placental Mitochondrial Dysfunction Induced by Cannabis Exposure

Teesta Naskar, Yoko Nomura, Randy Ellis, Angus Nairn, Yasmin Hurd

BACKGROUND: Cannabis is widely used during pregnancy, with a prevalence of 3–16% among pregnant women in the U.S. While prenatal cannabis exposure (PCE) affects fetal brain development, its molecular mechanisms remain unclear. This study examines PCE's effects on the placenta in human and rodent models.

METHODS: Placental biopsies were collected from cannabis-exposed and non-exposed women at delivery, and rat placental samples were obtained between gestational days 16–21. Proteomic analysis using LC-MS/MS identified differentially expressed proteins (DEPs). Human DEPs were analyzed using the limma R package, adjusting for confounders, while rat DEPs were assessed using one-way ANOVA. Pathway and protein-protein interaction analyses were conducted.

RESULTS: We identified 2,642 DEPs in human and 671 DEPs in rat placenta (FDR <0.05). Both models showed significant changes in oxidative phosphorylation and mitochondrial dysfunction. Key upstream regulators, β-estradiol and GABA were similarly altered in both species. Notably, several cytochrome P-450 enzymes (CYP11A1, CYP19A1), hydroxysteroid dehydrogenases (HSDs: 3β-HSD, 17β-HSD), and heat shock proteins (HSP60) were upregulated in human placenta.

CONCLUSION: Collectively our findings suggest PCE disrupts placental mitochondrial steroidogenesis. β-Estradiol regulates mitochondrial function modulating OXPHOS, ROS balance, and apoptosis. Maternal cholesterol is converted to progesterone via CYP11A1 and 3β-HSD, generating NADH for OXPHOS at outer membrane of placental mitochondria. Dysregulated NADH production disrupts redox balance, leading to oxidative stress. Upregulation of CYP11A1, CYP19A1, HSP60, and HSDs suggests altered progesterone-estrogen balance. This disruption, alongside mitochondrial dysfunction, may impair placental health, linking steroid hormone biosynthesis to oxidative phosphorylation and PCE-induced oxidative stress.

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Submit your abstract here:

Improving glioblastoma survival by combining YAP-TEAD inhibitors with surgical resection in preclinical xenograft models

Thenzing J. Silva-Hurtado, Balagopal Pai, Raymund L. Yong, Tracy T. Tang and Nadejda M. Tsankova.

Background: The infiltrative phenotype of glioblastoma (GBM) poses a major challenge to treatment, leading to incomplete tumor resection and inevitable recurrence by residual disease. Standard-of-care therapy does not inhibit GBM infiltration, and most preclinical models do not mimic surgical resection. The Hippo pathway, specifically YAP/TAZ-TEAD signaling, has been implicated in GBM plasticity and tumor migration, making it a promising therapeutic target.

Methods: We tested the preclinical efficacy of novel YAP-TEAD inhibitors from Vivace Therapeutics (VT), VT103 and VT104. To better replicate clinical GBM treatment, we also developed a surgical resection model in mice with PDX gliomas.

Results: Anti-migration efficacy of VT103 and VT104 in vitro was demonstrated using cell migration assays in three patient-derived GBM cell lines ($p<0.01$, each). VT103 and VT104 inhibited TEAD1 transcription activity, reducing TEAD1-target genes CYR61 ($p<0.001$) and CTGF ($p<0.05$) by qRT-PCR, confirming anti-TEAD pharmacodynamic activity. Pharmacokinetics analysis showed robust brain penetrance (Brain: Plasma >200%). Orthotopic PDX mice with infiltrative GBM-like tumors showed delayed progression after VT104 treatment vs. vehicle controls ($p=0.03$; $n=8$). In addition, we implanted the infiltrative PDX GBM line G16302-Akaluc in the frontal cortex, resecting the proliferative core six weeks post-implantation. Histological analysis confirmed tumor removal and residual disease at the margin. Resected mice exhibited significantly prolonged survival vs. non-resected controls (log-rank $p=0.0448$; $n=6$), with survival of 91-100 days in controls vs. 97-107 days in resected mice, paralleling clinical benefit in human GBM.

Conclusion: By integrating YAP-TEAD inhibition with surgical resection in PDX models, we now aim to evaluate the synergistic effects of standard-of-care, targeted YAP-TEAD inhibitor therapy and tumor debulking in a clinically relevant setting.

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Submit your abstract here:

Optimizing Audiovisual Recording Equipment for AI-Driven Psychiatric Research: A Feasibility Pilot Study

Shalaila Haas, Lauren Lepow, Theodore Servedio, Bailey Todtfeld, Maya Valenzano, Debora Gonzalez, Deborah Obiajulu, Heather Thibeau, Rachel Jespersen, Yulia Landa, Stephen Heisig, Einat Liebenthal, Carla Agurto Rios, Gaoussou Youssef Kebe, Marcelo Ciconnet, Muhammad Parvaz, Eduardo Castro, Marc Aafjes, Justin Baker, Guillermo Cecchi, Cheryl Corcoran, Rene Kahn

Background: The PREDiCTOR study leverages artificial intelligence and behavioral data to enhance mental health care for patients entering outpatient psychiatric treatment at one of six Mount Sinai Health System clinics. A key component involves capturing audiovisual (AV) data during clinical interactions to analyze behavioral markers predictive of treatment outcomes. This pilot study evaluated the feasibility, comfort, and acceptability of different AV setups for outpatient psychiatric research.
Methods: Twenty-six current MSHS outpatients, were recorded using five AV setups: Logitech Brio webcam, OBSBOT-Meet-2 webcam, single iPhone, dual iPhones, and Insta360 camera. Setups were selected after previous testing ensured adequate facial pixel density, field of view, and audio quality. Each participant experienced up to five minutes of recording with each setup and provided feedback on comfort, distraction, impressions, and willingness to consent to PREDiCTOR participation.
Results: The OBSBOT was rated the most comfortable and least distracting, followed by the Logitech. Both were described as small, unobtrusive, and blending into the environment. The single iPhone and Insta360 were the least preferred due to their intrusive positioning between them and the clinician. Consent rates reflected these preferences, highest for webcams (OBSBOT: 96.2%, Logitech: 84.6%) and lowest for the single iPhone (42.3%).
Conclusions: Webcams, particularly the OBSBOT, provide a feasible, minimally intrusive AV recording method for outpatient psychiatric research. Their high acceptability and consent rates support their integration into AI-driven studies like PREDiCTOR, where behavioral markers may enhance early detection and individualized treatment planning in precision psychiatry.

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Submit your abstract here:

Resilient Specific Sex-Conserved Transcriptomic Networks in the Nucleus Accumbens following Chronic Social Defeat Stress in Mice

Major depressive disorder (MDD) is a leading cause of disability and contributor to suicide, according to the World Health Organization. Chronic stress is a primary risk factor for MDD and is often modeled in rodents using the chronic social defeat stress (CSDS) paradigm. This approach identifies animals along a continuum of responses, from those developing depression-like abnormalities (susceptible) to those maintaining normal behavioral function (resilient). While informative, this model has been predominantly studied in male mice, leaving female mice underexplored. Considering depression's higher prevalence in women, understanding sex-specific molecular mechanisms underlying susceptibility and resilience is critical.

To address this, we adapted the CSDS model for female mice and used RNA-sequencing to analyze transcriptional changes associated with susceptibility-resilience across multiple brain regions. Comparing our data with male studies revealed striking sexual dimorphism in molecular adaptations linked to susceptibility or resilience. However, a cluster of genes uniquely upregulated in the nucleus accumbens (NAc) of resilient mice overlapped by ~40% between sexes.

We performed Weighted Gene Co-Expression Network Analysis (WGCNA) on resilient male and female mice, identifying convergent gene modules, with one pair displaying 25% overlap—the highest across sexes. These modules were highly enriched for differentially expressed genes upregulated in the NAc of resilient mice. Within these modules, two key driver genes, GPRIN1 and STX1A emerged as regulators, positively correlating with resilience in both sexes.
To investigate their roles, we used viral manipulation to overexpress GPRIN1 and STX1A in NAc neurons of male mice before CSDS, which induced pro-resilient effects. Ongoing research characterizes transcriptional, neuronal, and circuit-level functions mediated by these genes to uncover resilience mechanisms.

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Submit your abstract here:

Title: "Ventral hippocampal circuit mediating threat and safety"

Author: Tri Dong, Roger Clem

Abstract:

Heightened and persistent fear response is a hallmark of many psychiatric disorders including post-traumatic stress disorder (PTSD), which is clinically targeted through exposure therapy. Although exposure therapy is efficacious, the response rate is suboptimal as seemingly extinguished fear often returns, suggesting that extinction temporarily suppresses pathological fear. Indeed, the current theory holds that fear and extinction learning result in long-term memories of threat and safety that compete for control over behavior. In rodents, contextual fear-conditioning and extinction engage orthogonal populations of principal neurons (PNs), providing potential substrates for signaling these distinct associations. Recent work from our lab has shown that GABAergic somatostatin interneurons (SST-INs) in the ventral cornu ammonis 1 (vCA1) region are activated following contextual fear extinction, and manipulation of SST-IN activities modulate fear expression during extinction retrieval and relapse. Hence, SST-INs might gate the expression of context fear through selective microcircuit control over fear- and extinction-related PNs. However, whether this process is driven solely by SST-INs or through interaction with other hippocampal INs is unclear. In addition, vCA1 PNs send projections to various downstream regions implicated in valence processing; hence, fear and extinction-related memory may engage distinct outputs modulated by SST-INs. Overall, this project seeks to understand the circuit mechanisms that govern the activity of fear- and extinction-related neuronal ensembles to help improve recovery from emotional trauma.

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Submit your abstract here:

Age and Screen Time: How COVID-19 Redefined Media Consumption

Ty Bell, Faith Adams, Karmiella Ferster, Rachel Heisler, Muhammad Parvaz

BACKGROUND: The COVID-19 pandemic led to dramatic shifts in many aspects of our lives and how we spend our time. To better analyze these changes, the CoRonavIruS Health and Impact Survey (CRISIS) was created. CRISIS is a clinical instrument that enables researchers to examine the extent to which the pandemic has impacted the mental health and behavior of individuals. Limited research exists on how media use patterns change in response to crises on the scale of the pandemic, along with studies measuring these changes in correlation with age. This study aims to uncover how the COVID-19 pandemic influenced media consumption (TV, social media, and video games) across different age groups and the broader implications for mental health.

METHODS: Using CRISIS, media use was examined among 950 participants across three age groups: under 18, 18-25, and 25-40. The survey was administered before and after the lockdown, with data analyzed for frequency shifts in media use.

RESULTS: All age groups reported increased media consumption, with younger participants exhibiting the most significant rise in screen time and a higher non-disclosure rate. In contrast, older participants maintained relatively stable usage patterns, suggesting age-related differences in behavioral responses to the pandemic.

CONCLUSIONS: These findings highlight the need for public health strategies for media usage. By understanding media use trends in response to events such as the pandemic, we can be better prepared for these scenarios and everyday life.

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Role of dopaminoceptive cells in ventral hippocampus in cocaine action

Veronika Kondev, Arthur Godino, Brian Kipp, Elizabeth Kahn, Rita Futamura, Angelica Minier- Toribio, Alexa LaBanca, Tamara Markovic, Eric J. Nestler

Background: The vHPC exhibits topographical organization of D1- and D2-expressing cells, and its activity is critical for associative learning, emotional processing, and negative affect, and more recently drug seeking and drug taking. Our lab has previously identified that these D1 vs. D2 cells have opposing roles on innate approach-avoidance conflict, with D1 cells promoting anxiogenesis and avoidance, while D2 cells promote anxiolysis and approach.

Methods: Here, using interdisciplinary neuroscience approaches, including optogenetics, fiber photometry, and RNA-sequencing, we establish that these cells play non-overlapping roles in modulating reward-context representations.

Results: D1 inhibition, but not D2 modulation, is necessary and sufficient to promote expression of cocaine conditioned place preference (CPP). Rather than being involved in associative learning, D2 cell activation promotes positive reinforcement and preliminary data suggests that D2 activity also promotes voluntary consumption of cocaine. The propensity to relapse is defined by both associative learning processes (D1-dependent) and motivation (D2-dependent); as such, integration by these dopaminoceptive cells could represent new targets mediating relapse vulnerability.

Conclusions: D1 and D2 vHPC cells have distinct roles both from each other as well as compared to dopaminoceptive cells in the striatum. Future directions involve testing the contribution of D1 vs. D2 cells in regulating drug-induced reinstatement. These data will shed light on non-striatal dopaminergic regulation of motivated behavior, with a specific focus on the molecular and cellular determinants underlying relapse.

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Submit your abstract here:

Investigating Limits of Microglia Plasticity in the Healthy Brain, Aging, and Neurodegeneration
Vinaya Sahasrabuddhe, Anne Schaefer

Background:
Microglia, the resident macrophages of the central nervous system, continuously survey their environment and perform specialized functions that vary across brain regions. For example, microglia in the cerebellum and hippocampus exhibit high clearance capacity, while those in the striatum adopt a high-surveillance phenotype. With aging, microglia undergo progressive shifts, losing homeostatic features and gaining inflammatory characteristics, and in neurodegenerative diseases, they display even more extreme and heterogeneous states. While microglial diversity is well documented, it remains unclear whether these states are reversible or fixed. To address this, I employ a novel microglia transplantation approach.

Methods:
Acutely isolated microglia are stereotaxically transplanted into FIRE mice, a genetic model lacking endogenous microglia. By tracking microglial states over time, I aim to determine whether their phenotypic adaptations are plastic or fixed. Immunofluorescence, transcriptomics, and chromatin accessibility analyses assess their fate.

Results:
I optimized a protocol for adult-to-adult microglia transplantation, showing that transplanted microglia proliferate, migrate, and successfully integrate into the brain parenchyma. This approach is now applied to test plasticity versus stability in:

Brain Region-Specificity: Transplanting cerebellar microglia into the striatum will reveal whether region-specific characteristics are dynamically regulated by local cues or developmentally imprinted. Preliminary data suggest certain region-specific features remain stable post-transplantation.
Aging and Neurodegeneration: Microglia from aged (~20-month-old) and 5XFAD (Alzheimer's model) mice successfully engraft into adult brains, allowing investigation into whether aging- and disease-associated phenotypes can be reversed in a young, healthy environment.

Conclusion:
Microglia transplantation provides a powerful tool to dissect the plasticity and stability of microglial states. These experiments will yield critical insights into microglia adaptability in health, aging, and neurodegeneration, with implications for therapeutic strategies.

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Submit your abstract here:

Spatial metabolomics and metabolic rate analysis in the mouse brain

BACKGROUND: Elucidating metabolic processes in the brain requires tools that preserve tissue architecture while allowing for the measurement of dynamic metabolic fluxes. Conventional extraction-based approaches often lose spatial information, and the heterogeneity of brain regions makes it challenging to capture distinct metabolic phenotypes. We present mass spectrometry imaging (MSI), coupled with stable-isotope tracers, as a method that overcomes these limitations by simultaneously mapping metabolite distributions and labeling patterns within intact tissue sections.

METHODS: [U-13C]glucose was administered intraperitoneally to wild-type mice, and after reaching isotopic steady state, brain tissue was extracted and cryosectioned onto indium titanium oxide (ITO) slides. A matrix of α-cyano-4-hydroxycinnamic acid (CHCA) was applied via sublimation, and MSI data were acquired in positive mode at 25 µm spatial resolution. Data were processed and analyzed in R to generate ion distribution maps, perform segmentation analyses, and quantify 13C-enrichment in metabolites (e.g., glutamate, glutamine, GABA). Chemical standards were used to confirm metabolite identities, and MSI-derived isotopologue enrichments were compared to GC-MS data from parallel brain extracts.

RESULTS: Our protocol provides high-resolution spatial maps of both unlabeled (M+0) and labeled (M+n) isotopologues, revealing region-specific metabolic profiles in cortical and cerebellar areas. We confirmed metabolite identifications by matching observed m/z values with standards, and comparisons of 13C-enrichment data from MSI and GC-MS showed strong correlation ($R \approx 0.86$). Coefficients of variation remained below 25% across biological replicates, demonstrating the protocol's reproducibility.

CONCLUSIONS: By combining MSI with stable-isotope tracing, we establish a robust platform to visualize and quantify regional brain metabolism. Our approach preserves tissue architecture, enables detailed mapping of metabolic fluxes, and can be adapted to diverse tracers. These spatially resolved metabolomic analyses provide a powerful tool to characterize the chemical architecture of the brain in normal and pathological conditions.

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Early warning radar: Hypothalamic CARTpt neurons decode ambiguous threat signal

Xingliang Yang, Xueming Hu, Xingqi Guo, Xie Zili, Yachen Yang, Fang Gao, Nobuya Abe Kaikai Zang, Hongzhen Hu

Predator detection and false alarm silence based on cue induced exploration is essential for animal's survival. However, the neural mechanisms underlying the coding of ambiguous cues and the circuits driving exploration under uncertainty are unclear. In this study, we identify a group of neurons in the lateral hypothalamus that specifically respond to ambiguous threat cues in freely moving mice, as revealed by in vivo calcium imaging. And these neurons express the cocaine- and amphetamine-regulated transcript prepropeptide (CARTpt) (LHCARTpt). Optogenetic activating LHCARTpt neurons elicited arousal and curiosity, an ambiguous threats-evoked internal states, accompanied by increased focused exploration in varied contexts. Furthermore, we identified functional connections between LHCARTpt neurons and risk-decision-making circuits. Our findings reveal a neural basis for processing ambiguous threats, bridging the gap between two classic predator-related internal states-threat and safety.

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Submit your abstract here:

Single-Cell Spatial Transcriptomic Atlases of the Adult Human Hippocampus Reveal Neurogenesis

Xuan Cao*, Xinyi Wang*, Jaroslav Bendl, John F. Fullard, Donghoon Lee, Guo-Cheng Yuan, Panos Roussos

BACKGROUND: The dentate gyrus of the hippocampus is known to undergo adult neurogenesis, which contributes to brain plasticity and cognitive function. Single-cell transcriptomic profiling has revealed cellular diversity involved in adult neurogenesis. However, spatial organization of this diversity and the gene-regulatory mechanisms governing adult neurogenesis in human hippocampus remain to be explored.

METHODS: To address this, we created a spatially-resolved cell atlas of the human hippocampus by generating imaging-based in situ spatial transcriptomic and single-nucleus multiome(snATAC-seq and snRNA-seq) data from adjacent human hippocampus tissue sections, along with doublecortin(DCX) immunostaining imaging data.

RESULTS: Using both single-cell spatial transcriptomic and single-nucleus-multiome data from 12 adult human donors, we identified 7 major classes and 23 distinct cell subclasses, including 14 neuronal, 2 immune, 4 vascular, and 3 glial cell clusters from 785,060 high-quality hippocampal nuclei. We identified immature dentate granule cells(imGCs) in dentate gyrus from both spatial transcriptomic and single-nucleus-multiome data. Using multimodal data across multiple technologies, we detected imGCs, pointing to the presence of adult neurogenesis. State-of-the-art algorithms were applied to analyze spatially-resolved gene regulatory networks(GRNs) and cell-cell communication(CCC). Using single-nucleus-multiome data from 231,661 nuclei, we constructed enhancer-based-GRNs to identify cell-type-specific regulators and imGCs-associated regulators. By integrating spatial transcriptomic and single-nucleus-multiome data, we computed spatially-resolved whole-transcriptomic profiles and GRNs in individual cells. We further analyzed CCC to spatially map both cell-type-specific and imGC-associated ligand-receptor interactions.

CONCLUSIONS: We generated a comprehensive single-cell, spatially-resolved cell atlas of the human hippocampus, along with imputed whole-transcriptomic profiles and GRNs. Our findings also provide insights into the regulatory mechanisms of imGCs in adult human hippocampus. Together, our study offers a valuable resource for future research into hippocampal functions and related diseases.

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Compensatory Neural Mechanisms and Biomarker Identification in Mild Cognitive Impairment

Yasmin L. Yilmaz, Sagan K. Leggett, Mariana G. Figueiro , Ola A. Alsalman

Mild cognitive impairment (MCI) is a condition marked by cognitive and memory decline, often progressing to Alzheimer's disease (AD). Early diagnosis of MCI is crucial, with techniques like fMRI and PET imaging revealing differences in brain activity. Electroencephalography (EEG) offers a non-invasive, cost-effective method to track neural changes and identify potential markers for distinguishing MCI from normal aging.

This study involved 66 participants: 28 with mild cognitive impairment (MCI), 23 age-matched healthy controls (AmHC), and 15 young healthy controls (YHC). Participants were assessed using resting-state EEG, a 2-back working memory task, and the Karolinska Sleepiness Scale. EEG recordings were collected in a 5-minute session, followed by the working memory task and sleepiness assessment. Data were processed using EEGLAB, with a band-pass filter applied (0.1–55 Hz). Fourier-cross spectral matrices were computed across various frequency bands (delta to gamma). Comparisons included EEG functional connectivity, task performance, and sleepiness scores across the groups.

Participants with mild cognitive impairment exhibited significantly higher functional connectivity compared to age-matched healthy controls and young healthy controls across multiple brain networks, including the Central Executive Network (CEN) and Default Mode Network (DMN), particularly in the delta, theta, and beta frequency bands. These differences were most prominent in regions such as the posterior parietal cortex, prefrontal cortex, and insula. No significant Functional connectivity differences were found between AmHC and YHC groups.

This study explores how changes in brain activity are linked to MCI, showing how the brain tries to adapt to early cognitive decline. The results reveal that the higher functional connectivity in the default mode network (DMN) and salience network seems to be the brain's way of compensating to preserve cognitive function.

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Submit your abstract here:

Single-Cell Alternative Polyadenylation Atlas of the Human Brain in Alzheimer’s Disease and Aging

Yeon Choi, Pengfei Dong, Gabriel Hoffman, Jaroslav Bendl, Donghoon Lee, Kiran Girdhar, Prashant Fnu, John Fullard, Panos Roussos

BACKGROUND: Alternative polyadenylation (APA) generates isoforms of messenger RNAs (mRNAs) with distinct 3’ termini. Previous studies report that APA is regulated by cell type, age, and disease, necessitating comprehensive single-cell APA analysis in human disease. However, a single-cell view of APA in neurodegenerative diseases remains unexplored due to analytical challenges in large cohorts.

METHODS: We performed a systematic APA analysis on single-nuclei RNA-seq with the PsychAD cohort, comprising 1,494 postmortem brains including individuals with Alzheimer's disease (AD) and controls. We defined polyadenylation sites (PASs) by combining previous mRNA 3'-end annotations and published machine-learning based tool SCAPTURE. To identify differential APA events while adjusting for confounding factors, PAS counts were log-ratio transformed and tested using precision-weighted linear mixed models, with the recently developed pipelines crumblr and dreamlet.

RESULTS: We identified ~108,000 PASs across six major brain cell types and five age groups, spanning childhood to late adults. PAS usage exhibited strong cell-type specificity, with preferential use of downstream PASs in oligodendrocytes and upstream PASs in microglia. Genes with high cell-type PAS variability were enriched in AD, Parkinson’s disease, and oxidative phosphorylation pathways. In AD versus control analysis, we identified ~6,000 differential PAS usage events. A key tauopathy-related gene MAPT showed oligodendrocyte-specific increased use of upstream PASs in AD, while the canonical PAS remained unchanged. Aging was associated with increased use of downstream PASs in excitatory neurons, oligodendrocytes, and astrocytes.

CONCLUSIONS: This study provides the first large-scale, single-cell resolution view of APA dynamics in the human brain. We reveal widespread, cell-type-specific APA regulation in AD and aging, highlighting APA as a potential mechanism in disease progression.

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Submit your abstract here:

The interplay of DLX2, AP-1, and the BAF complex in activity-dependent gene regulation

Yiran Tao, Ruiqi Hu, Mark Youssef, Linda Lee, Nan Yang

BACKGROUND: Neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), are often associated with disruptions in gene regulation within GABAergic interneurons, which play a crucial role in maintaining excitatory-inhibitory balance in the brain. Dysfunction in GABAergic interneurons has been widely implicated in neurodevelopmental disorders. DLX2, a transcription factor essential for GABAergic differentiation, and c-FOS, an immediate early gene activated by neuronal activity, play crucial roles in gene regulation. Previous studies from our group have demonstrated that AP-1 (c-FOS) and DLX proteins come into close chromatin proximity following neuronal stimulation, suggesting a coordinated mechanism of transcriptional regulation. Additionally, the mSWI/SNF (BAF) complex, a chromatin remodeler, is known to facilitate enhancer accessibility in response to neuronal activity. Notably, mutations in genes encoding BAF complex subunits have been linked to NDDs/ASD, underscoring its critical role in neurodevelopment. However, how BAF integrates DLX- and AP-1-dependent transcriptional programs remains poorly understood.

METHODS: In this study, we investigate the role of BAF, DLX2, and AP-1 in activity-dependent gene regulation using HEK293T cells and iPSC-derived GABAergic neurons. Co-immunoprecipitation is performed to examine direct interactions between these factors, while CUT&RUN is utilized to assess chromatin accessibility and transcription factor occupancy under baseline and depolarized conditions.

RESULTS: Our preliminary data has confirmed direct interactions between the BAF complex and DLX2, providing evidence that BAF functions as a chromatin remodeling partner in DLX2-mediated gene regulation. Additionally, we observe that inhibition of BAF activity negatively impacts the expression of late response genes, suggesting its essential role in transcriptional programs that occur downstream of neuronal activity.

CONCLUSIONS: This study explores BAF's role in activity-dependent gene regulation in inhibitory interneurons, highlighting its impact on chromatin remodeling in neurodevelopment and disease.

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Submit your abstract here:

Sex differences in brain cell-type specific chromatin accessibility in schizophrenia

Yixuan Ma, Kiran Girdhar, Gabriel E. Hoffman, John F. Fullard, Jaroslav Bendl, Panos Roussos

Background: Our understanding of the sex-specific role of the non-coding genome in serious mental illness remains largely incomplete.
Methods: To address this gap, we explored sex differences in 1,393 chromatin accessibility profiles, derived from neuronal and non-neuronal nuclei of two distinct cortical regions from 234 cases with serious mental illness and 235 controls.
Results: We identified sex-specific enhancer-promoter interactions and showed that they regulate genes involved in X-chromosome inactivation (XCI). Examining chromosomal conformation allowed us to identify sex-specific cis- and trans-regulatory domains (CRDs and TRDs). Co-localization of sex-specific TRDs with schizophrenia common risk variants pinpointed male-specific regulatory regions controlling a number of metabolic pathways. Additionally, enhancers from female-specific TRDs were found to regulate two genes known to escape XCI, (XIST and JPX), underlying the importance of TRDs in deciphering sex differences in schizophrenia.
Conclusions: Overall, these findings provide extensive characterization of sex differences in the brain epigenome and disease-associated regulomes.

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Submit your abstract here:

Bipolar and Schizophrenia risk gene AKAP11 encodes an autophagy receptor mediating PKA-RI degradation and synaptic PKA activity regulation through SPHKAP-VAPA interaction

You-Kyung Lee, Cong Xiao, Xiaoting Zhou, Le Wang, Meghan G. McReynolds, Zhiping Wu, Eric Purisic, Henry Kim, Xianting Li, Zhiping Pang, Jinye Dai, Junmin Peng, Nan Yang, Zhenyu Yue

Protein-truncating variants in AKAP11 have been identified as risk factors for bipolar disorder (BD) and schizophrenia (SCZ), implicating a shared disease mechanism driven by AKAP11 loss-of-function. However, the neurobiological functions of AKAP11 remain largely uncharacterized. To investigate its cellular functions, we conducted an interactome analysis in CNS neurons from AKAP11-eGFP transgenic mice. This analysis revealed that AKAP11 interacts with the PKA-RI adaptor SPHKAP and the ER-resident autophagy-related proteins VAPA/B, which co-adapt and mediate PKA-RI complex degradation in neurons. Notably, our results show that AKAP11 deficiency leads to the accumulation of SPHKAP and expansion of PKA-RI-SPHKAP-VAPA puncta, indicating impaired clearance of these complexes. This disruption of complex degradation results in compartment-specific alterations in PKA activity. Further analysis in autophagy-deficient (Atg7-cKO) neurons confirmed that SPHKAP degradation is autophagy-dependent, supporting the role of AKAP11 in selective autophagy. These findings highlight the role of AKAP11 in maintaining neuronal function and suggest that its loss-of-function contribute to BD and SCZ pathophysiology through impaired autophagy and PKA regulation in neuron.

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An amygdala to anterior hypothalamic circuit gates negative valence and stress vulnerability

Zachary T Pennington, Alexa R LaBanca, Shereen D Abdel-Raheim, Madeline E Bacon, Afra N Mahmud, Patlapa Sompolpong, Austin M Baggetta, Yosif Zaki, BumJin Ko, Yu Feng, Zhe Dong, Alexander CW Smith, Paul J Kenny, Denise J Cai

BACKGROUND: The prior experience of stress is one of the most reliable predictors of adverse reactions to subsequent stress. One proposed mechanism for this phenomenon is the enhanced representation of negative valence. How stress-induced alterations in negative valence are instantiated in the nervous system remain poorly understood.

METHODS: We harnessed unbiased whole-brain activity mapping to identify circuits that are functionally remodeled by prior experience. In vivo calcium imaging with Miniscopes was performed on the anterior hypothalamus to assess processing of negative valence. Cell-type and projection-specific chemogenetic/optogenetic manipulations were carried out to assess the causal contribution of an amygdala to anterior hypothalamic circuit to negative valence processing.

RESULTS: We found that the anterior hypothalamic nucleus (AHN) – a region that to date has received little attention – displays heightened stress reactivity in previously stressed mice. This was accompanied by increased functional connectivity between the AHN and a threat-related limbic network. Using in vivo Miniscope imaging, we found that neuronal activity in the AHN encodes negative valence. Moreover, prior stress amplifies the proportion of valence-encoding AHN neurons. Providing causal support for the AHN's role in negative valence and stress sensitivity, stimulating AHN neurons enhances, and inhibiting their activity mitigates, reactivity to stressful events. Lastly, silencing amygdala inputs to the AHN abolishes the ability of prior adversity to increase stress sensitivity.

CONCLUSIONS: These findings define a key role of the AHN in gating negative valence signals from the amygdala and highlight a novel region that could regulate vulnerability to stressful life events.

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Submit your abstract here:

An interorgan neuroimmune circuit promotes visceral hypersensitivity

Zhen Wang, Xia Meng, Zili Xie, Hongzhen Hu, Brian S. Kim

BACKGROUND: Visceral pain disorders, including Interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) are debilitating conditions with a cardinal painful symptom and functional disorder but unknown etiology. Notably, although bladder and colon pathologies exist as isolated clinical entities, they commonly co-occur with each other and overlap in symptom profiles. Neuroimmune interaction has been postulated as an important mechanism underlying brain-body communication, while lacking in-depth mechanistic understanding on its role in direct communication between visceral organs.

METHODS: We interrogated neuroimmune signaling pathway involved in the crosstalk between the urinary bladder and colon using in vivo behavioral testing, visceromotor response recording, toxin and viral retrograde tracing, in vivo calcium imaging, intersectional genetics, whole tissue clearing and imaging, chemo-genetics, and virally mediated genetic manipulations, as well as novel humanized mice and antagonists.

RESULTS: We identify a mast cell-sensory neuron circuit that initiates bladder inflammation and simultaneously propagates neural hypersensitivity to the colon in a murine model of IC/BPS. We unveil anatomic heterogeneity of mast cells in relation to nociceptors in the bladder and their critical dependence on Mas-related G protein-coupled receptor B2 (MrgprB2) to promote visceral hypersensitivity. We uncover a population of polyorganic sensory neurons that simultaneously innervate multiple organs and exhibit functional convergence. Importantly, we demonstrate that pharmacological blockade of mast cell-expressed MRGPRX2, the human ortholog of MrgprB2, attenuates both bladder pathology and colonic hypersensitivity.

CONCLUSIONS: Our studies reveal evolutionarily conserved neuroimmune mechanisms by which immune cells can directly convey signals from one organ to another through sensory neurons, in the absence of physical proximity, representing a new therapeutic paradigm.

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Submit your abstract here:

Methylome-Wide Association Studies in the Million Veteran Program

Zhenyi Wu, Georgios Voloudakis*, Panos Roussos*

BACKGROUND: Genetically regulated gene expression (GreX) facilitates transcriptome-wide association studies (TWAS) in identifying putative causal relationships between genetic variation and disease. As a heritable intermediate phenotype, DNA methylation (DNAm) is a pivotal epigenetic mechanism involved in gene regulation, serving as a critical bridge between genetic variants and gene expression. To leverage this, we developed DNAm imputation models within the Million Veteran Program (MVP) cohort.

METHODS: A genome-wide methylation quantitative trait loci (mQTL) analysis was performed across different cis-windows to estimate the linear genetic associations. We trained an elastic-net model to impute the genetically regulated human whole blood DNAm. To streamline this DNAm-focused analysis, we established a comprehensive pipeline for data preprocessing, model training, and performance assessment. Downstream analysis including Methylome-Wide Association Studies (MWAS) on imputed methylations, QTL enrichments and Bayesian colocalization are performed to further investigate underlying molecular regulatory mechanisms.

RESULTS: Following stringent quality control, we assessed additive allele dosage effects on DNAm for 3,826,369 variants and 8,703 CpG sites on chromosome 21. We identified 2,489 significant CpG sites (28.6%) at a conservative Bonferroni threshold of $P < 5.75 \times 10\text{-}12$ and 6,128 significant CpG sites (70%) at FDR ≤ 0.05. The highest mean cross-validated prediction R2 between predicted and observed DNAm is 0.062 at a 50,000bp cis-window size. Notably, 172 CpG sites achieved a cross-validated R2 ≥ 0.5, highlighting the robust predictive capacity of our models for a subset of CpG sites.

CONCLUSIONS: Our pipeline uncovers key genetic contributions to DNAm in human whole blood. Future work aims to improve predictive power, extend analyses across diverse ancestries, and characterize the intricate relationship between genetic, epigenetic and transcriptomic variation to better understand their impact on complex traits and diseases.

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Non-invasive capture and manipulation of stress-induced brain activity

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Background: Stress-responsive neuronal circuits orchestrate systemic physiological adaptations critical for cardiovascular and immune functions (Poller et al.). However, their precise role in immune modulation, survival, and cardiovascular health remains unclear.

Methods: Here, we develop two mouse models to capture and manipulate stress-activated neurons in the brain. Using a tamoxifen-inducible, immediate early gene-dependent Cre mouse model (TRAP2/cFos), we capture all neurons activated during a 4-hour acute stress paradigm. By combining this model with a Designer Receptor Exclusively Activated by Designer Drugs (DREADD) system, we selectively reactivate previously captured neurons via clozapine injection (Trap2-DREADD). In a second model, we selectively ablate stress-activated neurons using diphtheria toxin receptor (Trap2-DTR). We use the Trap2-DREADD model to successfully recapitulate stress-induced immune manifestations such as systemic neutrophilia and leukopenia.

Results: Conversely, targeted ablation of stress-activated neurons using TRAP2-DTR model led to fatal outcomes upon restress, suggesting an essential role of these neuronal circuits in survival. While immune alterations following neuronal ablation remain to be characterized, our findings demonstrate the feasibility of TRAP2-based models in capturing stress-activated neural populations and manipulating their function.

Conclusion: This approach provides a powerful framework for dissecting neuroimmune and cardiovascular interactions and the physiological necessity of stress-responsive neuronal circuits.

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Enteric neuronal Piezo1 maintains mechanical and immunological homeostasis by sensing force

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BACKGROUND: The gastrointestinal (GI) tract experiences a myriad of mechanical forces while orchestrating digestion and barrier immunity. How the ~500 million enteric neurons that reside in the GI tract sense and respond to force remains unknown.

METHODS: We analyzed published single-cell RNA sequencing datasets and performed whole-mount immunostaining using Piezo1 reporters. Patch-clamp recordings and Ca^{2+} imaging were conducted to confirm the functional expression of Piezo1. To manipulate Piezo1+ enteric neurons, we employed intersectional approaches combining optogenetic and chemogenetic techniques for activation or inhibition. Various ex vivo and in vivo gut motility assays were used to assess the role of Piezo1 in gut peristalsis. Additionally, we utilized a DSS-induced colitis model to investigate the involvement of Piezo1 in gut immunity.

RESULTS: we identify cholinergic enteric neurons express Piezo1 to sense pressure and regulate neuronal activity. Optogenetic stimulation or chemogenetic inhibition of Piezo1-expressing cholinergic results in accelerated or retarded GI motility, respectively. Loss of Piezo1 in enteric cholinergic neurons prevents recognition of rising luminal intestinal pressure and disrupts GI motility. Additionally, we demonstrate the necessity of intrinsic enteric neuronal Piezo1 in regulating exercise-induced GI motility acceleration and preventing intestinal inflammation in models of IBD.

CONCLUSIONS: Piezo1 on cholinergic neurons is required to accelerate GI motility and to limit aberrant intestinal inflammation in response to internal and external forces.