The Friedman Brain Institute,
Neuroscience Graduate Program *and*
The Charles Bronfman Institute for Personalized Medicine
presents

The 15th Annual Neuroscience Retreat

MAY 12th, 2023

Retreat Organizers
Alexander W. Charney, MD, PhD
and Niamh Mullins, PhD

Icahn
School of
Medicine at
Mount
Sinai

THE FRIEDMAN BRAIN INSTITUTE
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15th Annual Neuroscience Retreat Committee

Retreat Organizers:

Alexander Charney, MD, PhD
Associate Professor – Psychiatry / Genetics and Genomic Sciences

Niamh Mullins, PhD
Associate Professor – Psychiatry / Genetics and Genomic Sciences

Retreat Administrators:

Veronica Szarejko, Danny Roldan, Nicole W. Simons, Vena Persaud and Jenny Rivera

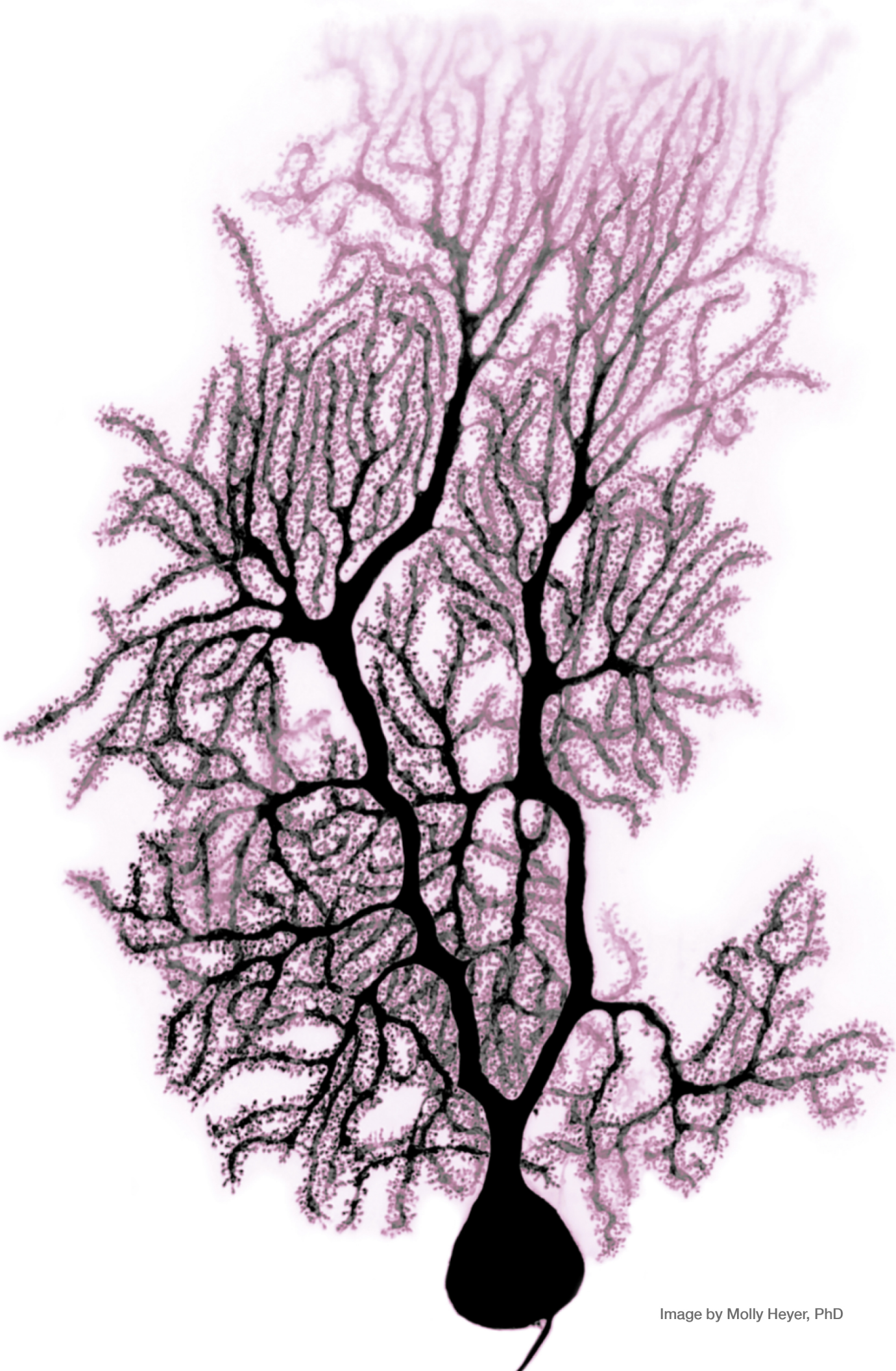

Image by Molly Heyer, PhD

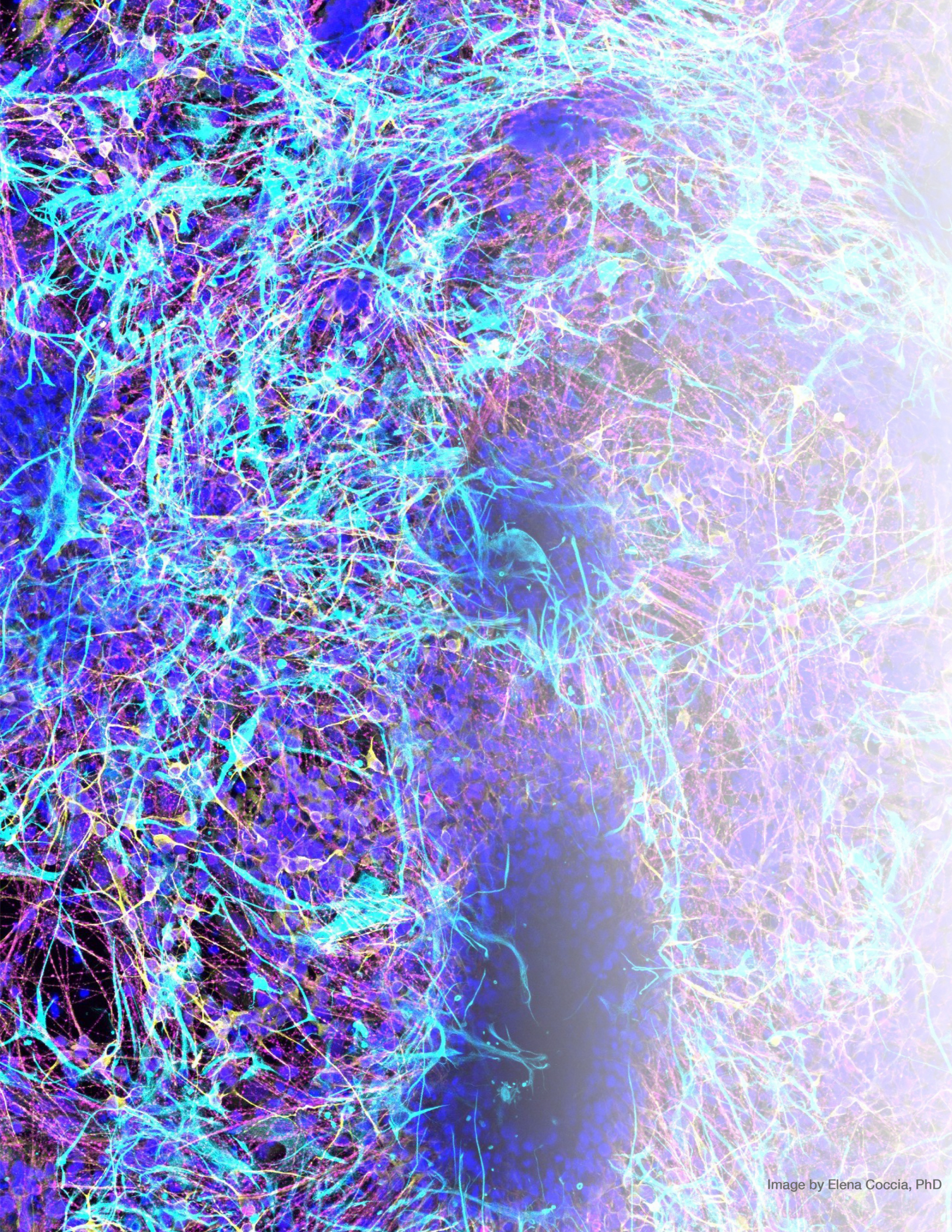

Image by Elena Coccia, PhD

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AGENDA

8:30am
Registration at South Hall Lobby, *Coffee, tea, pastries, fruit*

9:00 – 9:10am
Kick Off: Alex Charney, MD, PhD *&* **Niamh Mullins, PhD**

9:10 – 9:25am
Eric J. Nestler, MD, PhD on Friedman Brain Institute

9:25 – 9:40am
Paul J. Kenny, PhD on Nash Family Department of Neuroscience

9:40 – 9:55am
George Huntley, PhD on Graduate Student Program

10:00 – 10:45am
Keynote Speaker: Eric Schadt, PhD

10:45 – 11:00am
BREAK – Coffee / Raffle in Assembly Hall

11:00 am – 12:00pm
Spotlight Talks:

Muhammad Parvaz, PhD – *"Personalized neuroimaging"*
Martijn Figee, MD, PhD – *"Personalized neurosurgery"*
Nicole Simons, PhD Student – *"Personalized genomics"*
Isotta Landi, PhD – *"Personalized analytics"*

12:00 – 12:30pm
Student Talks

Zach Zeisler (PhD Student, Rudebeck Lab)
"A comparative analysis of amygdala neuron branching in macaques and mice"

Michael B. Fernando (PhD Student, Brennand / Slesinger Labs)
"Precise Therapeutic Targeting of Divergent Mechanisms from Rare NRXN1+/- Deletions"

Sarah Banker (PhD Student, Gu / Schiller / Foss-Feig Labs)
"Impaired Neural and Behavioral Navigation of Dynamic Social Relationships in Autism Spectrum Disorder"

AGENDA

12:30 – 1:30pm
LUNCH – Photo Booth

1:30 – 2:00pm
Postdoc Talks

Francesca Garretti, PhD (Goate Lab)
"A novel EIF2B3 variant as an APOE risk modifier in Alzheimer's disease"

Montserrat Puigdelloses Vallcorba, PhD (Hambardzumyan Lab)
"Reduction or loss of Msh2 confers resistance to temozolomide in glioblastoma"

Teesta Naskar, PhD (Hurd Lab)
"Prenatal cannabis exposure affects placental immune system dysregulation: sex implications"

2:00 – 3:00pm
Neuroscience Digest Talks

Paul O'Reilly, PhD: *"Polygenic risk scoring"*

Scott Russo, PhD: *"Mouse modeling"*

Nan Yang, PhD: *"Cell modeling"*

James Murrough, MD, PhD: *"Psychiatry clinical trials"*

Priti Balchandani, PhD: *"Neuroimaging"*

Yizhou Dong, PhD: *"Gene therapy"*

3:00 – 4:00 pm
Discussion Panel
"Translating Neuroscience Discoveries into Personalized Medicine at Mount Sinai"

Eric J. Nestler, MD, PhD • Paul J. Kenny, PhD • Dennis S. Charney, MD

4:00 – 4:45 pm
Poster Session – Open Bar
All ODD numbers will present their posters from 4pm to 4:45pm

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4:45 – 5:00 pm
Swap + Storytelling

Storytellers
Tiffany Lin (Nestler Lab)
Emma Hays (Schaefer Lab)
Enna Selmanovic (Hof / Dams-O-Connor Labs)

5:00 – 5:45 pm
Poster Session – Open Bar
All EVEN numbers will present their posters from 4pm to 4:45pm

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5:45 – 6:10 pm
Award Ceremony

THE FRIEDMAN BRAIN INSTITUTE

Presentations

Zach Zeisler

PhD Student, Rudebeck Lab
Nash Family Department of Neuroscience

A comparative analysis of amygdala neuron branching in macaques and mice

Background: The basolateral amygdala (BLA) is involved in a wide range of cognitive processes, from fear processing, to attention, to decision-making, and dysfunction in BLA is associated with nearly every psychiatric disorder. Such diverse roles are likely due to the wide-ranging projections of BLA. Yet, little is known about how single BLA neurons branch to multiple locations in the brain due to the limitations of extent techniques; even less is known about how branching might vary across species.

Methods: Here, we implement MAPseq, which uses a sequencing approach to read out the connectivity of neurons, to determine the single-neuron architecture of BLA projections. We injected a sindbis virus vector for MAPseq into BLA of two rhesus macaques as well as five mice. We then dissected and sequenced barcodes from target sites across frontal cortex, striatum, and hippocampus.

Results: We successfully sequenced over 3000 macaque and over 1600 mouse BLA neurons. First, we compared the bulk projection patterns of all sequenced BLA neurons, finding that they align closely with previous tract-tracing results.

Then, we identified differences between each species in the number of BLA neuron projection targets: a larger proportion of mouse BLA neurons branched to two or more targets. When we assessed whether any branching motifs were over- or under-represented compared to chance, we found that for both macaques and mice, bifurcations were more likely to be under-represented while quadfurcations were overrepresented.

Finally, we compare the network-level features of these projections by comparing inputs to medial prefrontal areas and ventral frontal areas. In monkeys, BLA neurons that project to dorsal anterior cingulate cortex (ACC) were highly likely to also branch to the ventral frontal cortex, consistent with these areas' shared roles in value-based decision-making. In mice, however, amygdala neurons that branch to ventral areas were more likely to project to infralimbic and prelimbic cortex, not ACC.

Discussion:
Our results identify novel similarities and differences between single-neuron projections from BLA in macaques and mice. Mouse neurons appear to be more widely broadcasting, while monkey neurons have more specific projection motifs. We also identified seemingly similar projections to medial frontal cortex in both species, though the areas implicated are not direct homologues.

Michael B. Fernando

PhD Student, Rudebeck Lab
Nash Family Department of Neuroscience

Precise Therapeutic Targeting of Divergent Mechanisms from Rare NRXN1+/- Deletions

Background: Neurexins are critical pre-synaptic cell adhesion proteins that organize the complex synaptic connections in the brain. Complex patterns of NRXN1 alternative splicing is fundamental to diverse excitatory and inhibitory neurocircuitry and is dramatically impacted in humans by rare copy number variants (CNVs) linked to a variety of neuropsychiatric disorders, by either altering the expression of wildtype isoforms (loss-of-function) or expressing novel patient-specific mutant isoforms (gain-of-function). Moreover, the functional impact of NRXN1a splicing has yet to be simultaneously compared across excitatory and inhibitory transmission, and its role in maintaining excitatory: inhibitory balance remains unknown.

Methods: Leveraging patient-specific NRXN1+/- hiPSCs with unique loss- or gain- of function deletions that confer distinct impacts on NRXN1 alternative splicing, we apply advance lineage conversion protocols to generate 2D human glutamatergic (iGLUT:ngn2) and GABAergic (iGABA:ascl1/dlx2) neurons, and 3D region specific cortical and subpallial organoids. Here, we integrate patch-clamp electrophysiology, RNA-Sequencing and RNA targeting approaches to comprehensively assess the impact of aberrant of NRXN1a splicing on synaptic function and circuit development.

Results: We observe cell-type-specific perturbations in synaptic function in NRXN1+/- neurons; decreased synaptic activity in iGLUT neurons and increased in iGABA neurons, consistent with cell-type-specific transcriptional signatures of synaptic genes. Loss of function studies in control neurons, likewise confirm that reduced NRXN1 decreases synaptic frequency in iGLUT neurons, and increases synaptic frequency in iGABA neurons. Reciprocally, ablation of gain-of-function mutant isoforms rescues synaptic frequency in iGLUT neurons. To therapeutically target aberrant splicing, we've identified a compound that recovers wildtype isoform expression, and designed an anti-sense oligo (ASO) to ablate mutant isoform expression, for loss- and gain- of function deletions, respectively.

Conclusions: Overall, there are distinct mutation-specific phenotypes in NRXN1+/- neurons that differ between glutamatergic and GABAergic neurons, linking cell-type-specific perturbations in NRXN1 splicing to divergent synaptic phenotypes. Our ongoing efforts to targeting NRXN1 splicing in isogenic strategies help causally link aberrant splicing to synaptic dysfunction by recapitulating and rescuing disease relevant phenotypes. We propose a new model whereby NRXN1 bidirectionally regulates glutamatergic/GABAergic synaptic frequencies to maintain excitatory: inhibitory balance. Finally, our work informed the design of future candidate precision therapies that may be capable of selectively reversing loss- or gain- of function mutations by ameliorating aberrant splicing.

Sarah Banker
PhD Student, Rudebeck Lab
Nash Family Department of Neuroscience

Impaired Neural and Behavioral Navigation of Dynamic Social Relationships in Autism Spectrum Disorder

Background: Autism Spectrum Disorder (ASD) is characterized by impairments in social functioning, including deficits in dynamic social reciprocity. Despite a multitude of neuroimaging studies investigating social dysfunction in ASD, the neural underpinnings of these impairments remain poorly understood. Utilizing a naturalistic task that probes dynamic aspects of social interaction in combination with functional magnetic resonance imaging, we took an innovative computational psychiatry approach to understanding the neural underpinnings of social deficits in ASD.

Methods: Participants with ASD (n=51; mean age: 26.97, sex: 43.14% female) and typical development (TD; n=24, mean age: 27.5, sex: 62.5% female) completed a choose-your-own-adventure game in which they interacted with virtual characters. Unbeknownst to the participant, each interaction shifted a given character's position in a behind-the-scenes plot of 'social space' framed by axes of social hierarchy and affiliation. Computational approaches extracted parameters reflecting dynamic social processes based on the trajectory of decision-making in the task. Post-task questions assessed subjective opinions about characters. In a subset of participants (ASD: n=34; mean age: 27.4, sex: 52.9% male; TD: n=28, mean age: 27.5, sex: 53.6% female), general linear models with parametrically modulated regressors assessed neural activity in association with characters' locations in social space. Welch's t-tests assessed group differences in behavior and neural activity; Pearson's correlations assessed relationships with symptom severity.

Results: Compared to TD individuals, those with ASD showed larger social distances (t(71.7)=-3.52, p<0.001) and less liking of characters (t(71.9)=2.25, p=0.027). Within ASD, increased social distances were associated with higher self-reported ASD symptoms (r(53)=0.28, p=0.035) and reduced empathic concern (r(53)=-0.38, p=0.004). Furthermore, ASD individuals with a larger discrepancy between self- and clinician-rated ASD symptoms (clinician > self) also showed a larger discrepancy between self-reported character liking and affiliative behavior (self-report > behavior), reflecting a social belief-behavior disconnect (r(51)=2.63, p=0.011). Compared to ASD, TD individuals showed increased neural tracking of social distances in the right posterior cingulate cortex (cluster-level p-FWE=0.001, peak-level p-FWE=0.007), replicating prior work (Tavares et al., 2015), as well as in the right temporoparietal junction (cluster-level p-FWE<0.001; peak-level p-FWE<0.001). Within ASD, reduced PCC tracking of social distances was associated with reduced empathic concern (r(31)=0.35, p=0.046).

Conclusions: Together, these results suggest that individuals with ASD have more distant relationships with virtual characters, show a belief-behavior disconnect in social functioning, and do not utilize neural circuits known to track social relationships to the same extent as TD individuals.

Francesca Garretti, PhD
Postdoctoral Fellow, GoateLab
Genetics and Genomic Sciences

A novel EIF2B3 variant as an APOE risk modifier in Alzheimer's disease

Background: Despite the strong association of APOE4 on Alzheimer's disease risk, a wide range of clinical outcomes exist within APOE4 carriers: some develop cognitive impairment as early as 30 years of age while others remain cognitively normal beyond 100 years. The range in clinical manifestation amongst APOE4 carriers suggests that there are genetic variants that modulate APOE-associated risk. We conducted stratified genome-wide association studies of APOE4 carriers at the extremes of age at onset to identify variants that modify risk. We identified a single variant in EIF2B3 encoding the amino acid substitution S404A as a candidate risk modifier. eIF2B3 is a subunit of eIF2B, a guanine exchange factor that is involved in translational control and the integrated stress response (ISR). Our lab has recently shown that APOE4 induces a constitutively upregulated ISR and aberrant protein translation in murine and human iPSC-derived microglia. This study focuses on understanding the role of APOE genotype on ISR and the effect of eIF2B3-S404A mutation in human microglia function.

Methods: APOE3/3 and APOE4/4 lines (n=5 per genotype) iPSCs derived- microglia are used to assess the effect of APOE genotype on ISR induction. Lymphoblastoid cell lines from four eIF2B3S404A carriers are used to elucidate the effect of EIF2B3-S404A on ISR induction. ISR is induced by thapsigargin and fatty acids. ISR markers are measured via western blot and protein translation is measured using a methionine analog and click-it chemistry.

Results: Our results show that LCLs from eIF2B3S404A conferred comparable baseline activation but hyperactivation upon challenge of the ISR when compared to eIF2B3S404 lines. APOE4/4 iMGL displayed a decrease in protein synthesis rates at baseline compared to APOE3/3 iMGL. In addition, APOE4/4 iMGL display a decreased response to stressors such as thapsigargin and fatty acids.

Conclusions: These data show that APOE genotype alone can alter microglial response to stress. In addition, the data provide important evidence that eIF2B3 is critically involved in the cellular response to stress and lend support to the hypothesis that a mutation in eIF2B3 deregulates the ISR, such as that induced by APOE4. Ongoing work is focused using CRISPR to knock-out EIF2B3 in APOE4 iPS and test its effects on iMGL function and response to stress. In addition, we are evaluating the therapeutic potential of ISR-inhibitor (ISRIB) drugs for reversing the effect of APOE genotype on stress response.

Montserrat Puigdelloses Vallcorba, PhD
Postdoctoral Fellow, Hambardzumyan Lab
Department of Oncological Sciences

Reduction or loss of Msh2 confers resistance to temozolomide in glioblastoma

Background: Glioblastoma (GBM) is the most common and aggressive primary brain tumor. The only intervention that has improved the survival rate of GBM patients over the past several decades has been combining temozolomide (TMZ) with radiotherapy (RT), which increased median survival by only ~2.5 months to where it currently stands at ~15 months (Stupp et al; 2005). Unfortunately, all GBM patients eventually die due to tumor recurrence. Intrinsic or acquired resistance to TMZ is a significant contributing factor to tumor progression, and various mechanisms have been suggested, including deficiencies in DNA mismatch repair (MMR) genes such as MSH2.

Methods: To generate tumors with reduced or abrogated Msh2, we utilized immunocompetent genetically engineered mouse models (GEMMs) based on the RCAS/tv-a gene transfer system in combination with mice that exhibited heterozygous and homozygous loss of Msh2. We then assessed survival in these mice, in addition to perform H&E staining to grade these tumors. To study the microenvironment of these tumors we performed immunohistochemistry (IHC) analysis. We also analyzed the effects of TMZ treatment on tumor-bearing Msh2 WT, HET and KO mice by investigating its survival.

Results: Utilizing patient GBM samples from the TCGA, we have identified a correlation between low MSH2 expression and shorter patient survival. To test the biological significance of Msh2 in GBM growth and resistance to TMZ and immunotherapy, we successfully generated (GEMMs) of GBM with germline or somatic loss of Msh2. When PDGFB was overexpressed in combination with the silencing of Tp53 to induce tumors, tumor-bearing mice with reduced or deficient Msh2 demonstrated increased tumor growth and shorter survival time compared to wild-type tumor-bearing mice. In addition, our results indicated that Msh2 deficiency increases the malignancy of gliomas and fosters changes in the tumor microenvironment of GBM resulting in increased angiogenesis and infiltration of TAMs. Finally, our data demonstrated that two weeks of TMZ treatment at a clinically relevant dose of 25 mg/kg provides a significant survival advantage in WT-tumor-bearing mice, while no efficacy was observed in tumor-bearing mice with either heterozygous or homozygous loss of Msh2.

Conclusions: In summary, decrease or loss of Msh2 leads to diminished survival in GBM-bearing mice and promotes changes in the tumor microenvironment. Furthermore, TMZ does not exert an antitumor effect in tumor-bearing mice with partial or complete loss of Msh2 gene. We are currently evaluating the role of Msh2 in the efficacy of immune checkpoint inhibitors in glioblastoma.

Teesta Naskar, PhD
Postdoctoral Fellow, Hurd Lab
Nash Family Department of Neuroscience

Prenatal cannabis exposure affects placental immune system dysregulation: sex implications.

Background: Cannabis is one of the most prevalent recreational drugs used during pregnancy, with an estimated prevalence of 3 to 16% among pregnant women in the United States. Several clinical and preclinical studies suggest that maternal cannabis use may exert long-lasting effects on neurodevelopment. However, potential molecular mechanism related to the effect of prenatal cannabis exposure on fetal brain development remains unclear. In this study, in order to gain insights into the prenatal environment, we investigated the effect of prenatal cannabis exposure on placental functioning in human and rodent model.

Methods: Placental biopsies were obtained from women with and without cannabis use while pregnant. Rat placental specimens were collected between gestational day 16 and 21 following cannabinoid (delta- and cannabidiol) exposure to dams. We performed transcriptomics using RNA-seq placentae of the human and rat cohorts. Differential gene and protein expression were analyzed using standard DEseq2 and DEqMS method. Identified DEGs were used for gene set enrichment analyses using the curated transcriptional pathways, and ontology libraries.

Results: Gene expression analysis identified 780 genes significantly altered in cannabis-exposed human placenta and 1713 expressed genes in rat placenta. Among the most significantly decreased genes in the human and rat placenta were those involved in immune function. Gene ontology and gene set enrichment analysis revealed that major differentially expressed genes included cytokine-mediated signaling pathway, neutrophil chemotaxis, inflammatory responses etc. Single-cell deconvolution of the RNA-seq data also emphasize cell-specific effects of cannabis. In addition, both the human and rat data suggest significant sex differences with male placenta showing more marked immune-related alterations. Analysis of proteomics data on the placental specimens is currently being performed.

Conclusions: The results confirm our previous study that prenatal cannabis exposure impacts the placental immune system in humans that we now demonstrate in our rat model is causally linked to cannabinoid exposure. The sex specific insights we observe emphasize stronger effects in the male placenta that has significant implications regarding sex differences as a consequence of in utero cannabis exposure and thus potentially on sex-specific effects on future offspring health.

ABSTRACTS - Poster Session

1. Jessa Alexander
2. Akbar Alipour
3. Kumayl Alloo
4. Corrine Azizian
5. Bergan Babrowicz
6. Marie Barbier
7. Tarik Bel-Bahar
8. Jacqueline Beltran
9. Natalia Biscola
10. Allison Bond
11. Samantha Brown
12. Eduardo Butelman
13. Ahmet O. Ceceli
14. Jungho Cha
15. Matthew Challman
16. Andrew Chan
17. Jennifer Chan
18. Alissa Chen
19. Maia Chester
20. Feng-Kuei Chiang
21. Gabriela Chiarotto
22. Alexandra Chisholm
23. Insup Choi
24. Thomas Christie
25. Sarah Colbert
26. Claire Coleman
27. Alberto Corona
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29. Ashley Cunningham
30. Diana Dangoor
31. Anika Das
32. Arianna Neal Davis
33. Jip de Bruin
34. Pamela Del Valle
35. Sean Thomas Delica
36. Lauren Dierdorff
37. Shilpa Dilip Kumar
38. Ricky Ditzel
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41. Romain Durand-de Cuttoli
42. Catherine Elorette
43. Marissa Farinas
44. Susie Feng
45. Brian Fennessy
46. Jacqueline-Marie Ferland
47. Ana Catarina Ferreira
48. Alexandra Fink
49. Rachel Fisher-Foye
50. Atsushi Fujimoto
51. Rita Futamura
52. Yared Gessesse
53. Jack Gomberg
54. Damian Gonzalez
55. Apoorva Goyal
56. Faris Gulamali
57. Swati Gupta
58. Dalia Halawani
59. Sara Hameed
60. RollieHampton
61. Satoka Hashimoto Fujimoto
62. Brittany Hemmer
63. Molly Heyer
64. Jan Hoffmann
65. Leanne Holt
66. Ahmad Huda
67. PhilipHwang
68. Zarghona Imtiaz
69. Azzurra Invernizzi
70. Yael Jacob
71. Mohammad Jodeiri
72. Tanvi Joshi
73. Mert Karabacak
74. Elizabeth Katanov
75. Benjamin Keller
76. Tarek Khashan
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78. Máté Kiss
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106. Jacqueline Overton
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113. Tanni Rahman
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116. Miguel Rodriguez de los Santos
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118. Bryce Rowan
119. Sharna Saha
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121. Marcos Schaan Profes
122. Alba Segura Amil
123. Jeremy Sherman
124. Sanutha Shetty
125. Blair Shevlin
126. Thenzing Judá Silva Hurtado
127. Joe Simon IV
128. Ivan Soler
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132. Angel Tang
133. Jaume Taura
134. Emily Teichman
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136. Alissa Valentine
137. Maya Verghese
138. James Vicari
139. Eric Vornholt
140. Allison C. Waters
141. Yolanda Whitaker
142. Kristen Whitney
143. Amelia Wieland
144. Emma Woodoff-Leith
145. Elisa Xu
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150. Hiba Zaidan
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152. Gregory Zilberg

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name Jessa Alexander

Job Title Research program coordinator

Lab Waters

Department Psychiatry and Neuroscience

Title: Neuropsychological assessment of changes in emotion class vocabulary over the course of treatment for depression with deep brain stimulation

Authors: Alexander J, Jacob Dahill-Fuchel, Shannon O'Neill,, Helen Mayberg, Waters Allison C.

Background: Verbal fluency is a standard neuropsychological domain, assessed using the Controlled Oral Word Association test (COWAT). Scores are interpreted as a measure of executive function, selective attention, and semantic accessibility. Patients with depression typically score lower than healthy individuals within the same socioeconomic categories. Semantic deficits in depression are comparable to those observed in patients with frontal lesions. While sensitive to states of depression, the COWAT probes word categories, such as groceries, that are irrelevant to the disease state. We theorized that critical insight could be drawn from the addition of an emotion word category, which might capture low emotional granularity and poorer mood outcomes observed in depression.

Methods: Five individuals diagnosed with treatment resistant depression (TRD) participated in a pilot study of this concept over the course of treatment with deep brain stimulation. An "emotions" category was added to the standard COWAT and administered at multiple timepoints: prior to DBS intervention and post DBS intervention. Patients were instructed to name "as many emotion words, or feelings, as you can," within a one-minute period, in addition to the COWAT, which probes two neutral categories (Animals, Groceries). The novel affective COWAT scores were compared to normative scores and across time in treatment.

Results: In the depressed patients, verbal fluency was equal to or lower than the normed average scores on semantic fluency in non-depressed individuals. Scores in the emotion word class were lower than scores in the neutral word categories. Overall, verbal fluency was enhanced with treatment. For some patients, the affective COWAT was insensitive to change with treatment. For most patients, emotional class fluency improved proportionally more than the neutral class over the course of treatment with DBS.

Conclusions: Though affective semantic fluency is not part of a standard neuropsychological battery, low accessibility of emotional vocabulary is shown to be a cross diagnostic risk factor in mood and personality pathologies predicting a higher likelihood of maladaptive self-regulatory behaviors, and more severe manifestations of anxiety and depression. Adding an emotional subset to the standard verbal fluency neuropsychological test, the COWAT, may help identify patients with low emotional granularity who could benefit from intervention targeting that specific skill domain.

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Full Name	Akbar Alipour
Job Title	Assistant Professor
Lab	BMEII
Department	Radiology

Quantification of the Brain Iron Metabolism in the Cognitively Declined Adults using 7T MRI

Akbar Alipour, Pinar Ozbay, Mackenzie Longan, Ameen Al Qadi, Mehmet Kurt, Bradley Delman, Trey Hedden, Priti Balchandani.

Background: The extracellular aggregation of beta-amyloid (AB) plaques is one of the hallmark pathology of Alzheimer's diseases (AD) that develops years prior to clinical symptoms. However, inconsistency in the rate of cognitive decline among subjects with AB pathology and ineffectiveness of anti-amyloid therapeutics to mitigate cognitive impairment suggest that other parameters, such as patterns of brain iron, may impact the risk of cognitive decline. In this study we leveraged improved MRI signal at 7T to explore susceptibility
changes in the iron-enriched regions among individuals with AD/MCI and healthy controls (HCs) through quantitative susceptibility mapping (QSM) with unprecedented resolution.

Method: In vivo MRI experiment was performed in AD/MCI and age-matched healthy subjects. Scanning was conducted on a 7T MRI scanner using 1Tx/32Rx Nova head coil. To calculate QSM, a 3D highresolution spoiled gradient echo (GRE) sequence was used (voxels size = 0.3x0.3x1.5 mm3). QSM was
used to measure susceptibility in the major iron-enriched structures, including red nucleus (RN), substantia nigra (SN), globus pallidus (GP), Caudate nucleolus (CN), putamen (PT), and dentate nucleus (DN).

Result: We found a significantly higher magnetic susceptibility in GP and DN in patients with AD/MCI compared with HCs. In AD/MCI the highest susceptibility values were found in the GP (233.5±12.7) and DN (214.7±10.4), verses 174.6±11.8 and 168.9±11.6 for GP and DN in the HCs, respectively. There were small differences in the susceptibility values between the other ROIs.

Conclusion: We reported an initial result for QSM at 7T in the AD/MCI subjects and appropriate age matched HCs. The main aim of the study was to investigate whether susceptibility values measured using ultra-high resolution QSM differ in the iron-enriched regions between these two populations. A significant
susceptibility value was reported in the AD/MCI compared with the HC in GP and DN regions. This observation clearly deserves further investigations in larger cohorts.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Kumayl Alloo
Job Title	Undergraduate Researcher
Lab	Benson and Huntley Labs
Department	Neuroscience

Differential Vulnerability by Sex and Genotype to Different Durations of Variable Stress in Mice Carrying a Parkinson's-Linked Lrrk2-G2019S Mutation

Kumayl Alloo, Christopher A. Guevara, Pamela Del Valle, Romario Thomas, Alexander Tielemans, Swati Gupta, Amelia Wieland, Jamal Magoti, Alexandra Magee, Kyomi Blake, Deanna L. Benson, George W. Huntley

Parkinson's is associated with the psychiatric non-motor symptoms of depression and anxiety that emerge early, appear to be independent of dopamine neuron loss, and are poorly understood. Risk for both Parkinson’s and depression is increased by stress, and previous work in the lab has shown that male mice carrying a knockin G2019S mutation in the Lrrk2 gene, which in humans greatly increases risk for PD, exhibit altered behavioral and electrophysiological responses to social stress. To determine whether social stress-effects are generalized to other forms and durations of stress, and to probe potential sex differences, we subjected young adult male and female wildtype (WT) and G2019S knockin (GS) mice to a standard daily variable stress (VS) paradigm for either 6 days (6d-VS) or 28 days (28d-VS). Utilizing a within-subject design, mice first underwent a battery of standard tests of anxiety and depression-like responses (open field test, social interaction test, and novelty suppressed feeding) to establish unstressed-baseline responses, followed by 6d-VS or 28d-VS, then re-tested in the same behavioral battery to probe for stress-induced behavioral changes. We found that under unstressed conditions there were no differences in several measures of anxiety-like behaviors attributable to the G2019S mutation in male or female cohorts. However, unique sex- and genotype-specific behavioral profiles emerged with the different durations of variable stress. We then used cellular activity profiling by cFos immunolabeling of different brain regions following 28d-VS to gain insight into differential brain activation patterns that may underlie different behavioral responses. We found sex- and genotype-distinct patterns of neuronal activation by cFos labeling which may reflect altered behavioral profiles. Together, these data suggest that the G2019S mutation drives a temporally evolving set of cellular and behavioral neural adaptations that differ from WT and between sexes. Such differential vulnerabilities may impact the onset of psychiatric symptoms in human PD patients. Future studies are probing the implication of immune factors in target brain regions, as LRRK2 and stress independently have been shown to regulate immune properties. Understanding these interactions will provide insight into the differential adaptations between individuals harboring the G2019S mutation, revealing novel targets for ameliorating mood-related symptoms associated with Parkinson’s.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Cellular and Transcriptional Correlates of Drug-Associated Renewal in the Nucleus Accumbens

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Background: Renewal of drug-seeking behaviors is often caused by the persistent memory retrieval of conditioned responses previously associated with drug contexts. This maladaptation is evident as the subjects are unable to apply their learned extinction when they revisit the original drug contexts. Such a process is associated with changes in the brain reward circuitry signaling extinction, including the nucleus accumbens (NAc). A thorough understanding of the neurobehavioral mechanisms responsible for the transfer of extinction memory to drug- associated contexts is needed to improve relapse treatments in the clinic.

Methods: We used a rat model of contextual drug self-administration (SA; conditioning) in which rats received cocaine or saline (controls) in context A, and then extinguished in a different (context B) context, followed by re-exposure to context A (ABA). This was combined with a chemogenetic approach to target medium spiny neurons (MSNs) in the NAc subregions (core/shell) that express either dopamine 1 or 2 receptors (D1 or D2) in transgenic rats (males/females) expressing Cre recombinase in such cells. Additional, circuit-based, and genome-wide approaches were also used to study the effect of extinction and renewal at the sex, behavioral, cellular, and transcriptional levels.

Results: We found that silencing either D1- or D2-MSNs of the NAc core in male rats (but not in females), significantly lowered drug-seeking behavior during renewal, suggesting that both neuronal types contribute to the cocaine-associated renewal. However, preliminary results show that when D1-MSNs were silenced in the NAc shell of male rats, there was an increase in drug seeking during renewal, indicating that D1-MSNs of the NAc shell reduce drug-seeking behavior triggered by context renewal. Ongoing experiments will address the role of D2-MSNs in Nac subregions in a sex-dependent manner. In parallel, chemogenetic stimulation, fiber photometry, and transcriptomic analyses will shed light on the neurobiological mechanisms of renewal- associated memories.

Conclusion: Together, our results comprehensively highlight the contribution of the NAc subregions, cells, and transcriptomic profile in a sex-specific manner, which is most relevant to people, clinically.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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TITLE: Understanding polygenic risk in aging using deep learning enabled histological mapping in human brain aging

Authors: Bergan M. Babrowicz, Kurt Farrell, Andrew T. McKenzie, Gabriel A. Marx, Jamie M. Walker, Timothy E. Richardson, Justin Kauffman, & John F. Crary

BACKGROUND: Polygenic risk score (PRS) serves as a proxy of cumulative genetic susceptibility. To validate and leverage these genetic predictors, there is a critical need to develop quantitative endophenotypes and deploy them in the risk score models. Recent studies using computer vision and machine learning have demonstrated the feasibility of generating the features using whole slide images from routine histological preparations of human post-mortem brain. Taken together, these techniques offer a unique approach to assessing risk for age-related and neurodegenerative changes alongside other clinical comorbidities.
METHODS: As a first step towards integrating PRS with our computer vision pipeline, we have leveraged summary statistics made publicly available on the UK GWAS catalog in conjunction with the computational modeling software PRSice. We used traits previously reported to be associated with dementia and aging that also have large publicly available GWAS summary statistics available for PRS derivation (e.g., vascular disease, depression, age, etc.) using our aging cohort (n=356) and multiple instance learning models on whole-slide images to generate unique endophenotypes (i.e. age, tangle burden, etc).
RESULTS: PRS scores were calculated for several other notable clinical features. When subclassifying our cohort using AI-derived traits on whole slide images we found several marked genetic risk differences between groups. Notably, those with a higher predicted age compared to actual biological age also had significantly higher risk for major depressive disorder ($p < 0.05$). Furthermore, PRS correlated better with our AI-generated age when compared to actual age.

CONCLUSIONS: The work performed here demonstrates the utility of integrating AI endophenotypes and genetics to understand routine and pathological aging.

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Studying the impact of Shank3-deficiency on the rat mesoaccumbens circuit

Marie Barbier, Keerthi Thirtamara Rajamani, Shai Netser, Shlomo Wagner, Hala Harony-Nicolas

Background: The ventral tegmental area (VTA), a core node of the mesolimbic circuit, is interconnected with the nucleus accumbens (NAc) via VTA dopaminergic projections. Despite the role of this reward system in social interaction, little is known about the impact of autism spectrum disorder (ASD) associated mutations on processing social reward and on the functional integrity of this pathway. In this work, we study the effect of a mutation in an ASD high-risk gene; Shank3, on the mesoaccumbens system in rats. We hypothesize that Shank3 mutation impairs neural activity within the VTA, causing abnormalities in accumbal dopamine transmission and leading to impairments in processing social reward.

Methods: To examine the impact of Shank3 mutation on neural activity within the VTA, we used the Shank3-deficient rat model and employed fiber photometry with GCaMP6 to record dopaminergic and GABAergic activity within the VTA, while rats were introduced to two rewarding choices, social and food. To examine the effect of the mutation on dopamine release in the NAc during the same paradigm, we used a dopamine sensor in the NAc (i.e., GRAB-DA).

Results: We found that in wild type rats, VTA dopaminergic neural activity was increased during social interaction as well as during food exploration. In Shank3-deficient rats, however, there was no increase in VTA dopaminergic activity but a significantly higher activity in GABAergic neurons, when compared to wild type littermates. These significant differences in neural activity were specific to interactions with social but not to food, where GCaMP6 signals were similar across genotypes. We further found that DA release in the NAc is impaired in Shank3-deficit rats during social interaction.

Conclusions: Our study demonstrates that Shank3 mutation has a deleterious effect on VTA neural activity and dopamine release, which could suggest that Shank3-deficient rats have a deficit in processing the value of social reward. To test this proposition, we are currently using operant chambers to examine social reward processing in Shank3-deficient rats. Furthermore, we are using optogenetics to examine the effect of activation or inhibition of VTA dopaminergic or GABAergic neurons on social interaction.

2023 Neuroscience Retreat

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Cortical activity underlying motivated attention to salient cues in individuals with cocaine use disorder.

T.S. Bel-Bahar, R.B. Shaik, R.Z. Goldstein, M.A. Parvaz

Background: Heightened motivated attention to drug-related versus other salient cues is a hallmark of substance use disorder and relapse risk. While brain networks involved with motivated attention to cues (or cue-reactivity) have been detailed with high spatial resolution using fMRI, the low temporal resolution of the technique renders it limited in examining cue-reactivity at a sub-second level. Accordingly, EEG-derived event-related potentials, such as the late positive potentials (LPP) have been used to reliably index motivated attention to cues at this higher temporal resolution. However, gaps in current knowledge exist about the cortical generators of these cue-induced LPPs.

Methods: EEG was collected from 86 individuals with cocaine use disorder ($\leq$ 30 days abstinent) while they viewed a series of pleasant, unpleasant, neutral, and cocaine-related pictures (LPP-generating task). We processed data into single-subject -500 to 2000 ms trial averages for each condition. Event-related sensor and source estimates were examined separately for each of the three affective conditions (i.e., pleasant, unpleasant, and drug) contrasted against the neutral condition. To examine these within-subjects salience effects, permutation t-tests were performed for early (400-1000 ms) and late (1000-2000 ms) LPP time windows.

Results: Across all participants and only for the early time window, the LPP amplitude was higher at fronto-central and lower at occipital sensors in the unpleasant compared to neutral condition ($pFDR<0.0008$). On the source level, the drug versus neutral contrast yielded greater activity in the left cingulate, parahippocampal gyrus, precentral, superior parietal, and right paracentral, posterior cingulate, caudal midfrontal, and posterior superior temporal sulcus ($pFDR<0.0007$).

Conclusion: These EEG-derived source maps of drug cue-reactivity overlap with brain regions identified with fMRI-assessed cue-reactivity in substance use disorder and emotion regulation, extending current knowledge about the cortical generators of the LPP elicited by drug relative to neutral cues. These preliminary results pave the way for identifying temporally and spatially precise mechanisms of motivated attention to salient cues in substance use disorder and point to the utility of EEG brain imaging for precision psychiatry.

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TITLE: Detecting physical activity and symptom changes in patients with depression using digital phenotyping

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BACKGROUND: Major depressive disorder (MDD) is one of the world's largest health problems and can go easily undetected. To enable early-intervention and develop new treatment options, there is a need to better understand the lived experience and temporal dynamics of mental health conditions. Previous work shows that depressed patients are more sedentary and that engaging in physical activity may be protective against depression (Teychenne et al., 2008). To explore the association between symptom severity and passively collected data features, we implemented the use of the research-based smartphone application "mindLAMP" in MDD patients and healthy controls (HC).

METHODS: N=45 participants were recruited to participate in this study for a 30-day period. Of the subjects recruited, 24 participants (13 MDD, 11 HC) who had sufficient active survey data and passive physical activity data were included in this preliminary analysis. Psychiatric status was established by the Structured Clinical Interview for DSM-V or the mini–International Neuropsychiatric Interview. Using the mindLAMP application, we collected two types of data: active data and passive data. Measures of active data consisted of daily ecological momentary assessments (EMA) measuring stress, intrinsic motivation, and depression while passive data included measures for step count. Correlations were used to analyze associations between different symptoms and daily step counts as a measure of physical activity. We hypothesized that increased physical activity would be associated with lower symptom severity across each of these measures.

RESULTS: There was a significant, moderate, positive correlation only between stress and average steps taken per day in MDD patients $r(11) = 0.60$, $p = 0.029$ but not in HC $r(9)= 0.41$, $p=0.216$. Additionally, when exploring the association between different symptoms across MDD patients we found a significant, strong, positive correlation between real-world longitudinal self-reports of stress and depression $r(11) = 0.85$, $p= 1.97 * 10\text{-}4$ and a negative correlation between self-reports of internal motivation and depression $r(11) = -0.77$, $p= 0.002$.

CONCLUSIONS: With ongoing recruitment, our preliminary results illustrate how smartphone sensors can provide unique insights into environmental contingencies that impact mood and allow for more dynamic assessments of depression.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Determination of size and spatial distribution of Myelinated Preganglionic Parasympathetic and Unmyelinated Fibers in Rhesus Macaques Ventral Roots

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BACKGROUND: In the conus medullaris (CM) of mammals, the sacral parasympathetic nucleus (SPN) provides preganglionic autonomic fibers to pelvic ganglia for autonomic control of bladder, bowel, and sexual function. The lumbosacral (LS) ventral roots (VRs) and spinal nerves are attractive and emerging targets for electrical stimulation to modulate autonomic function in a variety of neurological conditions, including spinal cord injury. One limitation for translational studies on neuromodulation is extensive inter-individual variability in the rostro-caudal distribution of autonomic fibers between LS VRs and lack of information on the spatial distribution of different fiber types within individual VRs.
METHODS: We performed a light microscopy (LM) and transmission electron microscopy (TEM) study of plastic resin-embedded L6-S3 VRs in female rhesus macaques (n=6) to evaluate size and spatial distribution of myelinated and unmyelinated fibers.
RESULTS: Myelinated fibers were segmented and preganglionic parasympathetic fibers (PPFs) were demonstrated within the L7-S2 VRs with extensive variation with regards to the most dominant segmental level for PPFs between animals. Using a new non-binary approach for determining the 2-dimensionaldistribution of myelinated nerve fibers within the L6-S3 VRs, a markedly higher degree of fiber clustering was detected in VRs with a high proportion of PPFs. For individual sacral roots (S1-S3), a positive correlation appears for the number of small myelinated axons within the PPF size range and the number of unmyelinated axons. Two size ranges of unmyelinated fibers were detected in S1-S3 VRs. A small proportion of very small unmyelinated fibers were detected across all VRs. In addition, a population of unmyelinated fibers with a larger diameter was detected in VRs with a prominent proportion of myelinated PPFs. Unmyelinated fibers also tended to cluster with small myelinated fibers in the PPF size range.
CONCLUSIONS: We conclude that PPFs include both myelinated and unmyelinated fibers, which form clusters within individual VRs. Neuromodulation strategies that target the CM and lumbosacral VRs in primates need to take into consideration an extensive variability in the rostro-caudal distribution of efferent PPF, patterns of PPF clustering within individual VRs, and the lack of myelination in a large subset of PPFs.

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Title: Sequential milestones underlying the development of adult neural stem cells in the hippocampus

Authors: Allison M. Bond, Dennisse Jimenez-Cyrus, Vijay Adusumilli, Guo-li Ming, Hongjun Song

Background: The dentate gyrus region of the hippocampus is one of only two regions in the adult mammalian brain where a population of neural stem cells is maintained throughout adulthood. Previously, we showed that Hopx-positive embryonic neural stem cells which contribute to developmental cytogenesis in the mouse dentate gyrus transition into quiescent adult neural stem cells, suggesting that a common lineage of neural stem cells contributes to developmental and adult neurogenesis. Quiescence is a hallmark feature of many adult stem cells, and presumably the transition to quiescence marks the shift from developmental to adult neural stem cell. However, the mechanisms underlying this critical transition remain completely unknown.

Methods: Here we investigated the dynamic properties of dentate gyrus neural stem cells during the early postnatal transition to a quiescence in male and female mice. We used immunohistochemistry to assay cell cycle phase occupancy, we used single-cell RNA-sequencing to detect genome-wide changes in gene expression, and we used flow cytometry to assay metabolic parameters, including autophagy, mitochondria and reactive oxygen species.

Results: We identified a timeline of molecular, cellular, and metabolic changes that define the transition to an adult neural stem cell state, including changes in cell cycle dynamics, the transcriptome, autophagy, and cellular ROS levels. While some neural stem cell changes coincided with the transition to quiescence, others occurred before or after cell cycle exit, indicating that a series of milestones underlies the transition to an adult neural stem cells state.

Conclusions: Together, our work supports a model wherein the transition to an adult neural stem cell state is not a singular switch from proliferation to quiescence, but is instead a more protracted, multi-step developmental process. Our study presents a framework from which future studies can build upon to investigate mechanisms driving the establishment and maintenance of the quiescent adult neural stem cell pool.

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Diabetes alters the transcriptional signature of cholinergic neurons in the brain reward circuitry

AUTHORS:
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BACKGROUND: Patients with diabetes are twice as likely to develop depression compared to the general population. Yet few studies have investigated how diabetes might induce transcriptional and functional alterations in brain regions involved in mood regulation. Within the brain's reward circuitry, cholinergic neurons regulate mood-related behavior and respond to dynamic fluctuations in insulin, thus underscoring the importance of studying this neuronal cell type in the context of diabetes.

METHODS: We performed translating ribosome affinity purification (TRAP) and RNA sequencing of cholinergic neurons in the nucleus accumbens (NAc) and medial habenula (MHb) using two different mouse models of diabetes. A cohort of male and female ChAT-NuTRAP mice (on a C57BL6/J background) received injections of either vehicle or streptozocin (STZ), a pancreatic beta cell toxin, to induce insulin-deficient diabetes. A separate cohort of male and female ChAT-NuTRAP mice were placed on either a control or high-fat diet (60% kcal from fat), as a model of insulin-resistant diabetes. We assessed chronic hyperglycemia via weekly blood glucose measurements and collected NAc and MHb samples at 6- and 12-week timepoints prior to performing TRAP mRNA purification and Illumina sequencing.

RESULTS: Differential expression and gene ontology analysis from our preliminary dataset revealed that chronic hyperglycemia induced marked changes in the mRNA expression profile of cholinergic neurons. Namely, we observed a significant upregulation in genes involved in dopamine metabolism, extracellular matrix regulation, and trans-synaptic signaling in the MHb at 12 weeks after STZ treatment. In addition, we identified changes in genes involved in the complement pathway and mitochondrial function. Our current efforts are focused on completing this analysis to include the 6- and 12-week timepoints as well as our high-fat diet samples.

CONCLUSIONS: Our preliminary results demonstrate that cholinergic neurons in two brain reward centers (NAc and MHb) undergo significant changes in gene expression as a result of chronic hyperglycemia. Future studies will focus on further exploring this dataset to identify novel gene targets that might play a role in modulating cholinergic neuronal function and affective behavior in our diabetic mouse models.

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Title: Overdose mortality rates from opioids or stimulants are higher in males than females, controlling for different rates of drug misuse: State-level data

Authors: Eduardo R Butelman1, Yuefeng Huang1, David H. Epstein2, Yavin Shaham2, Rita Z. Goldstein1, Nora D. Volkow2, Nelly Alia-Klein1

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Background: Misused opioids (mu-opioid receptor, MOR, agonists) and stimulants such as methamphetamine and cocaine (which target primarily dopaminergic and other monoaminergic transporters) are major causes of morbidity and mortality in the US. There is a lack of clarity in preclinical studies and in clinical literature as to whether females escalate self-exposure to MOR agonists and stimulants more rapidly than males. However, most epidemiological data in the US do indicate that males, compared to females, have greater overdose mortality rates for these drugs. It is unclear if these sex differences in mortality rates are mostly due to differences in levels of drug misuse in males and females, and whether they are limited to specific stages in the lifespan.

Methods: Study of de-identified publicly available epidemiological data from the CDC WONDER platform, examining overdose mortality at the state-level in the United States, for 2020-2021. Overdoses were analyzed separately for the following ICD-10 categories: Synthetic opioids (principally fentanyl), heroin, psychostimulants (principally methamphetamine) and cocaine. Data for males and females were stratified in 10-year age bins (overall range 15-74 years), and analyzed in multiple linear regressions controlling for major demographic factors, and for sex-specific levels of drug misuse, from the NSDUH survey (2018-2019).

Results: For each of the drug categories, males had significantly greater overdose rates than females. The mean male/female sex ratio of overdose mortality rates for the separate drug categories ranged from 2.4 to 2.9, showing robustly greater vulnerability in males. Intriguingly, the male/female ratios for misuse were of smaller magnitude. Multiple linear regressions adjusting for major demographic variables, and also for sex-specific levels of drug misuse, confirm that sex was a significant factor in overdoses for each of these drug categories. After stratification into age bins, the importance of sex as a factor also survived adjustment for all drug categories, especially in the 25-64 age range.

Conclusions: Despite the fact that mu-opioid agonists and stimulant drugs have different pharmacodynamic and pathophysiological effects, the rate of overdoses is robustly greater in males than females, taking into account different levels of drug misuse.

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Naturalistically tracking goals and habits over the course of inpatient treatment in heroin addiction
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Background: Heroin and other opiate overdose-related deaths have surpassed 100,000 in 2022, rendering paramount the need for neuroscience-based heroin addiction recovery biomarkers. Canonical learning theory accounts of drug addiction posit that with chronic use, the motivational control over drug use shifts from being goal-directed (dependent on the drug's hedonic value and ventral striatum) to habitual (dependent on a preceding cue/context and dorsal striatum). While the ventral to dorsal shift in motivational control has been documented in the context of drug self-administration in rodents, parallel evidence in humans is scarce. This discordance in findings across species could be related to the limitations imposed by currently used cross-sectional or narrow longitudinal motivational control measures, e.g., over-training simple lab-based associations that may not capture the complexities of human behavior. Computational methods have been applied to measure motivational control to enhance the study of habits in human drug addiction, classifying agents into those who are goal-directed and create an internal model of the environment (i.e., model-based) and those who are habitual and rely on cached outcome values (i.e., model-free). Previously, impairments in model-based choice in individuals with alcohol addiction were associated with relapse, a dynamic process, warranting a focus on this choice's potential fluctuations throughout short-term or extended recovery to track relapse risk.
Methods: Here, in a proof-of-concept study, we naturalistically tracked motivational control over 12 weeks of medication-assisted inpatient treatment in eight individuals with heroin use disorder (iHUD) and 16 demographically matched healthy controls (HC). We used a two-step decision task that captures model-based and model-free choice, deployed daily via smartphone (~3 mins, 35 trials/day), accompanied by ecological momentary assessments of craving and drug use. We estimated choice strategies in a generalized linear mixed-effects model as a function of the previous trial choice. Model-based and model-free choice were represented by the β of reward history*probability of reward availability interaction, and reward history main effect, respectively.
Results: Our preliminary analyses indicate lower model-based choice in the first week of task completion in iHUD (HC>iHUD β-model-based $p<.05$), suggesting impaired goal-directed control in iHUD in earlier phases of treatment. Longitudinal trajectory tracking and harnessing these results for prospective predictions of craving and drug use are pending further data collection/analyses.
Conclusions: Using a cutting-edge approach that intersects computational, naturalistic and longitudinal methods, our results may identify biomarkers of craving and relapse in iHUD. This research can inform motivation-based treatment/prevention targets to tackle the ongoing opioid epidemic.

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Weakening of functional network in progression from major depressive disorder to treatment-resistant depression

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Background: The transition from major depressive disorder (MDD) to treatment-resistant depression (TRD) across individual patients is highly variable. Clinical risk factors for TRD implicate the length of current episode (chronicity), the number of lifetime episodes (recurrence), and prior treatment exposures, but their relative or combined contribution to the progression of MDD is unknown. This study aimed to examine the intrinsic connectivity network (ICN) characteristics across illness progression, identifying risk factors contributing to global functional network alteration and associated brain networks.

Methods: Resting-state fMRI scans were acquired in 301 subjects (MDD=237, healthy controls (HC) = 35, TRD=29) from 3 independent cohorts with the same scanner. Three risk factors of depression were defined in MDD: past treatment exposure (naïve, past), chronicity (current episode duration>2yrs), and recurrence ($\geq$ 3 past episodes). Nodes were defined using 454 regions, including 400 cortical parcels corresponding to 17 intrinsic connectivity networks and 54 subcortical parcels. The functional connectivity (FC) matrix was extracted by computing correlation coefficients between the 454 nodes. Network characteristics, including the clustering coefficient and the global efficiency based on the weighted matrix, were calculated. In addition, we also calculated FC within- and between- subnetworks. A general linear model, including each risk factors, age, and sex, was performed to identify the effects of each risk factor on the functional networks using only MDD patients (N=237). Post hoc analyses were then performed with additional HC and TRD groups to examine whether findings are progression to TRD.

Results:The global efficiency was significantly affected by chronicity (p=0.034). Notably, post hoc analysis of global efficiency shows a significant difference between the nonchronic MDD and the TRD (p=0.007). Within subnetwork analyses found a significant effect of past treatment exposure in Visual B (p<.001), Somatomotor B (p=0.033), Dorsal attention B (p=0.041), and Limbic A (p=0.019) networks. These networks show a decreased connectivity in the past treatment group compared to the naïve group. Interestingly, the Somatomotor B network shows a decrease FC with illness progression from HC to TRD.

Conclusions: These findings suggest that decreased functional network integration toward TRD is associated with chronicity and past-treatment exposure has a significant effect on the Somatomotor B network that may contribute to progressive treatment-resistant.

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The polycomb repressive complex 2 (PRC2) regulates microglial responses to amyloid pathology

Matthew Challman, Pinar Ayata, Jess Crowley, John Murray, Sarah Neuner, Alison Goate, Alexander Tarakhovsky, Anne Schaefer

Microglia, the innate immune cells of the brain play an important role in the pathophysiology of Alzheimer's Disease (AD). Upon exposure to amyloid, one of the earliest molecular markers for AD, microglia induce a distinct transcriptional activation state characterized by phagocytic and lysosomal/endosomal genes. Concurrently, they surround amyloid plaques and are thought to mitigate disease pathology. Microglial activation states are driven by local cues which allow them to provide specific functions to support the microenvironment. We found that these states are regulated by the polycomb repressive complex 2 (PRC2), a methyltransferase complex that catalyzes the repressive histone modification H3K27me3. The loss of microglial PRC2 leads to progressive downregulation of many genes associated with Triggering Receptor Expressed on Myeloid cells 2 (TREM2), a signaling pathway that is strongly implicated in the microglial response to Alzheimer's Disease (AD), and lysosomal function, suggesting a role for PRC2 in the regulation of microglial amyloid responses. Our data using an AD mouse model with PRC2-deficient microglia shows that loss of PRC2 phenocopies TREM2 deficiency, supporting this idea. Beyond its role in the nucleus, PRC2 is present in the cytoplasm where its methyltransferase activity plays a role in signaling transduction and actin polymerization of immune cells. This raises the possibility that PRC2 is directly involved in microglial signaling responses regulating responses to amyloid pathology. Preliminary data confirms cytoplasmic localization of PRC2 in microglia, supporting this idea. We are currently testing this model, which would place PRC2 in a unique regulatory position, where its functions of epigenetic regulation and signal transduction converge to control a single functional response.

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Microglia responses to peripheral infection

Andrew Chan, Yajing Xu, Stefan Berghoff, Lena Spieth, Carles Martínez-Romero, Pinar Ayata, Eddie Loh, Li Shen, Adolfo García-Sastre, Anne Schaefer

As resident macrophages of the central nervous system (CNS), microglia are key regulators of tissue homeostasis through their ability to sense and respond to changes in their local microenvironments. For instance, microglia perform a tissue-specific function in detecting neuronal hyperexcitability and dampening it through adenosine production. While many microglial functions are induced in response to local signals, microglia are also capable of sensing changes in the periphery such as infection or tissue damage. However, the functional nature of their response to distant challenges is unknown. We hypothesized that microglia act as sentinel cells of the brain following peripheral infection to protect tissue integrity. We used Poly I:C as a viral mimic and mouse-adapted Influenza A virus as models to study the dynamics and the function of microglia responses to peripheral infection. Interestingly, we identified microglia populations that respond rapidly following peripheral influenza infection in both paradigms. Subsequently, we used translating ribosome affinity purification (TRAP) to profile the responses of microglia at different timepoints after infection. Microglia transcriptional activation preceded the peak of peripheral response to the virus as well as the onset of sickness behaviors. An interferon-responsive signature was localized to a subpopulation of microglia in the white matter, where we also observed a subsequent reduction in myelin-related genes highly expressed by oligodendrocytes. This was correlated with long-lasting changes in oligodendrocyte numbers and myelination, suggesting that peripheral infections could lead to far-reaching impacts on neuronal health and function. Our work identifies microglia as an early responding population in the CNS following peripheral infection and motivates additional experiments to investigate their specific contributions to oligodendrocyte and myelin alterations.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Jennifer Chan
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Title: Cellular mechanisms contributing to the persistent effects of pregnancy and postpartum experiences on brain function

Authors: Jennifer C Chan, Giuseppina Di Salvo, Ashley M Cunningham, Elizabeth Brindley, Sohini Dutta, Ian Maze

Background: Pregnancy represents one of the most incredible physiological stressors that one can experience over their lifetime, yet while the effects of environmental and psychological stressors are well-documented, how reproductive experiences produce lasting effects on the brain remain unknown. Moreover, prior pregnancy experience (parity) represents a risk factor for several brain disorders including perinatal/postpartum mood and affective disorders, strokes, and Alzheimer's Disease, yet not all individuals who experience pregnancy develop these disorders later in life. Therefore, there is great need to understand the biological processes that both orchestrate and disrupt parity effects within the brain in order to prevent subsequent disease susceptibility.

Methods: Our lab used mouse models to investigate how pregnancy and postpartum exposures dynamically and persistently alter the brain. We used bulk RNA-sequencing and behavioral assessments on age-matched female mice to tease apart the specific contributions of pregnancy, pup interactions, and postpartum stress. Finally, we used single nuclei RNA-sequencing to comprehensively define the impact of parity vs. postpartum stress effects on specific cell populations.

Results: Our lab identified the dorsal hippocampus (dHpc) as a brain region displaying robust transcriptional alterations well after offspring weaning. These changes indicate altered patterns of neuronal and glial composition compared to nulliparous females, and were associated with improved performance in context-dependent learning tasks, which are reliant on dHpc function.
Next, we demonstrated that pregnancy represents the most significant contributor of neuroplastic changes, with alterations in oligodendrocyte function following pup exposure also implicated as a potential driver of the parity-induced transcriptome. Thus, we next tested whether disruptions to maternal caregiving/pup interactions may impact oligodendroglial processes by utilizing a model of maternal separation stress. Our results show that this postpartum stress model inhibited both the transcriptional changes and behavioral improvements observed in control dams. Finally, analysis of >100,000 dHpc cells revealed effects of parity and postpartum stress on population-specific gene expression profiles, including within neuronal and oligodendroglial subclusters.

Conclusions: Our data suggest that pregnancy and postpartum exposures elicit long-lasting, pro-adaptive improvements in cognition, which are vulnerable to disruptions by stress. These studies provide insight into the molecular mechanisms contributing to the long-term effects of parity on the brain, as well as the environmental triggers that may interact with them to influence brain health.

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Full Name	Alissa Chen
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Sound Registration and Habituation in Social vs. Non-Social Contexts Relates to Misophonia and Psychiatric Symptoms

Alissa Chen, Jeanpierre Tenesaca, Sarah Banker, Jadyn Trayvick, Arabella Peters, Xiaosi Gu, Jennifer Foss-Feig, Daniela Schiller

Background:
For some individuals, social sounds (e.g., slurping) can induce aversive responses, suggesting impairments to social cognition. This is most prominent in misophonia, a condition in which people show hypersensitivity and intolerance to such sounds. Misophonia also associates with anxiety, obsessive compulsive traits, and autism spectrum disorders.

Methods:
Electroencephalogram (EEG) was recorded from adults with misophonia (n=16) or typical development (TD; n=14) during a sound habituation task wherein they listened to repeated triggers (e.g., slurping) associated with images of social (e.g., person eating) or mechanical (e.g., water pump) sources.

Results:
In the full sample, N100 event-related potentials to sound triggers in social context were significantly negatively correlated with trait anxiety ($r^2=-0.49$, $p<0.01$) and positively correlated with empathy ($r^2=0.58$, $p<0.001$), indicating enhanced pre-attentive registration of social sound cues is related to psychiatric traits. Indeed, individuals with misophonia reported less empathy than TD participants ($t=-4.23$, $p<0.001$). Habituation to social triggers also differed between TD and misophonia: TD participants showed greater habituation to triggers in a non-social context, whereas individuals with misophonia showed greater habituation to triggers in a social context ($p=0.04$) driven by an increased N100 response to the first social trigger ($t=-2.31$, $p=0.03$). Thus, TD participants better adapt to irrelevant mechanical sounds, while individuals with misophonia show exaggerated and sustained pre-attentive responses to identical sounds in a social context.

Conclusion:
These results suggest individuals with misophonia show aberrant early sensory responses and habituation following socially-generated triggers. Exaggerated registration of these sounds also relates to socially-relevant symptoms, including anxiety and empathy imp

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Full Name	Maia Chester
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Gut Feelings: Body Mistrust and Emotion Dysregulation in Bulimia Nervosa

Maia Chester, Thalia Viranda, Laura A. Berner

BACKGROUND: Altered interoceptive awareness, and specifically mistrust of internal body signals, has been implicated in both disordered eating and emotion dysregulation, but the cognitions that could explain these common links have not yet been investigated. Individuals with bulimia nervosa (BN), a disorder characterized by binge eating, purging, and emotion dysregulation, tend to expect eating to relieve their negative affect; however, little is known about how these beliefs may relate to body mistrust and influence difficulties accessing emotion regulation strategies seen in BN.

METHODS: We examined body mistrust, ER difficulties, and eating expectancies in 30 women with BN and 31 age-, BMI-, and FSIQ-matched healthy controls who completed the Eating Disorder Examination (EDE) and self-report questionnaires (Difficulties in Emotion Regulation Scale (DERS), Eating Expectancies Inventory (EEI), and the Multidimensional Assessment of Interoceptive Awareness (MAIA)).

RESULTS: Women with BN reported lower levels of body trust ($t(55.65)=-10.91, p< 0.001$), greater difficulties accessing emotion regulation strategies ($t(36.04)=7.11, p< 0.001$), and greater beliefs that eating helps manage negative affect ($t(56.65)=10.05, p< 0.001$) compared to their healthy counterparts. Within the BN group, robust regressions revealed that lower levels of body trust were associated with stronger beliefs that eating will help alleviate negative affect ($B=-1.75$, $SE=.88$, $p=.046$) and greater difficulties accessing adaptive emotion regulation strategies ($B=-3.16$, $SE=1.22$, $p< 0.01$). Further, stronger beliefs that eating will reduce negative affect were associated with greater difficulties accessing emotion regulation strategies ($B=.50$, $SE=.30$, $p=.011$), which were related to more frequent loss of control over eating ($B=.11$, $SE=.04$, $p< 0.01$).

CONCLUSION: Results highlight a critical role for body mistrust in maladaptive beliefs that eating will regulate emotions and in difficulties accessing other, more adaptive emotion regulation strategies in BN. These findings add to the growing literature suggesting that body mistrust may be a useful target in cognitive behavioral treatment, especially in addressing maladaptive cognitions (i.e., eating expectancies) and dysregulated emotions. Future longitudinal and ecological momentary assessment studies are needed to test whether expectations that eating will reduce negative affect mediate the relationship between body mistrust and emotion regulation difficulties, ultimately leading to more frequent symptoms.

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Full Name	Feng-Kuei Chiang
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Rostro-caudal gradient of structured representations in primate lateral prefrontal cortex

Feng-Kuei Chiang and Erin L. Rich

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BACKGROUND: During sequential or multistep behaviors like playing chess, neural ensembles in primate lateral prefrontal cortex (LPFC) form structured representations that are believed to be important for cognitive control. However, the LPFC is functionally heterogeneous, with a prominent rostro-caudal gradient suggested to correspond to abstract-to-concrete information processing. Here, we investigated how ensemble codes change according to this proposed gradient of abstraction in rhesus monkeys trained to organize a self-ordered sequential task.

METHODS: Two monkeys were implanted with four 64-channel Utah arrays along the dorsal LPFC in one hemisphere, and single-unit activity was analyzed. In the task, monkeys were trained to saccade to eight identical targets on a task screen, one at a time in any order, to collect a one-time reward from each target. Therefore, monkeys had to use working memory to track which targets had been visited and prepare for the next target selection. Single units were then grouped into ensembles recorded from each array, and methods of dimensionality reduction and unsupervised clustering were applied for each array to compare prediction accuracy of target location representation using the confusion matrix.

RESULTS: Ensemble activity represented target locations with more distinct structure in posterior (Area 8a including frontal eye field) compared to anterior (Areas 9/46) LPFC. This indicates that concrete location information is more clearly represented by more posterior LPFC neurons, which may be important for guiding saccadic eye movements. On the other hand, representations in anterior LPFC tended to merge with nearby targets which may be evidence that representations integrate space with more abstract task information.

CONCLUSIONS: Merging representations may relate to the structured organization of targets, such as sequences and other abstract strategies in the working memory task. Our results are consistent a rostro-caudal abstract-to-concrete gradient of ensemble representations in LPFC that may be critical for flexible, intelligent behaviors.

Funding: R01 MH121480, Whitehall Foundation Research Grant, FBI Seed Funds.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Gabriela Chiarotto
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Department	Neurology

Evaluation of Right Atrial Ganglionic Plexus (RAGP) morphology in Rhesus Macaques contribute to new strategies of cardiac autonomic modulation

Chiarotto GB, Biscola NP, Tompkins JD, Havton LA

BACKGROUND: The right atrial ganglionic plexus (RAGP) is a component of the intrinsic nervous system of the heart. The mammalian RAGP ganglia contain cholinergic neurons and receives cholinergic input, and RAGP influence is essential for normal sinoatrial node function. The RAGP is an emerging target of interest for therapeutic interventions, including electrical stimulation strategies for neuromodulation, in cardiac conditions. However, the synaptic and neural organization of the RAGP varies between species, and there is limited information on the detailed and fine structure of the RAGP in primates, including humans, to guide development of refined neuromodulation strategies.
METHODS: We aimed to characterize the neural organization of RAGP ganglia in adult rhesus macaques using light microscopy (LM) and transmission electron microscopy (TEM) after plastic resin-embedding of tissues.
RESULTS: Immunohistochemistry for PGP9.5 and LM analysis show the RAGP to be composed of multiple ganglia, which are interconnected by several nerve fiber bridges. Toluidine blue-stained LM sections of individual ganglia show clusters of ellipse-shaped neuronal somata with prominent nuclei, surrounded by a loose neuropil which includes small myelinated axons. TEM studies of RAGP ganglia show neurons with large nucleus and an organelle-rich cytoplasm. The RAGP neurons are surrounded by satellite cells with prominent nuclei and their processes in close apposition with the neuronal cell membrane. The neuropil includes dendritic profiles and axo-dendritic synaptic contacts, symmetric synaptic specializations and presence of clear spheroid vesicles and some dense-core vesicles in the presynaptic boutons. TEM studies of inter-ganglionic fiber bundles show small myelinated and predominantly unmyelinated fibers in multiple peripheral nerve bundles connecting individual ganglia. Each nerve fiber bundle is surrounded by a thick perineurium.
CONCLUSIONS: We conclude that the RAGP in primates show a complex synaptic organization with axo-dendritic contacts and ganglionic innervation by both myelinated and unmyelinated fibers. The RAGP model system in rhesus macaques may be used for future studies of cardiac physiology and cardiovascular dysregulation in e.g. aging, neuropathy, and neurological trauma to the spinal cord.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Alexandra Chisholm
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Neurobiological Underpinnings of Cannabidiol's Action in Attenuating Opioid Relapse

Alexandra Chisholm, Joseph Landry, James Callens, Randall J. Ellis, Jacqueline Ferland, and Yasmin L. Hurd

Background: Drug addiction is a chronic relapsing disorder characterized by cycling periods of compulsive drug use, abstinence, and relapse. Cannabidiol (CBD), a non-intoxicating cannabinoid, is currently under investigation as an anti-relapse treatment. Previously, our laboratory has demonstrated that CBD attenuates cue-induced heroin-seeking in an animal model of relapse. Clinically, our group also showed that CBD attenuates craving and anxiety induced by drug-associated cues in abstinent individuals with heroin use disorder. The exact mechanisms by which CBD exerts its anti-relapse effects are not well understood. The objective of the current study was to assess the effects of CBD treatment on heroin-seeking in conjunction with transcriptomic profiling in the nucleus accumbens (NAc) core and shell.

Methods: Male Long Evans rats were trained to intravenously self-administer heroin over 15 days followed by 14 days of forced abstinence. Rats were acutely injected with either vehicle or CBD (5 or 10 mg/kg, i.p) 24 hours prior to a drug-seeking session. Blood was collected 1 hr after the CBD administration, and brains were extracted 1.5 hours following the drug-seeking session. Plasma was used to measure endocannabinoid and CBD levels. NAc core and shell tissue was dissected and bulk RNA sequencing was performed.

Results: Both doses of CBD attenuated heroin-seeking during the drug-seeking test compared to vehicle controls. Acute CBD treatment increased CBD, 7-OH-CBD, anandamide, and arachidonic acid levels. Bulk RNA sequencing indicates distinct differential gene expression in the NAc core when compared to the shell including biological processes related to morphine addiction and synaptic transmission. Ingenuity pathway analysis revealed that CBD reverses canonical pathway alterations induced by heroin, particularly in the NAc shell. Ongoing analyses are examining cell-type specific effects of CBD in the NAc core and shell.

Conclusions: These findings suggest that CBD reduces cue-induced drug-seeking behaviors by altering biological pathways impacted by heroin in the NAc core and shell with an indication of greater impact in the NAc shell.

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2023 Neuroscience Retreat

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Autophagy restricts senescence and enables microglia to engage amyloid plaques in neuroprotection

Insup Choi, Minghui Wang, Seungyeul Yoo, Bin Zhang, Zhenyu Yue

Background: Microglia are essential for maintaining brain homeostasis, but when dysregulated, exert pathogenic functions in Alzheimer's disease (AD). Recent evidence has implicated senescent/dystrophic microglia in the pathogenesis of AD. It is unclear, however, whether microglial senescence is a cause or consequence of AD pathogenesis. Autophagy is a cellular degradation pathway that clears up protein aggregates and damaged cellular organelles. Autophagy is known to exhibit anti-aging/senescence effects. Here we report that autophagy restricts cellular senescence of microglia and confer neuroprotection in mouse models of AD.
Method: To examine the roles of autophagy in microglial senescence, we have established a microglia-specific autophagy-deficient mouse line using tamoxifen-inducible Cx3cr1CreER mice and Atg7Flox/Flox mice. To determine the impact of senescent microglia on AD, we crossed microglia-specific Atg7-deficient mice with 5xFAD mice which recapitulate amyloid plaque pathology in human AD.
Results: Cellular senescence-associated phenotypes, such as reduced proliferation, increased level of p21Cip1/Cdkn1a, a well-known cyclin-dependent kinase inhibitor that causes cell-cycle arrest and cellular senescence, accumulation of lipofuscin, and reduced the complexity of branch morphology, were observed in autophagy-deficient microglia at 6- and 12-months after silencing Atg7. Further, through single-cell RNA sequencing, we identified senescence-associated microglia (SAM) in Atg7-deficient microglia. Lastly, AD-associated phenotypes, including levels of oligomeric amyloid-beta, phospho-tau, and dystrophic neurites, were increased in 5xFAD mice harboring Atg7-deficient microglia compared to normal microglia.
Conclusion: Our study demonstrates that autophagy prevents microglia senescence, protecting the brain against AD.

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TITLE: Neuroinflammatory features of progressive supranuclear palsy

Authors: Thomas D. Christie, Jack Humphrey, Timothy Chang, Zhao Yi, Yuk Y Leung, Vishakha Patil, Wan-Ping Lee, Hui Wang, Ashvin Ravi, Natalia Han, Hadley Walsh, Soong Ho Kim, Claudia De Sanctis, Valeriy Borukhov, Diana K. Dangoor, Ricky M. Ditzel Jr, Megan Iida, Alicia Casella, Alan Renton, Towfique Raj, Alison Goate, Gerard Schellenberg, Daniel H. Geschwind, Adam Naj, John F. Crary, Kurt Farrell.

BACKGROUND: Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized clinically by problems with movement and a range of cognitive and behavioral changes. There are no disease-modifying treatments for PSP, albeit ongoing clinical trials exist. Ongoing genetic studies of related neurodegenerative disorders, including Alzheimer's and Parkinson's disease, have implicated genes related to immune regulation, especially innate immunity, in risk loci. Here we leverage the largest genome-wide association study of PSP to investigate genes contained in significant loci and their protein products to gain a more comprehensive understanding of their role in disease pathogenesis.

METHODS: Formalin-fixed paraffin-embedded (FFPE) tissue sections on charged slides were baked at 70 ºC, and immunohistochemistry was performed on a Ventana Benchmark XT autostainer. Slides were stained with antibodies for C4a, RUNX2, MOBP and STX6 (n=10 for cases vs. PSP). Images were captured on a light microscope at various magnifications. ImageJ was used to assess cellular features of neurodegeneration and inflammation quantitatively. Statistical analyses and graphs were generated using R.

RESULTS: We found a strong dystrophic axonal staining pattern of complement (C4a) observed around tau-positive coiled bodies in PSP, which was significantly higher than age-matched controls ($p < 0.05$). Compared to matched controls, nuclear RUNX2 staining in IBA1-positive microglia in PSP was infrequent. White matter MOBP patterning was marked in PSP and rare in controls. No significantly different observations were observed in patterning and quantity of STX6 signal.

CONCLUSIONS: Examination of the immune-related proteins found in significant genetic risk loci revealed an immunohistochemical signature that differentiated PSP from other neurodegenerative disorders. Data generated from this work could assist in diagnosis and elucidation of the pathogenesis of PSP and related primary tauopathies.

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Declining autozygosity over time: an exploration in over 1 million individuals from three diverse cohorts
Sarah M.C. Colbert, Frank R. Wendt, Gita A. Pathak, Drew A. Helmer, Elizabeth R. Hauser, Matthew C. Keller, Renato Polimanti, Emma C. Johnson

Background: Previous studies have hypothesized that autozygosity is decreasing over generational time. However, these studies were limited to relatively small samples (N < 11,000) lacking in diversity, which may limit the generalizability of their findings.
Methods and Results: In this report, we present data that partially support this hypothesis from three large cohorts of diverse ancestries, two from the US (All of Us and the Million Veteran Program, N=82,474 and 622,497, respectively) and one from the UK (UK Biobank, N=380,899). Our results from a mixed-effect meta-analysis demonstrate an overall trend of decreasing autozygosity over generational time (meta-analyzed slope=-0.029, se=0.009, p=6.03e-4). Based on our estimates, we would predict FROH to decline 0.28% for every 20 years decrease in chronological age. Using a chi-square difference test, we determined that a model including an ancestry-by-country interaction term fit the data best, indicating that ancestry differences in this trend differ by country. We found further evidence to suggest a difference between the US and UK cohorts by meta-analyzing within country, observing a significant negative estimate in the US cohorts (meta-analyzed slope=-0.058, se=0.015, p=1.50e-4) but a non-significant estimate in the UK (meta-analyzed slope=-0.001, se=0.008, p=0.945). We also found that the association between autozygosity and birth year in the overall meta-analysis was substantially attenuated when accounting for educational attainment and income (meta-analyzed slope=-0.011, se=0.008, p=0.167), suggesting that increases in education and income may partially account for decreasing levels of autozygosity over time.
Conclusion: To our knowledge, this is the largest demonstration of decreasing autozygosity over time in a modern sample (birth years 1904-2003), and we speculate that this trend can be attributed to increases in urbanization and panmixia, with differences in demographic and sociocultural processes leading to country-specific differences in the rate of decline. This decline has important implications for traits subject to inbreeding depression, including behavioral and psychiatric traits.

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A multi-omic atlas of the parahippocampal gyrus in Alzheimer's disease

Authors: Claire Coleman, Jaroslav Bendl, John Fullard, Courtney Micallef, Zhiping Shao, James Vicari, Erming Wang, Minghui Wang, Vahram Haroutunian, Bin Zhang, Panos Roussos

Background

Alzheimer's disease (AD) is the most common form of dementia worldwide. While forgetfulness and the loss of memory were always considered as the first disease symptoms, spatial navigation and orientation deficits have been increasingly shown in preclinical AD as an emerging cognitive biomarker. The parahippocampal gyrus (PHG) has been reported as critical in spatial memory, with a selection of publications suggesting a link between the PHG and AD, including the potential for MRI-measured atrophy of the PHG functioning as a biomarker for preclinical AD. Most published research on this brain region's role in the progression of AD to date has been clinical in nature. Next generation sequencing has been well established and holds great promise to assist in the development of novel therapeutics and biomarkers to prevent or slow the progression of this devastating disease.

Methods

Fluorescence-Activated Nuclei Sorting was utilized to generate neuronal and non-neuronal samples from AD cases and controls. We expanded the panel of antibodies to further sort non-neuronal samples to oligodendrocytes and microglia/astrocytes. We generated 126 RNA-seq and 122 ATAC-seq samples from 21 deeply phenotyped AD patients and 21 controls of the Mount Sinai NIH Brain and Tissue Repository. RNA-seq samples were integrated into a single analysis across all cell types and AD case/control status to perform a joint quality control analysis, same for ATAC-seq samples.

Results

Dimensionality reduction techniques were used to confirm successful clustering of samples by cell types except for outlying samples that were excluded. Differential expression analysis identified increased expression of MAPT and FBXO2 in the microglia and astrocytes of AD patients. MAPT encodes tau, a protein central to AD neuropathology, FBXO2 is involved in regulation of amyloid precursor protein. Most upregulated genes were in neuronal cells, including MAPK3, a gene involved in tau phosphorylation and amyloid deposition.

Conclusions

Several AD-associated genes were identified as upregulated in this study, with most showing their differences between AD patients and controls cell type-specifically. It suggests that the results from previous studies with bulk tissues should be interpreted with caution because of the confounding effect of cell type. By providing an extensive public resource of processed and quality-controlled data, along with raw and aligned data, we aim to empower other researchers to apply novel methods and perform integrative analyses on this highly variable, connected and complicated brain region's potential role in the progression of AD.

2023 Neuroscience Retreat

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Full Name	Alberto Corona
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Norepinephrine-sensing microglia in the habenula regulate adaptations to stress

Alberto Corona, Masago Ishikawa, Victor Mathis, Paul J. Kenny

BACKGROUND: Stress increases the propensity of lateral habenular (LHb) neurons to fire in phasic bursts of activity. Burst-firing of LHb neurons modifies monoaminergic neurotransmission in corticolimbic brain sites, which contributes to stress-related negative behavioral states. The mechanisms underlying this stress-induced maladaptive cellular plasticity are unclear. Stress is known to enhance norepinephrinergic (NE) transmission throughout the brain, which orchestrates physiological and behavioral adaptations to stress. Here, we investigated the role of NE signaling in stress-induced increases in LHb burst-firing.

METHODS: Norepinephrinergic (NE) transmission in the LHb was monitored using a genetically encoded sensor (GRAB NE). Single-cell RNA sequencing (scRNA-seq) was performed using the 10x Genomics Chromium and Illumina NovaSeq 6000 platforms. Microglia were depleted by permitting mice to consume chow containing the colony-stimulating factor-1 receptor (CSF-1R) antagonist PLX5622. Intrinsic activity patterns of LHb neurons were characterized using whole-cell current-clamp recordings.

RESULTS: Using GRAB NE and in vivo fiber photometry, we found that stressful events triggered time-locked changes in NE transmission in the LHb of mice. scRNA-seq showed that neurons and non-neuronal cells demonstrated striking transcriptional responses to chronic restraint stress in the LHb of mice. Inspection of the scRNA-seq data revealed that: (i) Only β2 adrenergic receptors (β2ARs) were robustly expressed in the LHb; (ii) β2ARs in the LHb were expressed almost exclusively by resident microglia. PLX5622-mediated depletion of microglia precipitated a stress-like increase in the propensity of LHb neurons to fire in phasic bursts of activity. Currently, we are investigating the effects of conditionally deleting β2ARs from habenular microglia on the activity patterns of LHb neurons and the expression of stress-related behaviors.

CONCLUSIONS: Our data suggest that stress-induced increases in NE transmission in the LHb engage microglia through β2ARs, and that these stress-sensing microglia regulate adaptations in the activity patterns of LHb neurons that drive stress-induced behavioral abnormalities. We hypothesize that microglia increase the propensity of LHb neurons to engage in burst firing through indirect mechanisms involving other populations of non-neuronal cells. The fact that β2AR expression in the LHb is restricted to resident microglia is important because β2ARs play crucial roles in coordinating adaptations to stress, which suggests that microglia are critical intermediaries of these actions in the LHb.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Transcriptional regulation of neuroprotective microglia subtypes in health and disease

Jessica Crowley, Pinar Ayata, Matthew Challman, Hayley Strasburger, Andrew Chan, Sebastian Werneburg, John Murray, Robert Sebra, Dorothy Schaefer, Alison Goate, Anne Schaefer

Commitment to a cell lineage is determined by the expression of certain transcription factors that regulate the coordinated expression of lineage-specific gene networks. Progenitor differentiation into myeloid or lymphoid lineages depends on the expression level of PU.1, where lymphoid cell commitment is associated with low levels and myeloid cells express high levels of PU.1. Myeloid cells give rise to tissue specific macrophages, including microglia; interestingly, we found that microglia expression of PU.1 in the adult brain is heterogeneous, raising the possibility that PU.1 level may define microglial gene networks and establishes unique functional subsets.

This may be relevant in Alzheimer's disease (AD), where a variant identified in the Spi1 (PU.1) locus confers a reduced expression of this transcription factor in myeloid cells and is associated with protection against AD progression.

Our preliminary data from Spi1 haploinsufficient and Spi1 overexpressing mouse models show that reduced PU.1 decreases microglia gene expression of myeloid gene networks and increases lymphoid networks. We propose a model in which PU.1 dosage regulates the prevalence of plaque associated microglia versus harmful inflammatory microglia subsets in AD, where reduced microglial PU.1 favors protective functional outcomes against disease.

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Department	Neuroscience

FUNCTIONAL ROLE FOR H3 SEROTONYLATION DURING CRITICAL PERIODS OF POSTNATAL BRAIN DEVELOPMENT

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BACKGROUND: The serotonergic (5HTergic) system is implicated in a wide range of neurodevelopmental and neuropsychiatric phenomena, including the regulation of mood and stress reactivity. While 5HT actions have been assumed to be mediated exclusively through 5HT receptors and their synaptic effects, recent studies have demonstrated the presence of nuclear pools of 5HT in dorsal raphe nucleus (DRN) serotonergic neurons and forebrain projection neurons. Our laboratory has established that 5HT forms covalent bonds with histone H3 glutamine 5 (H3Q5ser)–a process known as H3 serotonylation. We have further shown that H3 serotonylation plays key regulatory roles in establishing normal embryonic and adult patterns of brain transcriptional plasticity. However, functional roles for H3 serotonylation during early post-natal brain development, time points encompassing critical periods of neural plasticity, have largely been unexplored, and the impact of environmental stimuli (aberrant or otherwise) on this modification during early life remains unknown.

METHODS: We used molecular techniques to examine the regional and developmental expression of H3 serotonylation in male and female mice. Given the role of H3 serotonylation in gene regulation, we used FANS (Fluorescence-Activated Nuclear Sorting)-coupled CUT&RUN (cleavage under targets and release using nuclease) to profile the cell type-specific developmental regulatory landscape of the mouse prefrontal cortex (PFC) a brain region that receives reciprocal projections from and to the dorsal raphe nucleus (DRN) which in part influence feedback control of cortical 5HT release. We used early life stress (ELS) to examine how stress during critical windows of development leads to long-lasting changes in H3 serotonylation genomic enrichment.

RESULTS: Interestingly, we identified region- and developmental-dependent expression of H3 serotonylation, suggesting a developmental role for H3 serotonylation particularly in the PFC and DRN. FANS-coupled CUT&RUN revealed cell type- and developmental-specific genomic distribution of H3 serotonylation in the PFC of male and female mice which were perturbed by exposure to ELS.

CONCLUSIONS: Overall, we provide novel insight into the ways that H3 serotonylation regulations brain development and the mechanisms by which disruptions to this posttranslational modification cause aberrant pathophysiological states.

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2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Pathology

Title: Pathoanatomical mapping of activated EIF2α in vulnerable brain regions in progressive supranuclear palsy

Diana K. Dangoor, Kristen R. Whitney, Margaret M. Krassner, Kurt Farrell, Hadley W. Ressler, Thomas D. Christie, Abhijeet Sharma, Won-Min Song, Bin Zhang, Ana C. Pereira, John F. Crary

Departments of Pathology, Artificial Intelligence and Human Health, Neuroscience, Friedman Brain Institute, Ronald M. Loeb Center for Alzheimer's Disease, Genetics and Genomics Sciences, Pharmaceutical Sciences, and Neuropathology Brain Bank & Research CoRE, at the Icahn School of Medicine at Mount Sinai.

Background: Progressive supranuclear palsy (PSP) is a rare neurodegenerative movement disorder characterized neuropathologically by abnormal hyperphosphorylated tau (p-tau) aggregates in neurons, oligodendrocytes, and astrocytes, most notably in the peri-Rolandic cortex, basal ganglia, and brainstem. Most PSP cases are sporadic and linked to common structural genomic variation in the 17q21.31 MAPT locus. Genome-wide association studies have identified additional risk loci, including eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3). EIF2AK3 encodes a component of the unfolded protein response (UPR), a mechanism that restores protein homeostasis during endoplasmic reticulum (ER) stress. Studies have implicated dysregulation of UPR activation in multiple neurodegenerative diseases, including PSP. Our single-cell transcriptomic data suggests that EIF2 signaling is altered in PSP.

Methods: To further investigate the role of the UPR in this disease, we performed a pathoanatomical study of the most selectively vulnerable brain regions and cell types in PSP. We assessed formalin-fixed paraffin-embedded postmortem brain tissue from PSP patients and controls using routine histological stains and immunohistochemistry to detect p-tau and the activated UPR marker phospho-EIF2α (pEIF2α). Sections were scanned, and whole-slide images were scored semi-quantitatively for neurodegeneration, p-tau burden (neuronal and glial), and pEIF2α burden.

Results: We found pEIF2α immunopositive cells in brain regions vulnerable to PSP and at higher levels than in protected regions. Levels of pEIF2α positively correlated with p-tau burden.

Conclusions: These results support the hypothesis that dysfunction of the UPR may play a role in abnormal tau deposition and neurodegeneration in PSP. Exploring the upstream and downstream components of the UPR in response to tauopathy may provide further insight into the interplay between UPR activation and PSP pathology and progression.

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Full Name	Anika Das
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Role of High Fat Diet and Chronic Stress on Energy Metabolism

Anika Das

Background: Post traumatic stress disorder (PTSD) is a condition brought upon by intense stress, affecting brain and body functions. Previous research has demonstrated a strong comorbidity between PTSD and metabolic diseases such as obesity, diabetes, and heart disease. However, the brain-body pathways through which stress alters energy metabolism are largely unknown. Studies have shown that pro-inflammatory cytokines play an important role in lipid synthesis of various metabolic diseases. Furthermore, clinical data suggests a positive correlation between emotional eating (increased eating to cope with stress) and PTSD diagnoses in adults. Therefore, we hypothesized chronic stress paired with a high fat diet (HFD) would result in an upregulation of pro-inflammatory cytokines.

Methods: To test this hypothesis, C57BL/6 mice were run in the Stress Enhanced Fear Learning (SEFL) task and then given HFD for 14-weeks. After the initial stressor, half of the animals received weekly shocks as a reminder of the initial trauma, while the other half received no additional shocks. We then measured the expression of pro-inflammatory cytokines in gonadal white adipose tissue (gWAT) and liver samples using RTrt-qPCR.

Results: We observed interesting effects of sex and stress in pro-inflammatory cytokine expression from mice on HFD. Female mice that underwent repeated stress in conjunction with a HFD showed significant upregulation in MCP1, a key chemokine that regulates migration and infiltration of monocytes/ macrophages in gWAT. This effect was not observed in gWAT of repeatedly stressed males on HFD mice. Instead, the pro-inflammatory markers ILl-12p40 and IL-1b were upregulated in gWAT of repeatedly stressed males but not females on HFD. Additionally, repeatedly stressed males, but not females on HFD also showed an upregulation of MCP1 in the liver.

Conclusions: Our results indicate a sex difference in the pathway of metabolic dysregulation for chronically stressed males and females on HFD. The upregulation of MCP1 in the adipose tissue of repeatedly stressed female mice on HFD suggests insulin resistance in adipose tissue . While MCP1 upregulation in the liver of repeatedly stressed male mice on HFD is tied to fibrosis of the liver. Repeatedly stressed males on HFD also experienced an upregulation of IL-12p40 and IL-1b in adipose tissue. Research has demonstrated a link between IL-12p40 and IL-1b upregulation in adipose tissue to obesity and insulin resistance. Taken together, our work demonstrates that repeated stress in conjunction with HFD result in sexually dimorphic metabolic dysregulation of metabolic function.

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Single neurons in the human substantia nigra encode social prediction errors

Davis, A. N., Perl, O., Kopell, B. H., Heflin, M., Qasim, S. E., Na, S., Kishida, K. T., Montague, P., Saez I., & Gu, X.

BACKGROUND: Social decision-making is integral to healthy cognition and mental well-being. Social learning often entails encoding and adapting to social norms, which are agreed-upon rules of behavior among social groups. Social norms are learned through experience, whereby norm prediction errors (nPEs), or the difference between expected norms and true norms, drive internal norm adaptation, just as reward prediction errors (RPEs) drive reward expectation adaptation. Human intracranial electrophysiology (iEEG) studies have implicated substantia nigra (SN) units in RPE encoding (Zaghloul et al., 2009), which is consistent with the classical theory that RPEs are encoded by dopaminergic (DA) units (Schultz, Dayan, & Montague, 1997). Given that nPEs and RPEs share a common computational mechanism of adaptation, we predict that nPEs and RPEs also share common encoding by DA SN units. Here, we leverage behavioral computational modeling and human iEEG to elucidate the neural mechanisms underlying norm encoding and adaptation.

METHODS: We collected SN single-unit iEEG recordings in neurosurgery patients (n= 10 sessions, 6 subjects) as they played an ultimatum game, in which they were presented with a proposed split of $20, which they accepted or rejected. If the patient rejected, each party received $0. We then used computational modeling to infer the values of latent variables governing observed choice behavior. We modeled subjective utility using a Fehr-Schmidt (FS) model of inequity aversion, which we compared to four norm adaptation models including two Bayesian models and two Rescorla-Wagner functions. We selected the best norm adaptation model to compute trial-by-trial nPEs. We identified clusters from neural recordings using an offline spike sorting algorithm and putatively phenotyped DA units according to average firing rate and waveform morphology. Continuous firing rate at split reveal was compared across trials producing positive versus negative nPEs.

RESULTS: 10 out of 25 units were identified as putative DA units. The average firing rates of these DA units at split reveal differed significantly between trials producing positive versus negative nPEs.

CONCLUSIONS: We demonstrate that putative dopaminergic units in the substantia nigra (SN) encode the valence of norm prediction errors in social contexts. SN units play an integral role not only in processing unexpected financial rewards, but also in social norm adaptation, thus identifying this region as an important structure in social learning.

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Neurocircuitry of apathy in Parkinson's patients with subthalamic nucleus deep brain stimulation.

Jip de Bruin, Dr. Ki Sueng Choi, Dr. Brian Kopell, Dr. Helen Mayberg, Dr. Martijn Figee.

BACKGROUND: Parkinson's disease (PD) is a movement disorder related to pathology in parallel basal ganglia systems for motor and motivational control. Despite the effectiveness of subthalamic nucleus deep brain stimulation (STN DBS) for motor symptoms, its non-motor effects remain controversial. STN DBS patients frequently suffer from an increase in apathy. The present study therefore investigated the relationship between apathy and stimulation-related pathways in PD patients with STN DBS. With the primary objective to investigate the relationship between change in apathy from pre- to post-surgery and stimulation-related pathways. An increase in apathy from pre- to post-surgery was hypothesized to be associated with missing limbic cortical stimulation.

METHODS: Pre-operative MRI data and the patient-specific stimulation parameters were used to perform probabilistic tractography. Pre- and post-surgical apathy was evaluated in PD patients (N = 28) using the Starkstein Apathy Scale (SAS). The structural connectivity of patients with a significant increase in apathy (apathy change group, N = 13) was compared to the structural connectivity of patients without this increase in apathy (non-apathy change group, N = 15). The volume of tissue activated (VTA) around stimulation contacts was modeled on each patient's postsurgical CT. First, probabilistic tractography was performed to generate average structural connectivity maps for the two groups from VTA seeds to the whole brain. Next, seed to target probabilistic tractography was performed to calculate the structural connectivity from VTA seeds to cortical regions of interest (ROIs; the left limbic and motor cortex, left-sided ventral lateral prefrontal cortex, and ventral medial prefrontal cortex (vlPFC and vmPFC)). Finally, the structural connectivity between the stimulated STN target and the ROIs were correlated with apathy change score.

RESULTS: Confirming our primary hypothesis, apathy increase after 6 months of STN DBS was significantly correlated with lower connectivity between the stimulated STN and the left vmPFC ($R = -0.39$, $p = 0.042$). The change in apathy was independent of motor improvement ($N = 8$, $R = -0.5$, $p = 0.22$), motor connectivity ($R = -0.17$, $p = 0.38$) and medication changes ($R = -0.22$, $p = 0.27$).

CONCLUSION: These findings suggest that insufficient left-sided vmPFC stimulation contributes to apathy in PD patients receiving STN DBS. This novel characterization of apathy and its neurocircuitry in surgical PD patients may be the first step towards resolving post-surgical apathy in PD by co-stimulating non-motor pathways with a personalized targeting approach.

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Full Name	Pamela Del Valle
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Identifying the Cellular Basis of Melanoma and Parkinson's Comorbidity

Pamela Del Valle, Sarah Garcia Moreno, 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 fast 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 in humans: 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 further 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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Full Name	Sean Thomas Delica
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Modeling Sporadic Tauopathy in Patient iPSC-Derived Induced Neurons

Sean Thomas Delica, Kristen R. Whitney, Margaret M. Krassner, Kurt W. Farrell, Thomas D.Christie, Megan A. Iida, Hadley A. Walsh, Samuele Marro, Ruth H. Walker, Giulietta Riboldi, Steve Frucht, John F. Crary

Background: Progressive supranuclear palsy (PSP), a neurodegenerative tauopathy, is characterized neuropathologically by abnormal tau accumulation in the brain. PSP is often misdiagnosed as Parkinson's disease as it presents with an atypical akinetic rigid syndrome as well as variable cognitive impairment. There are rare cases of tau gene mutations that cause tauopathy, yet most are sporadic with associated common genetic risk alleles. The precise molecular cause of cell death in PSP remains unknown. However, irregularities in tau proteostasis such as hyperphosphorylation and accumulation, as well as other homeostatic signaling pathways have been implicated in PSP. Transducing human induced pluripotent stem cells (hiPSC) into neurons using viral genetic engineering techniques is a promising tool to study pathogenic mechanisms in vitro. The objective of this project is to generate lentiviral NGN2-induced glutamatergic neurons differentiated from PSP patient-derived hiPSCs and matched controls to determine to the extent to which PSP neurons recapitulate key disease molecular changes.

Methods: Fibroblasts were grown from PSP skin biopsies collected during autopsy or from living patients and reprogrammed into hiPSCs using Sendai virus. Sex- and age-matched control iPSC lines were selected from previous cell bank collections. HiPSCs were differentiated into glutamatergic neurons using an NGN2 tet-on lentiviral protocol and grown for one month. We will characterize total tau, phosphorylated tau, and tau isoform expression and distribution in induced neurons on the protein and RNA level by western blot, immunofluorescence, and qPCR.

Results: Four PSP and four control iPSC lines were differentiated into NGN2-neurons and maintained for 28 days. Characterization of disease-related phenotypes is currently ongoing.

Conclusion: We hypothesize that NGN2-induced neurons from PSP patients recapitulate key disease relevant features, including increased tau proteoforms and hyperphosphorylated tau proteoforms. This model may be useful for investigating underlying molecular tauopathy mechanisms, drug development, and cell therapies.

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Full Name	Lauren Dierdorff
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Dissecting Cortical Circuits Driving Motor Deficits in a Mouse Model of DDX3X syndrome

Lauren Dierdorff, Marta Garcia-Forn, Michael Flores, Praise Ola, Silvia De Rubeis

Background: Many individuals with autism spectrum disorder (ASD) present with motor problems, although the relationship between ASD and motor ability is poorly understood. DDX3X syndrome is a monogenic form of ASD that affects primarily females and presents with motor impairment, including hypotonia and/or hypertonia, abnormal gait, and movement disorder. DDX3X syndrome is caused by mutations in the X-linked RNA helicase DDX3X, known to regulate mRNA metabolism. DDX3X is key for the development of the neocortex and hindbrain, but how it impacts the formation and function of brain circuits is unknown. To date, the brain circuits underlying the motor phenotype in DDX3X syndrome have not been explored. Our lab generated a Ddx3x haploinsufficient mouse (Ddx3x+/− females) with construct and face validity for loss-of-function mutations. Ddx3x+/− females have motor delays and deficits and a misplacement of subcerebral projection neurons (scPNs) in primary motor cortex, which are neurons important for motor function. One type of scPN that we believe is particularly vulnerable to Ddx3x mutations is the corticopontine projection neurons, a population critical for motor control as these neurons initiate the cortico-ponto-cerebellar pathway connecting the cortex and cerebellum.

Methods: I first investigated corticopontine circuits by injecting a retrograde virus carrying GFP into the pontine nuclei, a region important for motor behavior and innervated by scPNs. I then performed rotarod and balance beam tests and stained for the immediate early gene c-Fos to investigate whether the corticopontine neurons are activated by the tasks. I also performed developmental and adult motor tests on a forebrain-specific line (Emx1-Ddx3x) to determine the role of the cortex in motor function. Lastly, I perform RNA-sequencing analyses on Fluorescence-Activated Cell Sorting (FACS) purified corticopontine neurons from Ddx3x+/- mice and control mice.

Results: My results show that execution of skilled motor tasks elicited neural activity in the cortex of control mice, however, the c-Fos+ cells did not significantly overlap with corticopontine neurons. A subsequent experiment revealed a difference in c-Fos+ cells in the primary motor cortex between control and mutant mice. Additionally, Emx1-Ddx3x mutant mice show developmental delays and adult motor deficits. Transcriptomic experiments are ongoing.

Conclusions: These deficits in cortical development in Ddx3x+/− mice provide basis to dissect the neural substrates of motor deficits observed in DDX3X syndrome with primary emphasis on the cortex.

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Full Name	Shilpa Dilip Kumar
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Department	Microbiology/ Neuroscience

EFFECTS OF ARP2/3 /FORMIN PERTURBATION ON DENDRITIC SPINES

Romario Thomas, Shilpa Dilip Kumar, Deanna L Benson

BACKGROUND: Synapses transfer information at rates regulated by their location, shape, and size. This depends on a stable network of a filamentous actin cytoskeleton. Synapses also encode information by changing shape or number, events that demand flexibility and depend on actin. Consistent with these roles several actin assembly agents and modifiers have emerged in screens for neuropsychiatric or neurological diseases. ARP2/3 is a single multiprotein complex which is important for nucleating branched filaments and experimental manipulations in the nervous system have shown that it is essential for enlarging synapses and for promoting nervous system maturation. The 15 or so members of the Formin family nucleate straight filaments. Virtually nothing is known about what individual Formin members do and why neurons express so many. To fill this gap in knowledge we are using pharmacological agents and CRISPR-based reagents to identify the Formin family members important for generating or maintaining synapse shape.

METHODS: Layer2/3 cortical neurons were labelled by ex utero electroporation of a tdTomato-expressing plasmid. After 14 days in vitro (DIV), guide RNAs and CAS9 were introduced using lentivirus or pharmacological agents were added for 30 mins at 21 DIV. Neurons were imaged with either Leica SP8STED3X or Zeiss LSM980 Airyscan2, with high resolution objectives and a zoom factor of 1.7. Z-stacks were collected to capture the entire volume of the dendrite.

Images were pre-processed, deconvolved and analyzed using Bitplane Imaris 10 software. Dendrites were identified and segmented using an ML-based filament tracing algorithm. Spines were detected and classified based on morphology. These parameters were exported into excel files and analyzed to quantify numbers and changes in morphology with perturbation of actin.

RESULTS: Preliminary results show that spines can be quantified and classified efficiently using the Imaris 10 software augmented with Labkit. To validate our strategy, we examined neurons following brief inhibition of Arp2/3 or Formins. Inhibition of Arp2/3 expands the percentage of filopodia at the expense of mushroom–shaped spines and long thin spines and inhibiting Formins increases the percentage of mushroom shaped spines. We are currently assessing the outcomes of Formin deletion.

CONCLUSION: Our data show that Imaris 10 can be used to screen for changes in synapse shape and is sufficiently sensitive to reveal changes in shape following 30 minutes inhibition. This approach will be used to characterize the Formins relevant to synapse structure.

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Full Name	Ricky Ditzel
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Title: An autopsy series of seven genetically confirmed cases of chorea acanthocytosis (VPS13A disease)

Authors: Ricky M. Ditzel Jr., Ruth H. Walker, Melissa J. Nirenberg, Amber M. Tetlow, Kourtni J. Lind-Watson, Kurt W. Farrell, Emma L. Thorn, Diana K. Dangoor, Ronald Gordon, Claudia De Sanctis, Gabriel Miltenberger-Miltenyi, Jack Humphrey, John F. Crary

BACKGROUND: Vacuolar protein sorting 13 homolog A (VPS13A) disease, historically known as chorea-acanthocytosis, is a rare neurodegenerative disorder caused by biallelic mutations in VPS13A, resulting in reduced or absent protein. Neuropathological features include neuronal loss in the striatum, most prominently in the caudate nucleus, with associated marked astrogliosis. There are no other known disease-specific cellular changes (e.g., protein aggregation). VPS13A localizes to contact sites between subcellular organelles, consistent with its recently-identified role in lipid transfer between membranes. To date, autopsy reports have been limited, often lacking genetic or biochemical diagnostic confirmation.

METHODS: In this study, brain tissues, clinical data, and other diagnostic data from seven clinically typical cases of VPS13A disease were collected from contributing centers. Tissues underwent routine, special, and immunohistochemical staining focused on neurodegeneration. Electron microscopy was performed in one case.

RESULTS: Immunoblots confirmed the loss of VPS13A protein in some cases, and sequencing identified VPS13A mutations in all cases, including novel variants. Gross examination showed severe striatal atrophy. Microscopically, there was neuronal loss and astrogliosis in affected regions. Luxol Fast Blue staining showed variable lipid accumulation with diverse morphologies, a finding that was further demonstrated by electron microscopy. Two cases had comorbid Alzheimer's neuropathologic changes; one had brainstem-predominant Lewy body pathology in the absence of clinical parkinsonism. We also noted the variable presence of rare degenerating p62- and ubiquitin-positive cells in affected regions. Calcifications were present in three cases, being extensive in one.

CONCLUSIONS: We present the largest autopsy series of biochemically- and genetically-confirmed VPS13A disease and report a detailed survey of histopathological findings.

2022 Neuroscience Retreat

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Cortical Reshaping in Multiple Sclerosis is Associated with Cortical Lesion Load and Worsening Disability

Jonadab dos Santos Silva, Francesco La Rosa, William A Mullins, Prasanna Parvathaneni, Josefina Maranzano, Daniel S Reich, Erin S Beck

Background: Cortical lesions are associated with disability in MS, but if and how they are related to local and global changes in brain structure is unclear. Additionally, global brain atrophy measures may not be sensitive to local atrophy in MS. Cortical curvedness is a vertex-wise measure of gyrus shape and may be more sensitive to local structural changes. We aimed to investigate changes in cortical curvedness longitudinally in MS, and the relationship between cortical reshaping, lesion load, and disability worsening.

Methods: 50 adults with MS (31 relapsing-remitting, 16 secondary progressive, and 3 primary progressive, age 49±11 years; 65% female; disease duration 12 years [IQR, 18]) underwent longitudinal 3T and 7T brain MRI and clinical assessments (median follow-up 2.8 years, range 0.9–4.1). Disability progression was defined as an increase in Expanded Disability Status Scale, 25-foot timed walk, or 9-hole peg test. Cortical and white matter lesions were manually segmented on 7T (0.5mm3 MP2RAGE [median of 4 acquisitions], 0.5mm3 T2*w GRE) and 3T (FLAIR, MP2RAGE, T2w) images respectively. 3T T1w MP2RAGE images were used for longitudinal cortical reconstruction (FreeSurfer), with pial curvedness calculation and vertex-wise GLM analyses of longitudinal changes and cluster correction for false discovery rate. Vertex-wise local effect of lesions was investigated by comparing ROI-based perilesional to non-perilesional metrics, which were converted into intrasubject across-vertices z-scores. SPSS 26 was used for statistical analyses.

Results: Although total brain volume did not change longitudinally (-0.6±2.9%, P=0.714), pial curvedness underwent diffuse reduction (all PFDR<0.05, corrected for age and sex). Binomial logistic regression accounting for age, sex, follow-up time revealed greater global curvedness loss in patients with worsening disability (OR 306.43 [95% CI, 2.43 – 38599.71], P=0.020), but no difference in cortical thickness or volume. Multivariate GLM accounting for age, sex, and follow-up time explained 16% of variance in global curvedness loss (P=0.026), which was predicted by higher baseline cortical (F=5.5, P=0.023) but not white matter lesion volume (F=3.8, P=0.058). Curvedness loss was greater in areas surrounding cortical lesions than in non-perilesional regions (Z =-5.73, P<0.0001).

Conclusions: Cortical curvedness change may be a sensitive measure of local structural changes and is associated with disability progression. Even over a relatively short follow-up time, cortical lesions are associated with global and local changes in changes in curvedness. Further studies may elucidate how cortical lesions drive cortical remodeling and how

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Effects of high fat diet and chronic stress on fear and metabolic functions

Samuel J. Duesman

BACKGROUND: Post-Traumatic Stress Disorder (PTSD) occurs after the experience of a traumatic event and affects about 6% of the US population . Recent studies suggest PTSD diagnosis is a predictor of obesity and metabolic dysfunction. Additionally, the link between stress and metabolic dysfunction has been demonstrated to be sex-dependent in clinical populations. However, little is known about how diet influences stress-related behaviors in conjunction with metabolic dysregulation in males and females. Our study aims to determine the effects of a high-fat diet (HFD) paired with a chronic stress after a trauma-like intense stressor on fear behaviors and metabolic health using mice as model organisms.

METHODS: For this study, we used a the stress enhanced fear learning (SEFL) protocol that recapitulates multiple aspects of PTSD-like stressor. We then gave mice ad-libitum access to high fat diet (HFD) or chow for 14 weeks. Within each diet (HFD or chow), half of the animals were given weekly shocks as a reminder of the initial trauma and the other half were not administered additional shocks. Freezing behavior was recorded weekly for 14 weeks. We performed a glucose tolerance assay to assess the animals ability to clear a bolus of glucose from the body. We then collected metabolic data continually for 72-hours. Finally, we performed a gradient light open field test to assess anxiety-like behavior.

RESULTS: Our results showed that non-chronically stressed male mice on HFD displayed high levels of freezing behavior throughout the 14-week period. However, non-chronically stressed female mice on HFD showed extinction of fear with freezing levels being significantly reduced after 14 weeks. Freezing remained high in both chronically stressed males and females on HFD throughout the 14-week period. Chronically stressed females on HFD also showed increased glucose intolerance, a characteristic of type 2 diabetes, after 14 weeks. We also observed a non-significant trend of decreased locomotion in during the light phase of the gradient light open field test and a non-significant trend towards a binge-eating phenotype in chronically stressed females on HFD.

CONCLUSIONS: Our results clearly demonstrate that stress and diet interact in a sex-specific manner to affect behavior and metabolic outcomes. These results indicate that understanding the sex-specific effects of diet and chronic stress are crucial for developing avenues for treatment that utilize personalized medicine.

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Linking Brain-Wide Activity Patterns during Neuroeconomic Decision Making to Aggression

Brian Sweis, Antonio Aubry, Long Li, Julian Sackey, Farzana Yasmin, Salma O. Elhassa, Sanjana Ahmed, Eric Nestler, Scott Russo, Romain Durand-de Cuttoli

BACKGROUND

Aggression is an evolutionarily conserved response to a perceived threat that spans a large range of diverse behaviors, including those that may be adaptive and protective as well as those that may be pathological and dangerous to others. Circuits recruited during the expression of aggression, in addition to circuits known to subserve social interactions themselves, are critical nodes of the brain's reward system. However, it is unclear how pathological aggression may “hijack” key reward circuits in the brain, contributing to maladaptive reinforcement of aggression. Because the brain has evolved to use multiple decision-making systems, simple tests of reward value may be unable to access computational subtleties that may be altered in the brains of aggressive individuals.

METHODS

We characterized decision-making profiles of 40 outbred Swiss Webster mice screened for aggression and then tested on the neuroeconomic task, “Restaurant Row.” Mice had limited time each day to forage for their sole source of food investing in rewards of varying costs (delays from 1-30s signaled by tone pitch) and value (unique flavors tied to four spatially cued locations). On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene.

RESULTS

We found that the majority of brain regions revealed decreased levels of c-Fos expression in highly aggressive animals versus non-aggressive animals. Using an unbiased, open-ended analysis approach, top region hits revealed strong negative correlations between aggression and c-Fos expression, regions that lie in the medial wall of the prefrontal cortex (mPFC) (including the anterior cingulate, prelimbic, and infralimbic cortex) and are known to be engaged by the Restaurant Row task. Using this approach, we also found that several regions across the limbic system covaried with numerous key metrics from the Restaurant Row task, suggesting specific regions may be interacting in order to give rise to complex decision-making profiles. Using a focused analysis, we found that individual differences in subjective value covaried with c-Fos expression in the mPFC, scaled along its dorsoventral axis.

CONCLUSIONS

These data reveal how brain-wide studies of aggression may reveal changes in circuits affecting only certain types of decision being processed. These findings set the stage for future experiments manipulating circuit-specific computations, including within functional sub-regions of the mPFC, in order to augment multiple valuation algorithms underlying aggression.

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Full Name	Catherine Elorette
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Title: Chemogenetic inhibition of amygdala increases resting-state functional connectivity, LFP coherence, and neural spiking activity in macaques

Authors: Elorette, C*1; Fujimoto, A*1; Stoll, F1; Fujimoto, SH1; Fleysher, L2; Russ, BE#1,3; Rudebeck, PH#1

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Background: Despite widespread use of fMRI resting state functional connectivity (FC), how transient changes in neural activity within a structure affects brain-wide FC remains unclear. To address this, we combined resting state fMRI, acute LFP recording, and manipulation of neural activity using chemogenetics in non-human primates. The DREADD (designer receptors exclusively activated by designer drugs) chemogenetic system allows for the selective and reversible manipulation of neural activity in large tissue volumes, which is essential in non-human primates.

Methods: We injected inhibitory DREADD construct AAV5-SYN1-hM4Di-HA bilaterally into amygdala in two rhesus macaques. We evaluated the effects of systemic administration of highly-selective DREADD ligand deschloroclozapine (DCZ, 0.1 mg/kg) or vehicle during resting state fMRI. Whole brain functional images were acquired on a 3T scanner (1.6mm isotropic). We compared changes in FC after drug injection using ROIs derived from cortical, subcortical, or whole brain atlases. In a similar resting state paradigm, we then confirmed the effect of amygdala inhibition on neural activity by comparing neural spiking activity in the amygdala, and LFP coherence between the amygdala and ventrolateral PFC (VLPFC) after administration of DCZ or vehicle.

Results: Compared to vehicle, activating the DREADD receptors with DCZ increased whole brain FC, and specifically FC between amygdala and the striatum and mediodorsal thalamus ($p < 0.05$). In a hypothesis driven analysis, we observed an increase in FC between amygdala and VLPFC after DCZ injection using an amygdala seed-based approach ($p < 0.05$, $30 \leq$ voxel clusters). Electrophysiological recording of neural spiking activity showed an increase in the amygdala after DCZ compared to vehicle ($p < 0.05$). Comparison of the LFP coherence between the amygdala and VLPFC showed an increase in coherence after DCZ as compared to vehicle ($p<0.05$).

Conclusions: These findings show a direct link between local neural activity and brain-wide functional connectivity, although the directionality of the effects was unexpected. Further experiments will assess how inactivating amygdala efferent pathways alters functional connectivity.

Funding: NIH

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Transcriptomic analysis of the hippocampal formation using single nucleus RNA sequencing in Alzheimer Disease and Aging

Authors: Marissa Farinas, Esma Karlovich, Joon Ho Seo, Abhijeet Sharma, Kurt Farrell, Kristen Whitney, Anjalika Chongtham, Diede Broekaart, John F. Crary, Ana C. Pereira

Background: Alzheimer Disease (AD) is the most common cause of dementia and is characterized by progressive memory loss and decline in other cognitive domains such as visual-spatial tasks, language, and executive function. The hippocampal formation is one of the earliest affected regions in AD and displays differential vulnerability to tau pathology, with the entorhinal cortex (EC), subicular complex, and CA1 showing susceptibility while the DG and CA3 are more resilient. The molecular signatures driving this hippocampal susceptibility and resilience to tau pathology in AD are still largely unknown. We hypothesize that cell type specific differences in gene expression underlie the selective vulnerability or resilience of different hippocampal subfields in aging and AD.
Methods: Three age-matched AD and control donors were selected for snRNA-seq based on clinical and neuropathological variables. Fresh frozen postmortem brain tissue containing the hippocampus and entorhinal cortex were sectioned and stained with hematoxylin and eosin (H&E), NeuN, AT8, and 4G8 for histopathological characterization. We micro-dissected the hippocampal subfields (DG, CA3+CA2, CA1, subicular complex) and EC using a validated segmentation protocol followed by nuclei isolation. Nuclear suspensions were processed on the 10x Genomics platform, counted, and sequenced using Illumina NovaSeq. Analysis was performed in R using the Seurat package.
Results: Using a newly validated segmentation protocol, we reliably annotated and micro-dissected hippocampal subfields from fresh frozen postmortem brain tissue. After quality control filtering, we recovered ~205,000 nuclei and identified all major cell types based on previously established cell-type-specific markers genes, as well as five hybrid cell populations. We preliminarily established the top three subfield-specific excitatory neuron markers in CA1, DG, subicular complex, and EC of control donors. Additionally, differential gene expression between AD and control donors revealed enrichment of cell-type specific pathways both common and unique to the hippocampal subfields.
Conclusions: The results of our study provide novel insight into the transcriptional markers of differential vulnerability and resilience in the subregions within the hippocampal formation at the single cell level. Future work will include more in-depth analysis of DEGs comparing AD and control donors within each subfield as well as between subfields within AD or control donors.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Susie Feng
Job Title	PhD Candidate
Lab	Shuman Lab
Department	Neuroscience

Hippocampal-Entorhinal Desynchronization in Chronically Epileptic Mice

Susie Yu Feng1, Lucia Page-Harley1, Keziah Diego1, Zhe Dong1, Sophia Lamsifer1, Julia Schnipper1, Albert Jurkowski1, Denise Cai1, Tristan Shuman1
1-Friedman Brain Institute

BACKGROUND: Temporal lobe epilepsy is one of the most common types of epilepsy in adults and causes pervasive memory impairments which significantly impact patients' quality of life. In pilocarpine-treated epileptic mice, we have recently found desynchronized interneuron firing between the CA1 and dentate gyrus regions of the hippocampus (HPC) but it remains unclear whether these effects are driven by impaired inputs from upstream medial entorhinal cortex and when these deficits emerge following epileptogenesis. We have recently found progressive spatial memory deficits in epileptic mice that emerge between 3 and 8 weeks after pilocarpine suggesting that specific network processes may break down across this time period. Cognitive processes require precise communication between circuits, and thus we hypothesized that altered timing between HPC and MEC may contribute to epilepsy-associated cognitive deficits. In this project, we tested whether MEC-HPC synchronization is disrupted in epileptic mice before and after progressive memory deficits emerge.

METHODS: We have performed simultaneously in-vivo electrophysiology with 512-channel silicon probes in HPC and MEC of epileptic and control mice running in virtual reality. We recorded at two time points (3wk and 8wk post pilocarpine) to capture progressive changes during the development of epilepsy.

RESULTS: In HPC, we detected early onset deficits in epileptic animals at 3wk post pilocarpine, including reduced theta power and coherence, and disrupted interneuon phase locking. Within MEC, we detected no changes in theta power or spike timing, but found a progressive decrease in theta coherence. Between MEC and HPC, we found substantial progressive deficits in theta coherence and spike timing across regions, suggesting that MEC-HPC synchronization may play a key role in the onset of memory deficits.

CONCLUSIONS: Together, this data reveals a progressive late-onset impairment in the timing of MEC inputs into HPC through the development of epilepsy, which matches with the progressive spatial memory deficits observed in epileptic mice.

FUNDING: R01NS116357, CURE Taking Flight Award, AES Junior Investigator Award, AES predoctoral fellowship

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Brian Fennessy
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Lab	Charney Lab
Department	Genetics and Genomic Sciences

Title: Phenotype-by-phenome-wide association study of treatment resistant depression

Authors: Brian Fennessy, Brandon J Coombes, Lauren Lepow, Jorge A Sanchez Ruiz, Prakash Adekkanattu, Vanessa Pazdernik, Gregory Jenkins, Euijung Ryu, Myrna Weissman, Mark Olfson, J John Mann, Jyotishman Pathak, Joanna M Biernacka, Alexander Charney

Background: Major depressive disorder (MDD) is a highly prevalent and debilitating disorder. Treatment-resistant depression (TRD) is generally defined as inadequate response to at least 1-2 antidepressants of sufficient dose, duration, and adherence. Using this qualitative definition may not capture the heterogeneous nature of MDD, given patients present with several depressive subtypes, psychiatric comorbidity, and coexisting medical illnesses. Quantitative scoring of TRD could facilitate personalized care. Here, we defined three measures of TRD and performed a phenotype-by-phenome-wide association study (PhePheWAS), using two different biobanks with linked electronic health records (EHR).

Methods: We selected patients with at least one MDD-related diagnostic code and at least one antidepressant prescription from BioMe (N=4085) and the Mayo Clinic Biobank (N=12994). For the qualitative outcomes, we defined TRD status as a patient having either (1) one or more or (2) two or more antidepressant “switches” defined as a treatment trialed for at least 30 days but switched to a new treatment within 14 weeks. The quantitative measure of TRD was defined as (3) the number of unique antidepressants that a patient was prescribed for at least 30 days. We performed a PhePheWAS for each phenotype by testing for association across the entire phenome as measured by phecodes, accounting for multiple potential confounders. Results from the two biobanks were meta-analyzed.

Results: Of the 17079 patients, 1625 (9.5%) had at least one switch, 229 (1.3%) had at least two switches, and had an average of 2.2 unique antidepressants (range: 1 to 12). We found consistent significant associations across the three measures of TRD including with anxiety disorders (1: OR=1.8, p-value=4e-20; 2: OR=2.5, p-value=4e-9; 3: OR=1.4, p=1e-104) and suicidal ideation (1: OR=2.3, p-value=1e-13; 2: OR=4.0, p-value=3e-11; 3: OR=1.4, p=3e-39). Notably, the quantitative measure had the most statistically significant associations with 142 phecodes associated with the number of antidepressants prescribed, followed by 18 phecode associations for the $\geq$1 antidepressant switch and 7 for the $\geq$2 antidepressant switches.

Conclusions: Using a quantitative measure of TRD yielded more statically significant results compared with two qualitative outcomes. This superior statistical power may aid the detection of genetic correlates of TRD in future analyses and might prove useful in the rapid clinical assessment of treatment resistance. Further analyses will incorporate polygenic risk scores into this analysis to identify genetic factors that increase likelihood of TRD in MDD.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Jacqueline-Marie Ferland
Job Title	Instructor
Lab	Hurd lab
Department	Psychiatry/Neuroscience

Title: Cannabidiol alleviates cue-induced anxiety linked to alterations in the lipidome and transcriptome within the nucleus accumbens shell

Authors: Jacqueline-Marie N. Ferland, Alexandra M. Chisholm, Randall J. Ellis, Joseph A. Landry, James E. Callens, Yasmin L. Hurd

Background: Anxiety disorders affect ~18% of the US population every year. Cues previously associated with a fearful event have been shown to precipitate acute anxiety experiences, especially for conditions like post-traumatic stress disorder. Cannabidiol (CBD), a non-intoxicating constituent of cannabis, has been shown to reduce stress-induced social anxiety and cue-induced drug-seeking and craving, suggesting it may be effective in mediating behavioral responses to cues. However, clinical and preclinical results indicate mixed efficacy of CBD for anxiety, and few have addressed the neurobiological mechanisms underlying these effects.
Methods: To test the efficacy of CBD on cue-precipitated anxiety-like behavior, adult Long-Evans male rats underwent a footshock protocol with the presence of a distinct lemon oil or control, neutral odor cue. Light/dark box and open field were used to assess anxiety-like behavior in the presence of the cue associated with the shock. Rats were given either 10 mg/kg CBD or vehicle 1hr prior to the behavioral tests.
Results: CBD did not reduce anxiety-like behavior in rats in the neutral condition or reduce encoding of the cue, but reversed the heightened avoidance behavior in animals exposed to the lemon oil cue associated with the repeated shock-pairings. A multi-omics approach of the lipidome and transcriptome of the nucleus accumbens shell, a region involved in the extinction of fear, revealed CBD altered levels of N-acylethanolamines, a class of endocannabinoid lipids, and transcripts related to mitochondria function and synaptic plasticity. Ongoing analyses are examining cell-specific effects of CBD.
Conclusions: These results suggest that CBD may be well suited to alleviate cue-induced anxiety via multiple biological pathways in the nucleus accumbens shell.

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2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Ana Catarina Ferreira
Job Title	Postdoctoral Fellow
Lab	Joseph Castellano
Department	Neuroscience

Neuronal TIMP2 regulates hippocampus-dependent plasticity and extracellular matrix complexity

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The functional output of the hippocampus, a brain region subserving memory processes, depends on highly orchestrated cellular and molecular processes that regulate synaptic plasticity throughout life. The structural requirements of such plasticity and molecular processes involved in this regulation are poorly understood. Specific molecules, including tissue inhibitor of metalloproteinases-2 (TIMP2) have been implicated in processes of plasticity in the hippocampus, a role that decreases with brain aging as expression is lost. Here, we report that TIMP2 is highly expressed by neurons within the hippocampus and its loss drives changes in cellular programs related to adult neurogenesis and dendritic spine turnover with corresponding impairments in hippocampus-dependent memory. Consistent with the accumulation of ECM in the hippocampus we observe with aging, we find that TIMP2 acts to reduce accumulation of extracellular matrix (ECM) around synapses in the hippocampus. Moreover, its removal results in hindrance of newborn neuron migration through a denser ECM network. A novel conditional TIMP2 KO mouse reveals that neuronal TIMP2 regulates adult neurogenesis, accumulation of ECM, and ultimately hippocampus-dependent memory. Our results define a mechanism whereby hippocampus dependent function is regulated by TIMP2 and its interactions with the ECM to regulate diverse processes associated with synaptic plasticity.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Alexandra Fink
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BACKGROUND: Mood is defined as a human's conscious perception of their internal affective state. It has been theorized that mood is an internal adaptive state that signals the availability of reward in one's environment and guides decision-making. Computational modelling of mood has been used to describe the behavioral mechanism of reward-guided decision-making's impact on one's internal mood state. An important reward signal related to mood is the counterfactual prediction error, as the difference between actual reward received during decision-making and the maximum potential reward that would have been received, had an individual made a different decision. Negative CPEs (nCPEs) represent "what could have been" and underlie feelings of regret, which are hypothesized to be heightened in depression. Excessive feelings of regret induced by accumulation of nCPEs induce ruminative states on negative reward outcomes and may reinforce depressed mood. The computational and neural substrates mediating nCPEs and mood responses represent a potential mechanism whereby symptoms of rumination and depressed mood arise.
METHODS: We investigated the behavioral and neural impact of nCPEs on mood in intractable epilepsy patients implanted with stereotactic EEG probes for seizure monitoring. Patients suffer from a high (~40%) comorbidity rate with depression, and therefore provide a unique opportunity to probe mood and reward computations across depression states while simultaneously recording neurophysiology data from cortical and subcortical brain structures rarely available in humans. Patients played a monetary gambling task where they chose between a safe bet or risky gamble that had a 50% probability of resulting in a better or worse outcome. After each trial, patients were shown both how much money that earned, and how much they would have earned had they chosen the alternative option. Patients also numerically rated their mood state throughout the game, allowing for an explicit quantitative estimation of their momentary subjective well-being. Using computational modeling, we related self-assessed mood states with recent reward outcomes.
RESULTS: Computational modelling revealed that nCPEs had stronger associations with negative mood outcomes in patients with comorbid depression. Electrophysiological results show that high frequency activity in the orbital frontal cortex encodes a neural representation of nCPE signals.
CONCLUSIONS: Preliminary results support the hypothesis that patients with comorbid depression have heightened sensitivity to negative counterfactual outcomes, resulting in feelings of regret. Heightened sensitivity is reflected in stronger associations in computational models of mood as well as neural activity patterns in the orbitofrontal cortex. These data provide new insights into the neural correlates of disrupted representations of reward value through the novel combination of intracranial recordings and computational modeling of reward and mood.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Rachel Fisher-Foye
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Lab	Russo
Department	Neuroscience

TITLE
Neuroimmune mechanisms underlying reward deficits in depression

AUTHORS
Rachel L. Fisher-Foye, Romain Durand-de Cuttoli, Flurin Cathomas, Antonio V. Aubry, Long Li, Lyonna F. Parise, Alexa R. LaBanca, Kion T. Winston, Sara Costi, Caleb J. Browne, Eric J. Nestler, James W. Murrough, Scott J. Russo

BACKGROUND
Major depressive disorder (MDD) is a leading cause of disability worldwide, creating an immense burden on countless individuals and the greater global population. One prominent symptom associated with MDD, is anhedonia: the loss of interest for hedonic stimuli. In parallel, several clinical and pre-clinical studies have linked exposure to stress and MDD, a stress-related psychiatric disorder, with alterations of the peripheral immune system. However, the neuroimmune mechanisms that lead to brain circuit alterations and ultimately to behavioral alterations are not well understood.
METHODS
Here, we investigate the impact of stress on blood-brain barrier (BBB) integrity, peripheral immune marker infiltration into the brain, and subsequent effects on the physiology of neurons in brain reward centers controlling anhedonia. We then assess reward deficits in a novel mouse version of the probabilistic reward task (PRT) after chronic exposure to social defeat stress (CSDS) and with or without manipulating BBB integrity or peripheral immunity. This task, first developed in humans, is well-positioned to extract stress-induced reward deficits relevant to MDD.
RESULTS
We found that in mice exposed to CSDS, alterations of the BBB lead to infiltration of peripheral monocytes into the ventral striatum. We also found that a direct consequence of this infiltration is a perturbation of the neuronal function in the nucleus accumbens and subsequent reward sensitivity deficits in the PRT. Namely, following CSDS, susceptible mice showed a blunted response bias but not unstressed control or resilient mice. Next, we found that artificially opening the BBB using a viral knock-down of the Claudin-5 tight junction protein led to an exaggerated impact of a sub-threshold stressor on reward sensitivity in the PRT.
CONCLUSION
Our results indicate that chronic stress causes systemic inflammation and that alterations of the BBB lead to an infiltration of immunity markers into the ventral striatum, altering neuronal function and, ultimately, causing major reward deficits. To bring a translational dimension to this project, we work with the Depression and Anxiety Center at Mount Sinai on using human PRT datasets and blood samples to inform our preclinical findings through an existing liquid biomarker pipeline established by our groups. This study will provide a critical understanding of the neuroimmune influence on reward deficits in MDD and advance the development of new personalized immune-based therapeutics to treat depression.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Atsushi Fujimoto
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Lab	Rudebeck lab
Department	Neuroscience

Title: Brainwide correlates of probabilistic choice for novel and familiar options in macaque monkeys.

Authors: Atsushi Fujimoto*, Catherine Elorette*, Satoka H Fujimoto, Lazar Fleysher, Brian E Russ#, and Peter H Rudebeck#
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# co-last authors

Background
Identifying the best course of action requires exploiting the value of known options but also learning about the value of novel options to maximize rewards. Despite this, the distinct brain mechanisms that support these processes are poorly understood. Recent studies suggested that ventro-lateral prefrontal cortex (vlPFC) is critical for learning reward values, but it is unclear how this area represents new and known values. Using fMRI we assessed how vlPFC interacted with other brain areas as macaque monkeys made choices between novel or familiar options in a stimulus-based probabilistic reward learning task.
Methods
We trained four female macaque monkeys (Macaca mulatta) to perform a probabilistic choice task, in which they were required to choose between visual stimuli that were associated with either 90%, 50% or 30% of juice reward. Monkeys underwent whole brain fMRI scans while performing the task with blocks of trials where either familiar or novel stimuli were presented.
Results
All four monkeys performed at a very high level in Familiar blocks (> 82%), while they showed distinct learning curves in Novel blocks as they learned which stimulus was associated with the highest probability of reward. All animals showed different levels of switching behavior depending on the reward feedback and ongoing block type ($p < 0.01$, two-way ANOVA). Whole-brain fMRI analysis showed that several areas including bilateral vlPFC were activated in both Novel and Familiar blocks but activity was higher in Novel blocks. Functional connectivity analysis showed that the vlPFC to amygdala pathway was associated with a decision to switch in Novel blocks.
Conclusions
Our data provide new insight into the neural mechanisms of probabilistic learning and decision-making. Specifically, our results indicate that vlPFC and its connection to amygdala play a crucial role in guiding learning about novel stimuli.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name Rita Futamura

Job Title PhD Student

Lab Nestler lab

Department Neuroscience

Transcriptomic analysis of the nucleus accumbens after heroin self-adminsitration implicates Mbd3 as a key regulator of relapse susceptibility

Rita Futamura, Caleb J Browne, Xianxiao Zhou, Aarthi Ramakrishnan, Angélica Minier-Toribio, Marine Salery, Arthur Godino, Bin Zhang, Yasmin L Hurd, Li Shen, Eric J Nestler

BACKGROUND: Repeated opioid use causes molecular changes in the nucleus accumbens (NAc), a brain region critical for coordinating motivated behavior and reward processing. Dysfunction of the NAc can perpetuate compulsive drug-seeking and drug-taking behaviors to the extent of which voluntary control over these behaviors is lost. Further, molecular changes within the NAc may support long-term susceptibility to relapse despite cessation of opioid use, induced by drug-related cues or re-exposure to the drug itself triggering intense drug craving. However, transcriptome-wide regulation within the NAc induced by opioid-seeking behavior has not been previously examined.

METHODS: Ongoing studies in our laboratory have identified broad patterns of transcriptional regulation throughout the brain reward circuitry induced by volitional opioid exposure and drug-seeking behavior using intravenous heroin self-administration in mice. In these studies, mice self-administered saline or heroin for 15 days and underwent a 30-day homecage forced abstinence period, after which mice were challenged with either saline or heroin, returned to the self-administration context for a 2-h drug-seeking test. Immediately following this test, animals were euthanized and the NAc was dissected for RNA sequencing. DESeq2 was used to identify differentially expressed genes, factor analysis was used to identify genes associated with addiction-relevant behavioral outcomes, and multiscale embedded gene co-expression network analysis (MEGENA) was used to identify gene networks and key hub genes contributing to heroin-seeking.

RESULTS: Here, we focus on how transcriptional regulation within the NAc contributes to drug-seeking behavior. We identified a highly significant gene network in this brain region that is enriched with upregulated genes induced by heroin-primed drug-seeking using MEGENA. Within this network, methyl-CpG binding domain protein 3 (Mbd3), one of the most significantly upregulated genes within the NAc in this condition, was found to be a key hub gene. In addition, exploratory factor analysis linking behavioral outcomes from self-administration with gene expression uncovered a positive association between Mbd3 and a composite measure of addiction-like behavior.

CONCLUSION: Taken together, these data suggest that Mbd3 is an important driver in controlling this gene network that associates with relapse-like behavior. Ongoing efforts include determining the cell-type-specificity of Mbd3 regulation in NAc D1 or D2 medium spiny neurons, manipulating Mbd3 using knockdown and overexpression approaches, and examining changes to behavior that promote drug craving, and ultimately, relapse.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Yared Gessesse
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Department	Cardiovascular Research Institute at Mount Sinai

Beating Tubluar Micro-Heart Models for Acceleratd Drug Discovery

Yared Gessesse, Arpad Marka, David Sachs, Kevin Costa

Background
The cost of developing new drugs is dominated by its many stages of testing, including in vitro assays, animal testing, and clinical trials. However, the overwhelming majority of drugs passing preclinical tests, including animal testing, fail during clinical trials and do not proceed to market [1]. This suggests that animal testing might not always be a good model to determine a drug's potential for success; therefore searching for new models is imperative. Organoids, which are 3-D self-assembled spheroidal cultures derived from stem cells, are one of these new model types; but due to their sphericity, they do not represent most organs, which are tube-like.
Methods
In order to create tube-like organoids, we can use chips with microfluidic channels to simulate a body-like environment: in our case, the heart. In the Costa lab, we are designing polydimethylsiloxane(PDMS)-based microfluidic chips to create a tubular human micro-sized heart model. Using custom robotic machines, chips are seeded with stem cells and then differentiated into cardiac muscle and endothelial cells.
Results
By simulating the environmental factors during heart development we were able to grow a pumping tube of cardiac muscle cells connecting two microfluidic channels, driving fluid flow between them. The micro organ had similar function and size to a ~22 day old human embryonic heart.
Conclusions
The ultimate goal is to discover the environmental factors which can repeatedly and reliably induce the cells to form such tubes. This model can then be used for testing the effects of drugs on human hearts, and also to reveal the effects of environmental factors, such as microgravity, on the human heart. A select number of our chips are scheduled for launch to the International Space Station in 2023 to study these topics.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Jack Gomberg
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Lab	Nash Family Center for Advanced Circuit Therapeutics
Department	Neurology

Association of White Matter Abnormalities and Differential Treatment Outcomes to Cognitive-Behavioral Therapy or Antidepressant Medication

Jack Gomberg, Jungho Cha, Juna Khang, Boadie Dunlop, Edward Craighead, Helen Mayberg, Ki Sueng Choi

Background:
First-line treatment for major depressive disorder (MDD) include cognitive behavioral therapy (CBT) and/or antidepressant medications (ADM). However, these treatments can be highly effective in one patient but ineffective in another with similar MDD symptom presentations. Previous treatment selection biomarker studies using resting state fMRI implicate differential subcallosal connectivity to the left anterior insula, left ventromedial prefrontal, and left periaqueductal gray in CBT and medication remitters (Dunlop AJP 2017). Structural connectivity changes that might mediate these functional connectivity patterns are unknown. Therefore, we evaluated pretreatment White matter (WM) integrity in treatment naïve MDD patients as a function of differential 3 month clinical outcome to monotherapy with CBT or ADM.

Methods
A retrospective analysis of diffusion-weighted imaging scans (DWI) was performed in 110 treatment naive MDD patients randomized to 12 weeks of CBT or ADM. Subjects were grouped into CBT or ADM remitters (HDRS17 score <7 at 10 and 12 weeks) and CBT or ADM failure (HDRS score change <30%). A Whole brain fractional anisotropy (FA) map was calculated for each subject using Fdt toolbox in FMRIB and Tract-Based Spatial Statistics (TBSS) generated for statistical comparison across outcome groups. A voxel-wise 2 x 2 ANOVA: treatment (CBT/ADM) by outcome (remitter/nonresponder) was performed using the AFNI 3dMVM toolbox. Lastly, Regional WM changes were correlated with HDRS score changes with treatment.

Results
A significant treatment by outcome interaction was identified affecting WM tracts adjacent to the left insula, left supplementary motor area, and left hippocampus ($p < 0.001$ uncorrected). Post hoc analysis revealed ADM remitters and CBT nonresponders show higher FA values in the left insula and SMA compared to both ADM nonresponders and CBT remitters, similar to the location and differential pattern of functional connectivity. In contrast, ADM remitters and CBT nonresponders show lower FA in the left hippocampus compared to ADM nonresponders and CBT remitters. Of the identified treatment-specific findings, only the left insula showed a significant correlation ($r=0.089$; $p=0.001$) with magnitude of clinical response, but only in the ADM treated group.

Conclusion
These findings identify differential WM integrity in WM tracts adjacent to the insula, SMA, and hippocampus in remitters and failures to CBT and ADM. As with functional connectivity findings, structural connectivity patterns may define imaging biotypes that impact capacity to respond to first line MDD treatment and guide optimal treatment selection.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Damian Gonzalez
Job Title	associate researcher
Lab	Mobbs
Department	Neurosciences

Title: Phenothiazines increase lifespan and are protective in 2 C. elegans models of aging related diseases
Authors: Damian Gonzalez, Rachel Litke, Charles Mobbs

Introduction:
Until now, most drugs developed for a given age-related disease (such as Alzheimer's Disease (AD), ALS, diabetes, etc.) are based on specific targets and are at best symptomatic treatments. The Geroscience hypothesis states that age is a major risk factor for age related diseases and neurodegenerative diseases in particular. We hypothesized that generally protective drugs against aging could plausibly protect against aging related diseases. Using phenotypic screens, we identified phenothiazines as a class of drugs protective of aging and proteotoxicity in a C. elegans muscle model of AD. In the present studies we assessed the effect of exposure to phenothiazines on HD PolyQ repeats induced paralysis in a C. elegans muscle model of Huntington's disease (HD), AM140 strain.
Methods: Adult AM140 strain of C. elegans were exposed to our 3 most protective phenothiazine compounds (triflupromazine, trifluoperazine and chlorpromazine) in liquid medium at a concentration of 8uM. Worms were filmed every 2-3 days until all worms were immobile. Videos of worms were scored for HD PolyQ repeats induced paralysis. A Kaplan-Meier survival analysis was conducted using Prism software.
Results: All 3 phenothiazines tested significantly ($p<0.005$) delayed HD PolyQ repeats induced paralysis in our C. elegans model of HD.
Discussion: Phenothiazine compounds reported to increase lifespan and delay Abeta induced paralysis in C. elegans also delay HD PolyQ repeats paralysis in C. elegans. These results support the hypothesis that manipulations increasing lifespan and targeting hallmarks of aging can delay aging related diseases.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Apoorva Goyal
Job Title	Associate Researcher
Lab	Schaefer
Department	Neuroscience

In-Vitro regulation of Dopamine receptor D1 (Drd1) in primary microglia
Apoorva Goyal, Hayley Strasburger, Anne Schaefer
Nash family Department for Neuroscience, Centre for Glial Biology

Our recent research has identified a negative feedback mechanism for neuronal regulation mediated by microglia, which when attracted to active synapses generate ADO from ATP, thereby limiting excessive neuronal activity. In vitro studies have revealed that, in addition to ATP, microglia respond to a variety of neurotransmitters and signals, including Dopamine. We hypothesized that microglia in the striatum, being a region of dense dopaminergic innervation, would be able to respond to dopamine and modulate the homogeneous neuronal population of Medium Spiny Neurons (MSN). In support of this idea, through single nuclei sequencing we found that striatal microglia express the dopamine receptor, Drd1a. Using primary microglia culture, I study how Drd1a expression is induced in microglia and how the downstream signalling works. Our recent data have revealed that dopamine does not induce Drd1a expression and that activation of the Drd1a receptor using a D1 agonist induces downstream signalling through increased production of cAMP in vitro. Additionally, given our recent data, I will investigate how cAMP influences microglial function to understand how D1 signalling affects microglia. This information will help us understand the cellular mechanism by which microglia regulate neuronal activity in the striatum.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Faris Gulamali
Job Title	Medical Student
Lab	Charles Bronfman Institute of Personalized Medicine
Department	Medicine

Title • Author/s • Background • Methods • Results • Conclusions

Title: Training and Internal Validation of a deep learning system to non-invasively perioperatively detect elevated intracranial pressure

Authors: Faris F. Gulamali, Ashwin S. Sawant, Annie Chang, Ben Fox, James Desman, Brian S. Soong, Naveen Arivazhagan, Neha S. Dangayach, Girish N. Nadkarni,

Background: Perioperative intracranial hypertension can lead to a range of negative postoperative complications such as vomiting, nausea, headache, delirium, amnesia, weakness, PTSD, seizures, coma and cognitive impairment. The gold standard for measuring intracranial pressure is through invasive intracranial pressure monitoring. However, this can lead to increased risk of infection, additional bleeding, and costs 10,000-40,000 dollars per patient. Here, we develop an algorithm that can detect elevated intracranial pressure by using non-invasive modalities.

Methods: We utilize the MIMIC-III waveform database, which is an openly available database, to train a machine learning model to predict elevated intracranial pressure in real time. We extract patients with relevant waveform data from the database, and segment the data into 1 second long intervals, generating a total of 35 million independent data points. We split the dataset into training, validation and test subsets.

Results: We extracted 344 patients with measured intracranial pressure waveforms. We train our model on a single A100 GPU over 20 million waveforms for 1 epoch with a batch size of 4, and a learning rate of 0.007. Our model achieves a training accuracy of 0.90 and a validation and test accuracy of 0.86.

Conclusions: Improvements in model architecture, loss function, and data scaling and normalization are anticipated to increase the performance of our algorithm. Further work will correlate predictions of elevated intracranial pressure with clinical interventions and outcomes associated with intracranial hypertension such as placement of an extraventricular drain and stroke.

2023 Neuroscience Retreat

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Full Name	Swati Gupta
Job Title	Postdoctoral fellow
Lab	Deanna Benson
Department	Neuroscience

AMPAR subunit composition and trafficking are impaired in striatal projection neurons expressing Parkinson's associated Lrrk2G2019S mutation.

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Nash Family Department of Neuroscience at Mount Sinai

Background: Parkinson's is a debilitating, late-onset neurodegenerative disorder. However, much earlier, patients can exhibit non-motor cognitive and psychiatric symptoms that are often more disabling than motor symptoms. Abnormalities in corticostriatal connections are suspected to contribute to these non-motor behaviors but exact cellular mechanisms are unknown.
Methods: We used electrophysiological, pharmacological, biochemical, cell biological and super-resolution microscopy approaches to interrogate synaptic AMPAR subunit trafficking dynamics and function in spiny projection neurons (SPNs) that express the common G2019S pathogenic Parkinson's mutation in Leucine-rich repeat kinase 2 (Lrrk2).
Results: We found by Western blot analysis that total GluA1 and GluA2 subunit levels are unchanged in G2019S SPNs compared to WT SPNs. However, in mutants, there is a significantly increased synaptic membrane incorporation of GluA1 over GluA2 subunit selectively in D1R SPNs. Live-cell imaging of a SEP-GluA1 construct and antibody-feeding assays demonstrate that excessive surface GluA1 reflects a failure in constitutively internalizing and recycling GluA1 subunits. This trafficking defect is selective for GluA1, as transferrin receptors recycle normally. Additionally, we found that while PKA phosphorylation of GluA1 at S845, which is necessary for induction of LTP, is intact in G2019S SPNs, forskolin-stimulated GluA1-S845P containing AMPARs fail to reach the surface under conditions that drive surface accumulation of GluA1-S845P at WT SPN synapses. Finally, induction of chemical LTP failed to drive insertion of GluA1 containing AMPARs to the surface of G2019S SPNs compared to WT SPNs.
Conclusions: Collectively, our data show that Lrrk2G2019S has an SPN subtype-specific impact on GluA1 trafficking at baseline and under activity-dependent conditions which may constrain normal synaptic plasticity mechanisms leading to cognitive or psychiatric symptoms in human mutation carriers.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Neuroscience

Inactivation of the xenobiotic response pathway promotes peripheral axon regeneration

Dalia Halawani 1*, Yiqun Wang 1,2*, Aarthi Ramakrishnan 1, Molly Estill1, Yuhuan Li 1,3, Li Shen 1, Roland H. Friedel 1,4, Hongyan Zou 1,4

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BACKGROUND: Dorsal root ganglia (DRG) neurons have a remarkable capacity to regenerate that is dependent on transcriptional and epigenetic activation of pro-growth gene expression programs. Xenobiotic metabolites could dramatically impact the regenerative capacity of injured neurons. Xenobiotic sensing is mediated by the aryl hydrocarbon receptor (AhR) and it obligate partner aryl hydrocarbon receptor nuclear translocator (Arnt/Hif1b), both of which are members of the bHLH-PAS family of physiological, metabolic, and environmental sensors. Currently, little is known on the role of the xenobiotic response pathway (XRP) in neurons, and specifically how it may intersect with injury-induced transcriptional programs to affect axonal regeneration.
METHODS: Unbiased bioinformatic analysis of transcription factor motifs within regeneration associated differentially hydroxymethylated regions was used to identify bHLH-PAS family members as enriched. Xenobiotic sensing was studied in primary neurons and whole DRGs using treatment with xenobiotic ligands, endogenous AhR agonists, and antagonists. The effect on axon regeneration was analyzed in vitro using neurite outgrowth assay and in vivo using nerve crush injury model. Role of xenobiotic sensing was interrogated using genetic deletion models combined with bulk RNAseq.
RESULTS: Axonal injury upregulates AhR expression in DRGs in a time-dependent manner. Exposure of DRG neurons to xenobiotics triggered AhR nuclear translocation and expression of xenobiotic responsive genes, while AhR antagonists achieved the opposite. AhR activation prior to injury did not alter axonal regeneration. However, stimulation of AhR activity after injury attenuated neurite length, while antagonizing AhR promoted longer neurite outgrowth and augmented expression of RAGs. Neuronal-specific deletion of Ahr promoted axonal regeneration and motosensory recovery in vivo. Mechanistically, we show that the growth promoting effect of Ahr ablation is contingent on Hif1a. Preliminary gene set enrichment analysis of AhR target genes demonstrated involvement not only in cell-autonomous functions (detoxification and transcription regulation by RNA Polymerase II and III), but also in non-cell autonomous processes, such as neuroimmune and neuroglial interactions.

CONCLUSION: Collectively, our data demonstrate that activation of the XRP in the context of neuronal injury is deleterious for regeneration. XRP inactivation through AhR deletion may represent a novel therapeutic strategy to augment axonal regeneration.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Anhedonia Mediates Antidepressant Treatment Response to KCNQ2/3 Channel Opener Ezogabine and is Associated with Reward Sensitivity in Major Depressive Disorder

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Background: Studies have shown that the KCNQ2/3 channel opener Ezogabine reduces symptoms of anhedonia and depression in patients with Major Depressive Disorder (MDD). Based on the hypothesized role of the reward system in the mechanism of action of KCNQ2/3 channel openers, we tested whether reduction in anhedonia could predict the decrease in depression symptoms. In addition, we tested whether Ezogabine use or decrease in anhedonia was correlated with increased reward sensitivity in the Probabilistic Reward Task (PRT), a behavioral task aimed at measuring reward bias, a component of anhedonia.

Methods: Forty-five individuals with MDD were enrolled in a randomized placebo-controlled clinical trial. Participants completed clinical assessments before and after the five-week treatment course including the Snaith-Hamilton Pleasure Scale (SHAPS), a validated measure of anhedonia, and the Montgomery-Asberg Depression Rating Scale (MADRS), a validated measure of depression. With forty individuals, a RM ANOVA with group (Ezogabine/Placebo) as a between-subjects factor and Time (pre-post treatment) as a within-subjects factor was conducted along with a mediation analysis. In a subgroup of 19 participants with validated PRT, linear regression analysis was performed.

Results: MADRS scores significantly decreased in both groups: Placebo Baseline Average = 26.19(5.08), Placebo Outcome Average = 19.19(9.83); Ezogabine Baseline Average = 28.79(6.27), Ezogabine Outcome Average = 12.74(8.94), with significant between-group differences, $p<0.001$. However, SHAPS scores decreased significantly only in the Ezogabine group: Ezogabine Baseline Average = 38.32(6.22), Outcome Average = 26.95(8.37), with significant between-group differences $p<0.001$. SHAPS scores significantly mediated the relationship between Ezogabine and treatment response, ($p<0.001$). Decreases in SHAPS scores were significantly associated with increased reward sensitivity in the PRT ($p<0.05$). However, treatment group and changes in MADRS scores were not associated.

Conclusion: Results of this study suggest that Ezogabine may have a specific effect on anhedonic symptoms, which then drives changes in depression. Furthermore, our finding that decreases in anhedonia are associated with increased reward bias is consistent with prior studies. Future work should examine how Ezogabine may improve anhedonia and develop alternative behavioral measures of capturing such improvement.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Assessing early plasticity of pancreatic neural structure in obesity and diabetes

Rollie Hampton, Maria Jimenez-Gonzalez, Alexandra Alvarsson, Rosemary Li, Kavya Devarakonda, Keya Thakkar, Diego Espinoza, Sarah Stanley

BACKGROUND: Pancreatic islets are richly innervated and neural signals contribute to physiological glucose control. However, the roles of pancreatic innervation in obesity and diabetes remain poorly understood. Published studies suggest obesity reduces pancreatic innervation but rely on genetic models of obesity and 2D immunohistochemistry. The effects of obesity on pancreatic nerve function are unknown. Determining the effects of high-fat diet (HFD) on pancreatic nerve structure and function may provide novel insights into the mechanisms and pathophysiology of diabetes.

METHODS: To test the hypothesis that HFD causes rapid structural changes in pancreatic innervation, C57Bl6 mice were randomized to 1 week HFD or low-fat diet (LFD) groups. Metabolic phenotyping was determined. Pancreata were cleared and immunolabeled using iDISCO+ and imaged by lightsheet (4X) and confocal (10X) microscopy. Imaris software allows for unbiased quantitative volumetric analysis.

To assess whether altered neural signals may contribute to metabolic defects with obesity, we targeted DREADD expression to pancreatic sympathetic fibers by simultaneously injecting a retrograde AAV that expresses cre into the pancreas and AAVDJ with cre-dependent expression of activating DREADD into the celiac ganglia of WT mice fed a LFD or HFD. To determine whether the effects of obesity and T2D on the pancreas can be reversed by restoring neural signals, we stimulated pancreatic parasympathetic nerves using injection of cre-dependent hM3D(Gq)-mCherry or mCherry viral constructs into the pancreatic duct of ChAT-IRES-cre mice fed LFD.

RESULTS: 1 week HFD significantly impairs glucose tolerance and insulin sensitivity and significantly reduces plasma insulin and glucagon. HFD significantly remodels pancreatic sympathetic innervation with increased sympathetic fiber density to alpha cells. Activation of pancreatic sympathetic fibers, mimicking the increased sympathetic drive seen in 1wk HFD, impairs glucose tolerance while targeted activation of pancreatic parasympathetic nerves to oppose increased sympathetic activity restores insulin secretion and glucose tolerance.

CONCLUSIONS: HFD causes rapid remodeling of islet innervation with increased sympathetic nerves. Targeted activation of pancreatic sympathetic nerves mimics the effects of obesity and T2D. Targeted activation of pancreatic parasympathetic nerves improves glycemic control, suggesting the potential reversibility of the rapid changes HFD mediates. Future studies will assess pancreatic nerve structure and function with long-term HFD-induced obesity and diabetes. We will also determine whether pancreatic parasympathetic innervation is required to maintain euglycemia.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Neuroscience

Title: Revealing the effect of subcallosal ACC deep brain stimulation on brain-wide networks in non-human primates

Authors: Satoka H. Fujimoto, Atsushi Fujimoto, Catherine Elorette, Davide Folloni, Lazar Fleysher, Ki Sueng Choi, Brian E. Russ, Helen S. Mayberg, Peter H. Rudebeck

Background: Deep brain stimulation targeting subcallosal anterior cingulate cortex and adjacent white matter (SCC-DBS) is a promising therapy for treatment resistant depression (TRD). However, the neural mechanisms through which SCC-DBS facilitates recovery from depression are not fully characterized, making it difficult to optimize treatment for all patients. Notably, it remains unclear how DBS alters brain-wide circuits in healthy brains, an essential first step in determining the mechanisms that are engaged by DBS. Thus, the aim of this study was to establish how SCC-DBS works in healthy brains, focusing on determining the brain-wide network-level functional and anatomical effects of white matter stimulation.

Methods: Modeling the approach used to successfully treat TRD patients, we implanted SCC-DBS electrodes in two rhesus macaques. Specifically, we identified the confluence of the cingulum bundle (CB), forceps minor (FM), and uncinate fasciculus (UF) using diffusion tractography imaging (DTI). We then implanted a DBS lead unilaterally in this location, the other hemisphere serving as a control. One month after electrode implantation, stimulation (5mA, 130Hz, 90μsec) began and was maintained for 6 weeks. Whole brain resting-state functional MRIs (rs-fMRIs) and DTI were acquired before electrode implantation and following 6 weeks of scACC-DBS stimulation to reveal the functional and anatomical effects of SCC-DBS. Functional data were analyzed using a seed-based comparative-connectome approach where scACC-DBS stimulation induced changes in functional connectivity (FC) were determined. Fractioal anisotrophy (FA) was calculated from DTI data to investigate the anatomical white matter changes.

Results: After 6 weeks of SCC-DBS stimulation, FC between SCC (Area 25) and the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), the main components of the default mode network, were decreased. FA was increased in CB in the stimulated hemisphere which connects the SCC and PCC. Further, we confirmed that DBS-induced FC and FA changes were consistent across animals.

Conclusions: Chronic SCC-DBS changes brain-wide functional and structural networks connected to the SCC. Specifically, functional changes were predominantly in DMN and white matter changes were prominent in the stimulated CB. Thus, our data reveals the specific effects of scACC-DBS on brain-wide functional and anatomical connectivity, information essential for establishing the neural mechanisms of DBS for TRD, as well as the biological bases of pathologically depressed mood.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Brittany Hemmer
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Microglia activation is regulated by blood-borne factors in the context of aging and Alzheimer's pathology

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The brain exhibits diminishing function with age, rendering the brain susceptible to neurological disorders, such as Alzheimer's disease (AD), for which aging is the strongest risk factor. Given the urgent and universally unmet need to lessen the impact of AD, novel approaches are needed to curtail the influence of risk factors for the disorder. Emerging evidence has revealed rejuvenation of the aged CNS by exposure to young blood factors, raising the possibility that CNS function can be improved by targeting pathways in the systemic environment. Studies have yet to evaluate how microglia may sense and respond to youth-associated plasma factors to mediate plasma-induced changes in aging and AD. Using heterochronic parabiosis, we find that aged mice sharing blood with young mice exhibit reduced hippocampal microglial activation. In the context of AD pathology, 7-month-old APP-knockinNL-G-F mice systemically treated with young plasma exhibited reduced plaque pathology in the hilus, a phenotype potentially driven by microglia. To determine if individual factors present in young plasma regulate microglial state in the context of aging, aged mice were systemically treated with two youth-associated blood-borne factors, TIMP2 or CSF2, resulting in a decrease in microglial activation in hippocampus compared to vehicle-treated aged mice. Upon exposure to environmental challenges present in aging and AD, a subset of microglia acquire a disease-associated microglia (DAM) phenotype thought to be protective in response to debris. In addition to its role as a secreted protein acting on cells, we find that TIMP2 is expressed by microglia, is a marker of the DAM transcriptional profile, and co-localizes with lysosomal marker CD68, suggesting that it may play a cell-intrinsic role regulating microglial state. Mice lacking TIMP2 display hippocampal microgliosis, and RNA-seq analysis revealed biological processes associated with increased microglial activation were observed in TIMP2 knockout primary microglia relative to WT. We have developed a microglial TIMP2 conditional knockout model to further dissect the role of TIMP2 in regulating microglial function. Our results argue that microglia are responsive to youth-associated plasma proteins, and these proteins may regulate aging and AD phenotypes. Characterization of blood-CNS communication may facilitate development of therapies that target detrimental aging processes to limit onset of neurodegenerative diseases.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Molly Heyer
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Lab	Paul Kenny
Department	Neuroscience

Cerebellar microRNA-206 regulates Purkinje cell excitability and sensorimotor gating

Mary (Molly) P. Heyer, Masago Ishikawa, J. Erol Evangelista, Avi Ma'ayan, Guoping Feng, and Paul J. Kenny

BACKGROUND: The cerebellum is historically known for its roles in motor learning and coordination, but emerging evidence implicates this highly conserved region in more complex behaviors related to cognition, affect, and reward. Furthermore, cerebellar dysfunction is increasingly linked to the pathogenesis of schizophrenia, autism, and other neurodevelopmental disorders. The cerebellum shares extensive reciprocal connectivity with the neocortex, basal ganglia, and hindbrain nuclei, and is thought to convey sensory experiences that shape cortical development and function. Nevertheless, the genes, cells, and circuits that govern cerebellar interactions with higher-order brain circuits are poorly understood. A schizophrenia-associated microRNA, miR-206, has been found to be highly expressed in Purkinje cells of the cerebellum, suggesting a role in regulating cerebellar gene networks and circuitry.

METHODS: RNAscope in situ hybridization was performed to detect the cell type-specific expression pattern of miR-206. Mice with a constitutive or conditional targeted deletion of miR-206 were generated and tested in a large behavioral battery. miR-206 expression was rescued by intravenous delivery of an AAV vector specifically targeting Purkinje cells. Purkinje cell activity was studied via whole-cell patch clamp and extracellular electrophysiological recordings. Putative target pathways were uncovered using high-throughput sequencing of RNA isolated by crosslinking immunoprecipation (HITS-CLIP) and translating ribosome affinity purification (TRAP) after miR-206 deletion in Purkinje cells.

RESULTS: Using brain-wide in situ hybridization, we find that miR-206 is uniquely expressed in cerebellar Purkinje cells. miR-206 knockout mice exhibit impaired pre-pulse inhibition—an endophenotype of schizophrenia, stress-induced hypolocomotion, reduced extinction of fear memories, and sex-dependent cognitive deficits. Pre-pulse inhibition impairments were recapitulated by conditional deletion of miR-206 in Purkinje cells, and viral rescue of miR-206 expression in Purkinje cells reversed these deficits, suggesting that altered cerebellar output in the adult underlies these behavioral abnormalities. Consistent with this possibility, spontaneous firing frequency was increased and pacemaking channel current was decreased in Purkinje cells after miR-206 deletion. HITS-CLIP and TRAP after loss of miR-206 in Purkinje cells revealed possible target mRNAs in pathways related to neuronal excitability, glutamate signaling, and schizophrenia and bipolar disorder.

CONCLUSIONS: Together, these findings suggest that miR-206 regulates cerebellar Purkinje cell function and downstream sensorimotor, cognitive, and affective behaviors relevant to schizophrenia and other neurodevelopmental disorders.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Jan Hoffmann
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Department	CVRI

Title: Enhanced slow wave sleep after myocardial infarction limits cardiac inflammation and preserves heart function

Authors: Pacific Huynh*, Jan Hoffmann*, Walter Jacob, Abi Yates, Teresa Gerhardt, Sukanya Goswani, Seonghun Yoon, Cameron McAlpine. *: authors contributed equally

Background:
We should spend a third of our life asleep, yet 35-50% of adults do not get sufficient sleep. Sleep is known to protect against cardiovascular disease, but the mechanisms connecting sleep and the brain with cardiovascular health remain poorly defined. Here, we report a bidirectional relationship between sleep and cardiac injury in a murine model of myocardial infarction (MI).

Methods:
To assess sleep architecture after MI, female C57Bl/6 mice of ~10-14 weeks of age were implanted with devices to record EEG and EMG signal telemetrically. Briefly, EMG electrodes were inserted into the cervical trapezius muscle. Placement of EEG electrodes was achieved using a microdrill to perforate the skull, with leads placed to make contact with the dura. After one week of recovery, MI was induced through permanent ligation of the left anterior descending coronary artery, with sham operated mice serving as controls. Mice were then followed for up to 21 days.

To examine the effect of sleep fragmentation (SF) after myocardial infarction, a subset of mice were placed in SF cages immediately after MI surgery. In SF cages, a sweep bar runs along the cage bottom every 2 min during the light cycle (ZT 0-12) and is stationary during the dark cycle (ZT 12-24). Control animals are placed in cages with a stationary sweep bar. Micro-ultrasound was performed at key timepoints to assess cardiac function. Mice were sacrificed at days 3, 7 and 21 post-MI and immunophenotyping of the heart, blood, bone marrow and brain was performed via flow cytometry. Biochemical analysis was also performed to assess markers of inflammation, cardiac injury and stress via qRT-PCR and immunoassays.

Results:
We find that MI leads to neuroinflammation and recruitment of TNFα-producing monocytes to the brain. MI also augments slow wave sleep abundance and drive. Blocking immune cell migration or Tnfα production dampens slow wave sleep drive and abundance post-MI. To test the importance of sleep post-MI, we subjected animals to sleep fragmentation. Relative to mice allowed to sleep habitually, SF reduced survival post-MI and raised hematopoiesis and immune cell generation in the bone marrow leading to increased Ly6Chi monocytes in the blood and the infarcted myocardium. SF impaired cardiac function including decreased ejection fraction and stroke volume.

Conclusions:
Our findings suggest that MI elevates slow wave sleep abundance which protects the heart from overt inflammation to maintain cardiac function.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Leanne Holt
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Elucidation of the Astrocyte-Specific Transcriptome Following Exposure to Cocaine.

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BACKGROUND: Drug addiction represents an enormous healthcare burden. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly implicates astrocytes in disorders of the nervous system, including addiction. Indeed, candidate genes in astrocytes have been identified and, furthermore, manipulation of astrocyte function has been demonstrated to influence rodent behavioral responses to cocaine administration. However, the astrocyte-specific transcriptome following exposure to drugs of abuse has not yet been investigated.

METHODS: We utilized whole cell sorting of astrocytes and RNA-sequencing to investigate the astrocyte-specific transcriptome in several key brain regions involved in reward-processing, including the nucleus accumbens (NAc) and prefrontal cortex (PFC), following cocaine self-administration, withdrawal, and "relapse". Cut & Run Sequencing in isolated astrocytes reveals astrocytic CREB target genes. A multi-omic approach reveals direct and indirect downstream consequences of transcription factor CREB's regulation in astrocytes. Additionally, viral manipulation of CREB activity in NAc astrocytes was performed in combination with cocaine conditioned place preference (CPP) and self-administration (SA) to determine the role of astrocytic CREB in addiction-related behaviors.

RESULTS: We determined that astrocytes exhibit a robust transcriptional response, including regionally and contextually-specific transcriptional signatures. Subsequent analysis revealed CREB as a predicted upstream regulator of this abnormal transcription. Furthermore, overexpression of CREB in NAc astrocytes resulted in reduced neuronal activity, increased CPP for cocaine, and increased drug-seeking in SA. RNA-Seq reveals potential molecular mechanisms underlying astrocytic CREB's regulation of neuronal activity and addiction-related behaviors.

CONCLUSIONS: The astrocyte transcriptome robustly responds to cocaine administration, with both regional and contextual specific signatures, and viral manipulation of astrocytic CREB alters behavioral responses to cocaine. Current studies are directed at the role of astrocytic CREB's contribution to the pathophysiology of addiction.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Ahmad Huda
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Department	Friedman Brain Institute

Background: Impulsivity is defined as the inability to control behavioral impulses and thoughts, leading to urge-based action. Clinical evidence shows heroin-dependent individuals as exhibiting greater impulsivity and reward seeking traits. Therefore, impulsivity has a strong relationship with substance use disorder (SUD) vulnerability. A study by Miller et al. 2018, found that, the transcription factor Crem plays a critical role in the mediation of impulsive action in the nucleus accumbens core (NAcC). Furthermore, we observed that overexpression (OE) of Icer, an isoform of Crem, reduced impulsivity and heroin taking behavior compared to controls. However, the underlying neurobiological mechanisms of Icer are unknown. Our research question is: does Icer mediate the neuroplasticity of neurons?

Methods: We have two approaches to address this question. In the first approach, we investigate how Icer OE may induce physical changes in the neuron. To this end, we use primary striatal neuron cultures, viral transduction, immunocytochemistry, confocal microscope imaging, and NeuronStudio softwares to analyze potential changes in dendritic spine density. In the second approach, we study the genes and neurobiological pathways that are regulated due to Icer OE. We conducted bulk RNA Sequencing of the NAcC of Icer OE male rats to determine differentially expressed genes (DEGs). Relevant ontologies were identified through Enrichr analysis. After identifying DEGs of interest, we will conduct qPCRs to validate the DEGs.

Results: We have imaged a subgroup of the animals and captured confocal microscope images to show dendritic spines. We will continue to collect images of the remaining sample to carry out the analysis using NeuronStudio. From the Enrichr analysis of the DEGs, many neuronal systems and Gabaergic pathways emerged. Within these pathways, a few genes are related to neuron development and plasticity: PRKCG, CDH13, GABBR2, RAB3A, SYN2, SYN1, PPFIA3, GNAO1, and PRKG1. Specifically, the SYN1 gene correlated positively with impulsive action behavior.

Conclusion: By continuing this line of research, we hope to better understand the neurobiological systems contributing to attenuation in impulsive and drug taking behavior induced by Icer OE in regard to neuroplasticity. This information can help to identify potential drug targets to combat the opioid epidemic.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Age associated changes to modulation of neuronal gain by microglia

Philip Hwang, Hayley Strasburger, Ana Badimon, Andrew Chan, Brittany Hemmer, Malli Ganesana, Sophia Lamsifer, Iván Soler, Jill Venton, Erin Calipari, Joseph Castellano, Viviana Gradinaru, Tristan Shuman, Anne Schaefer

Aging in mice and humans is associated with alterations to neuronal circuit excitability and function, increased seizure susceptibility, and neurodegeneration. Our recent studies have identified microglia as novel regulators of neuronal activity and function, maintaining homeostatic levels of neuronal activation by responding to ATP released during neuronal activation and metabolizing the signal into localized adenosine, thereby serving as brake pads for hyperexcitation. Moreover, our recent data suggests that in addition to seizure prevention, microglia may modulate the overall gain of neuronal activity, which becomes important during behaviors such as learning and memory as well as sleep. We further found that age-associated increases to pro-inflammatory gene expression in microglia is related to changes in key genes of this homeostatic mechanism, suggesting that this neuroprotective function may be altered in aging. When coupled with the documented effects of aging on memory and sleep, I hypothesize that microglia play a critical role in aberrant neuronal responses and network dysfunction in the aging brain. Using microglia specific knockout of the rate-limiting enzyme for adenosine generation (Entpd1/CD39), I investigate the microglial role on adenosine generation and its effects on neuronal network function using in vivo calcium imaging and EEG/EMG recordings. These results will inform further investigations into how age may be affecting this modulatory function of microglia. This information is critical to our understanding of the cellular mechanisms by which microglia regulate neuronal function, leading to the development of novel approaches for the treatment of age-associated disorders.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Neuroscience Department

Title: Heterogeneity of reward responses in human Substantia Nigra neurons

Authors: Zarghona Imtiaz, Brian H. Kopell, Salman Qasim, Arianna Neal Davis, Lizbeth Nunez Martinez, Matt Heflin, Kaustubh Kulkarni, Ignacio Saez

Background: Adaptive reward-guided behavior relies on learning the appropriate values for choices involving uncertain outcomes. Reward prediction errors (RPEs) are efficient learning signals that represent the difference between expected and obtained rewards in reward driven learning. Studies in human and nonhuman primates have shown that the spiking of dopamine neurons in the ventral tegmental area and the substantia nigra (SN) reflects responses to unexpected rewards and RPEs. However, in rodents there exists a much more complex and heterogeneous constellation of responses in dopaminergic neurons, which can reflect not just unexpected rewards but also unexpected losses or salient events regarding of valence. Whether this functional heterogeneity exists in the human dopaminergic system is unknown, partially due to the difficulty of recording from individual neurons in the human brain. Here, we leveraged invasive Deep Brain Stimulation (DBS) interventions for the treatment of Parkinson's disease to intraoperatively record spiking activity from individual neurons in the SN. We sought to test the hypothesis that there is functional heterogeneity in the responses of individual human dopaminergic neurons and that distinct sub-populations of dopaminergic neurons encode unexpected rewards and losses.

Methods: Parkinson's disease patients played a two-armed bandit slot machine task while undergoing DBS surgery in which they sought to maximize reward by choosing among different uncertain options that could result in wins, losses, or no reward outcomes. We carried out multi-unit recordings from the SN, identified putative dopaminergic neurons and studies their time-locked responses to different types of trial outcomes.

Results: We carried out recordings in n=11 patients (mean age = 66.42), yielding n=17 putative dopaminergic neurons. Neurons showed significant variation in responses to reward outcomes, with some cells preferentially responding to rewards and others to losses. At the group level, there were no significant differences in spiking following wins/losses, but we observed increased spiking of loss-responsive neurons as losses accumulate in contiguous trials.

Conclusion: These results provide evidence for the existence of heterogeneous reward responses in human putative dopaminergic neurons, which also showed an accumulating sensitivity to repeated negative outcomes. These data provide new insight into the role of human dopaminergic neurons in reward learning and suggest that reward responses in the human dopaminergic system is not limited to RPE encoding.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Title:Neuro-Environmental interactions: a time sensitive matter.

Author Names: Azzurra Invernizzi, Elza Rechtman, Stefano Renzetti, Claudia Ambrosi, Lorella Mascaro, Roberto Gasparotti, Cheuk Y. Tang, Donald R. Smith, Roberto G. Lucchini, Robert O. Wright, Donatella Placidi, Megan K. Horton and Paul Curtin

Introduction: Resting state (rs) neurophysiological dynamics are typically assessed through the control of sensory and perceptual environments during testing conditions. Here, we investigated the effects of temporally-distal environmental inputs, specifically metal exposures experienced up to several months prior to testing, on rs functional dynamics.

Methods: In 124 participants (53% females, ages: 13-25 years) enrolled in the Public Health Impact of Metals Exposure (PHIME) study, we measured concentrations of 7 metals in biological matrices and acquired resting-state functional magnetic resonance imaging scans. Using graph theory metrics, we computed global efficiency (GE) in 111 brain areas (Harvard Oxford Atlas). A predictive model based on ensemble gradient boosting was used to predict GE from exposure biomarkers. Models were adjusted for age and sex, and model performance was evaluated by comparing predicted versus measured rs functional dynamics. Finally, SHAP scores were used to evaluate feature importance. Complete overview of the framework used is presented in Figure 1.

Results: Observed rs dynamics were significantly correlated with rs dynamics predicted from our model utilizing chemical exposures as inputs ($P < 0.001$, $R = 0.36$, VE=13%; Figure 1, panel C). Feature importance metrics indicated that biomarkers of lead, chromium, and copper contributed most to prediction of GE metrics.

Conclusions: Our results indicate that a significant component of resting state dynamics, comprising approximately 13% of observed variability in GE, is driven by past and persistent metal exposures. These finding emphasize the need to estimate and control the influence of past and current chemical exposures in the assessment and analysis of rs functional connectivity.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Psychiatry Department

Older Brain Age Prediction Linked to Early Age Onset among Depression and Epilepsy Patients

Yael Jacob, Gaurav Verma, Laurel Morris, Lara Marcuse, Madeline Fields, James Murrough, Priti Balchandani

BACKGROUND: Normal aging is known to alter the brain in multiple ways detectable through neuroimaging. Accelerated biological aging has been hypothesized as a mechanism underlying clinical and cognitive deterioration of several pathologies such as epilepsy and depression. Therefore, identifying brain aging patterns in patients with brain pathologies to determine whether and how they differ from healthy normal aging is of great need. Previous studies have shown that brain network topological organization, specifically its efficiency (the ability of the system for parallel information flow and integrated processing among distributed regions), is associated with age, implying older brains exhibit reduced efficiency. Using resting-state functional magnetic resonance imaging (rsfMRI), we investigate if estimated brain age according to functional brain network efficiency is deviant from chronological age in major depressive disorder (MDD) and Epilepsy patients (EP).
METHODS: RsfMRI were acquired from 36 healthy controls (HC), 29 MDD, and 27 EP patients using 7-Tesla MRI. The averaged time-course of 82 segmented regions were extracted and pairwise correlation matrix was calculated. We then calculated the global efficiency (Eglob), which is the average inverse shortest path length in the network. A linear regression model was then applied using the HC Eglob to predict age controlling for gender. The same model was subsequently used to predict MDD and EP ages. Brain-predicted age differences (brain-PAD) were defined as the predicted age minus the chronological age. Linear regression analysis was conducted to assess the association between brain-PAD and a clinical measure of age at onset among patients, controlling for gender.
RESULTS: As expected, Eglob significantly predicted chronological age among HC ($r=-0.62$, $p=5.38E-05$). Applying this model to the EP dataset resulted in a significant correlation between predicted and true age ($r=-0.64$, $p=0.00035$). However, applying the model to the MDD dataset, resulted in reduced accuracy with no correlation between predicted and true age ($r=0.067$, n.s). Brain-PAD among both EP and MDD was significantly associated with the subjects' disorder age at onset ($r=-0.75$, $p=1.5E-05$ and $r=-0.62$, $p=0.00026$, respectively), indicating that prediction of an older brain is associated with early age disorder onset.
CONCLUSIONS: Our results demonstrate that lower whole-brain global network efficiency during rsfMRI was significantly associated with older chronological age, replicating previous studies. Importantly, we found that patients with early age onset exhibit reduced brain network efficiency and are thus predicted as older brains. These results suggest that brain functional changes in early-onset patients mimic or exacerbate brain aging.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Mohammad Jodeiri
Job Title	Postdoctoral Fellow
Lab	Ables
Department	Psychiatry

Astrocytic Lipid Metabolism in Reward Circuit, Therapeutic Target for Diabetes-Induced Mood Disorders Mohammad Jodeiri Farshbaf1, Jessica L. Ables1,2.
1-Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY
2-Nash Family Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY
Background: Diabetes is a complex metabolic disorder which correlates with genetic and environmental factor. Comorbid depression governs diabetic patients and leads to mental disorders in a long-term. Brain's reward circuitry has fundamental role in controlling the mood disorders. The medial habenula (MHb) is a part of reward circuit and major source of the cholinergic neurons in the brain. Through projecting to interpeduncular nucleus (IPN), MHb influences serotonin, dopamine in midbrain. Abnormalities in reward circuit lead to mood disorders such as depression. Studies showed that diabetes and hyperglycemia influence cholinergic neurons in central nervous system. Acetylcholine, the main neurotransmitter of the cholinergic neurons, is synthesized from acetyl-CoA and choline. Therefore, cholinergic neurons might be susceptible population of neurons to metabolic changes. Astrocytes are the first line of the cells in brain to respond to metabolic changes. Astrocytes store lipid droplets (LDs) and use them, through β-oxidation, during metabolic stress. Interestingly, we find that LD changed in MHb and IPN in response to diabetic hyperglycemia in differently. Also, our findings show hyperglycemia influenced lipid accumulation in astrocytes in MHb.
Methods: Male and female C57BL/6J mice were injected intraperitoneally of streptozotocin in HBSS. After preparing 40-µm-thick coronal tissue sections, primary antibodies against GFAP and BODIPY493/503 were used for immunohistochemistry. Results: Our results show STZ induces diabetes in male mice while female mice are resistant to it. Studying the MHb and IPN in STZ-induced diabetes show significant increases in astrocyte numbers in IPN at 6 weeks. We find LDs decrease significantly in MHb at 12 weeks after hyperglycemia. Interestingly, IPN shows different pattern about LDs, at 12 weeks after hyperglycemia LDs increases in IPN. Moreover, we find astrocytic LDs are decrease in MHb after 12 weeks but in IPN it shows increasing pattern. Conclusion: Our finding suggests that reward circuitry shows different responds to hyperglycemic conditions. Neutral LDs and astrocytic lipids are changed in MHb and IPN differentially and it may represent in behavioral level. Further studies about metabolic change in astrocytes and lipid oxidation in MHb and IPN will open new therapeutic avenues to discover the impact of diabetes on reward circuitry.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Tanvi Joshi
Job Title	Graduate Student
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Department	Oncological Sciences and Neurosurgery

The Role of Aquaporin 4 in Glioblastoma-associated Vasogenic Cerebral Edema

Tanvi Joshi(1,2), Dolores Hambardzumyan(2)

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Background: Over 200,000 individuals are diagnosed with primary and metastatic brain tumors in the USA annually. Vasogenic cerebral edema is a severe complication that occurs in a majority of these cases, leading to a significant increase in intracranial pressure, accompanying neurological deficits, and increased mortality rates. It is postulated that vasogenic cerebral edema forms due to fluid accumulation in the brain resulting from a compromised blood-brain barrier (BBB). Despite its frequency and severity, very little is known about edema resolution. Edema in glioblastoma (GBM) patients is almost exclusively managed by dexamethasone (DEX), which has recently been found to have several drawbacks, including immunosuppression and interference with radiation therapy. Thus, there is an urgent need to better understand mechanisms of edema formation and resolution in GBM in order to identify alternative treatment strategies. The water channel aquaporin 4 (AQP4) is a critical player in the brain's water homeostasis, with increased levels in GBM compared to the normal brain. This study focused on gaining more insight into the role of AQP4 in GBM-associated edema.

Methods: We used the RCAS/tv-a system, a somatic cell type-specific gene transfer system, to generate de novo GBM with different driver mutations in Aqp4 knockout (KO), heterozygous (HET), and wild-type (WT) mice. We then assessed survival in these mice in addition to performing a wet/dry assay for edema content. To study AQP4 distribution and astrocyte coverage, we employed multiplex IF staining combined with RNAScope of tumors. We also studied the effects of anti-VEGFA treatment on tumor-bearing Aqp4 WT and KO mice by investigating survival, edema content and vessel leakage.

Results: Tumor-bearing mice in an Aqp4-deficient background showed increased edema content, decreased survival and altered astrocyte morphology compared to WT mice across tumors with different driver mutations. The source of AQP4 in GBM was confirmed to be astrocytes and not tumor cells. Moreover, anti-VEGF treatment only improved survival and decreased vessel leakage in WT tumor-bearing mice.

Conclusions: Our results suggest that AQP4 is important for edema resolution and vascular normalization of tumors and its loss reverses reactive astrogliosis, which is a well documented reaction of astrocytes to pathological conditions. Ongoing studies are focused on characterizing how Aqp4 loss in astrocytes affects their ability to resolve edema and get activated using single-cell RNA sequencing.

2023 Neuroscience Retreat

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Full Name	Mert Karabacak
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Developing a Rapidly-Deployable, Personalized Scoring Model for Accurate Mortality Risk Prediction in Moderate and Severe Traumatic Brain Injury Patients

Mert Karabacak, Kristen Dams-O'Connor, Zachary Hickman, Konstantinos Margetis

Objectives: This study aimed to develop a simple, rapidly-deployable model for high-accuracy mortality risk prediction after moderate and severe traumatic brain injury (TBI) and compare its performance with two established models.

Methods: We used data from the Trauma Qualıty Program (TQP) to develop a simple summary score ranging from 0-100 based on age, the admission Glasgow Coma Scale (GCS) component subscores, and pupillary reactivity data. We then compared the predictive accuracy of this concise score to that of the Corticosteroid Randomisation After Significant Head Injury Trial (CRASH)-Basic and International Mission for Prognosis and Analysis of Clinical Trial in TBI (IMPACT)-Core models. The primary outcome was in-hospital mortality. Secondary outcomes were 3-day, 7-day, 14-day, and 30-day mortalities.

Results: The cohort for the primary outcome included 318,280 patients with TBI. Our model [the area under the curve (AUC) = 0.827, 95% confidence interval (CI) 0.816 – 0.838] had better discrimination (DeLong test p values < 0.001) than the CRASH-Basic (AUC = 0.803, 95% CI 0.792 – 0.814) and IMPACT-Core (AUC = 0.789, 95% CI 0.777 – 0.800) models, and calibration (our model = 0.018, CRASH-Basic = 0.020, IMPACT-Core = 0.020) in predicting in-hospital mortality for TBI patients. Our model similarly outperformed the CRASH-Basic and IMPACT-Core models for our secondary outcomes.

Conclusions: This novel post-TBI mortality prognostic tool described herein can be calculated rapidly at the bedside using readily available data and was found to be more accurate than two existing, widely used models for predicting mortality in patients with TBI.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Elizabeth Katanov
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Department	Neuroscience

Influence of inhibitory neuron spike timing on seizure generation in the hippocampus.

Elizabeth Katanov, Zoe Christenson Wick, Paul A Philipsberg, Sophia I Lamsifer, Cassidy Kohler, Tristan Shuman

BACKGROUND: Network-wide oscillations, such as theta, orchestrate and organize the spiking of individual neurons in a phenomenon known as phase locking. Phase locking has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. We've recently found altered theta phase locking of inhibitory neurons in the dentate gyrus of epileptic mice with spontaneous seizures and cognitive deficits. While phase locking has been widely studied in a variety of contexts using correlational methods, the direct, causal influence of this phenomenon has never been determined. Thus, we aimed to directly test the hypothesis that inhibitory theta phase locking can bidirectionally control seizure susceptibility in control and epileptic mice.

METHODS: To test these hypotheses, we developed a low-latency closed-loop optogenetic system to bidirectionally control inhibitory phase locking to theta in head-fixed control and pilocarpine-treated epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of parvalbumin (PV)+ and somatostatin (SOM)+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring latency to seize after delivering a proconvulsant.

RESULTS: Using our closed-loop optogenetic system in awake behaving mice, we have succeeded in precisely altering the phase locking of hippocampal interneurons and we have preliminary evidence that there is a cell-type specific deficit in phase locking of PV+ dentate interneurons in chronic temporal lobe epilepsy. We have also found preliminary evidence suggesting that, in epileptic mice, re-aligning inhibitory spiking of PV+ cells to the preferred phase of theta diminishes seizure activity compared to stimulating at a non-preferred phase of theta. Further, we show that mis-aligning inhibitory spiking of PV+ cells to the non-preferred phase increases seizure susceptibility in control mice.

CONCLUSIONS: Theta phase locking of inhibitory spiking seems to play an important and causal role in one of the most concerning elements of epilepsy: hyperexcitability. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal the potential of oscillation-driven stimulation as an effective epilepsy therapeutic.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Benjamin Keller
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Stress-related Fear Behaviors and Cardiorespiratory Functions
Keller, B., Duesman, S., Shetty, S., Das, A., Patel, S., Sparman, N., Rajbhandari, P., Rajbhandari, A.K.

Background: Post Traumatic Stress Disorder (PTSD) has a profound and long-lasting adverse impact on health and behavior in the brain and the body. Preclinical research suggests that broad stimulation of the vagus nerve, a major parasympathetic pathway, is effective for treatment of PTSD symptoms in humans. Currently, vagus nerve stimulation involves the activation of a heterogeneous population of cell types, but our knowledge of specific cell populations that drive its effects are lacking. Research suggests that Pituitary adenylate cyclase-activating polypeptide (PACAP) and its receptor PAC1 are integrally involved in stress mechanisms, thus we investigated the role of PACAPergic pathway stemming from the vagal nodose ganglion (NDG). To achieve this, we selectively stimulated PACAPergic neurons originating in the NDG as well and selectively deleted neuronal PAC1 in the dorsomedial nucleus of the solitary tract (dmNTS) and studied the effect on freezing and anxiety-like behavior in mice.

Methods: In Adcyap1-2A-Cre mice we micro-infused AAV8-hSyn-DIO-rM3D(Gs)-mCherry into the NDG to allow for downstream chemogenetic excitation of PACAP-expressing neurons in the NDG. In PAC1fl/fl mice we micro-infused AAV2-hSyn-GFP-cre into the dmNTS to allow for Cre-recombinase-dependent deletion of PAC1 in neurons of the dmNTS. We had these groups of mice go through stress-enhanced fear learning (SEFL) model of PTSD-like fear, open field light gradient task, and elevated plus maze (EPM) to capture anxiety-like phenotypes and a series of PTSD-like fear related behavioral tasks. Additionally, we performed non-invasive pulse oximetry to acquire data on heart rate variability.

Results: PACAPergic stimulation of the nodose ganglion resulted in a trend of reduced fear expression during SEFL as well as enhanced fear extinction. It also resulted in a decrease in anxiety-like behavior in mice in the EPM and a rescue of heart rate variability (HRV). Deletion of PAC1 in the dmNTS showed a trend of reduced anxiety-like behavior in the open field light gradient task. Deletion of PAC1 did not have any effect on fear expression during SEFL or HRV.

Conclusion: These results indicate that selective stimulation of PACAPergic neurons originating from the NDG can coordinate peripheral cardiorespiratory signals as well as central mechanisms of stressors. Our results suggest that deletion of PACAPs cognate receptor PAC1 in the dmNTS shows a slight anxiolytic effect. These results demonstrate the potential of genetically defined vagal neurons in regulating stress in conjunction with cardiorespiratory aspects. Additionally, this research sheds light on the need to understand brain and body interactions for the development of novel therapeutic avenues.

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Full Name	Tarek Khashan
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The effect of MeCP2 mutations on microglia phenotype and function in Rett Syndrome

Tarek Khashan*1, Mara Graziani *1, Daniele Mattei2, Roy Missall1, Alice Buonfiglioli1, Lot De Witte1
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Rett syndrome (RTT) is a neurodevelopmental disorder caused in most cases by a mutation in the X-linked MECP2 gene. MeCP2 is a transcriptional regulator ubiquitously expressed in all cell types in the brain. Most of the studies on Rett syndrome focused on revealing the effect of MeCP2 mutation on neuronal phenotype and function. Although neuronal dysfunction is central in RTT, synaptic pruning and neurogenesis are regulated by other brain cells, such as microglia, and the dysfunction of these cells could contribute to other aspects of the RTT phenotype. Studies on mice have shown that MeCP2 deficiency affects microglia phenotype and function. In addition, restoration of MeCP2 in MeCP2-null mice led to improvement of RTT symptoms. Based on these animal studies, a contribution by microglia to the pathogenesis of RTT has been hypothesized. However, these results have been subject of controversy. Moreover, due to the limited research on human microglia models, the microglial role in RTT remains unclear.

Here, we generated microglia from iPSC lines of Rett patients, and healthy female controls to investigate the effect of MeCP2 mutation on microglia phenotype and function in humans. Flow cytometry and immunocytochemistry were performed to evaluate protein expression of MeCP2 and a panel of microglial markers. The effect of a loss of function of MeCP2 on phagocytosis of myelin and synaptosome was analyzed. Additionally, the response to inflammatory triggers, such as Lipopolysaccharide (LPS), IL-4, IL-6 and dexamethasone was also measured via ELISA immunoassay. The characterization of the transcriptome of RTT versus healthy microglia is in progress.

We observed differences in the expression of microglial markers as well as the phagocytic capacity between microglia expressing the wild-type or mutant MeCP2 gene.

These preliminary data show that a mutation in MeCP2 gene may have a role in altering microglia functioning in Rett syndrome.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Michelle Kim
Job Title	PhD Student
Lab	Harony-Nicolas
Department	Neuroscience

Title: The impact of juvenile social isolation on social behavior and VTA-DA neuron activity
Authors: Michelle Kim, Marie Barbier, Hala Harony-Nicolas

Background: In humans, isolation during childhood and adolescence is known to increase vulnerability to depression, anxiety, and substance use. These conditions are connected to maladaptive social behaviors, such as aggression, social anxiety, and social withdrawal. Studies in rodents have also shown that isolation precipitates changes in social behavior later in life. However, there is a gap in understanding how isolation during adolescence impacts social behavior as well as neural circuitry mediating social reward. To close this gap, I use in vivo fiber photometry recording to examine how juvenile social isolation (jSI) impacts neural activity of dopaminergic (DA) neurons of the ventral tegmental area (VTA) and comparing VTA-DA neuron activity between group-housed (GH) and jSI rats during social behavior.

Methods: At weaning age, male rats are assigned to either jSI or GH conditions for 3 weeks. Following this period, all rats are injected with TH-Cre in conjunction with a Cre-dependent GCaMP to express GCaMP in dopaminergic neurons in the VTA, then re-housed and re-socialized with a novel age and sex-matched rat until they reach adulthood (approximately P60). Once rats reach adulthood, I examine behavior following jSI through a battery of behavioral tasks to assess anxiety, social preference, and social reward processing. Additionally, I record VTA-DA GCaMP6 signal during social interaction.

Results: At the behavioral level, my preliminary data shows that jSI has no deleterious impact on anxiety-like behaviors, social investigation, or social preference. However, my fiber photometry recording data show that while VTA-DA neurons in GH rats display increased activity during social interaction, no increase in activity is detected in the VTA-DA neurons of jSI rats.

Conclusions: My findings suggest that while jSI does not impact social behavior in adulthood, it may impact VTA-DA activity during social investigation and possibly impact the experience and processing of social reward. We are currently following the same experimental design in female rats and examining whether there are sex differences in how jSI impacts behavior and/or VTA-DA neuron activity.

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Full Name	Máté Kiss
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Interleukin-3 coordinates glial–peripheral immune crosstalk to incite multiple sclerosis

Máté G. Kiss1,2,3†, John E. Mindur3†, Abi G. Yates1,2, Donghoon Lee2,4, John F. Fullard2,4, Atsushi Anzai3, Wolfram C. Poller1,3, Kathleen A. Christie5,6, Yoshiko Iwamoto3, Vladimir Roudko7, Christopher T. Chan3, Pacific Huynh1,2, Henrike Janssen1,3, Jeffrey Downey1,3, Achilles Ntranos8, Jan D. Hoffmann1,2, Walter Jacob1,2, Sukanya Goswami1,2, Sumnima Singh1,3, David Leppert9, Jens Kuhle9, Seunghee Kim-Schulze7, Matthias Nahrendorf3, Benjamin P. Kleinstiver5,6, Fay Probert10, Panos Roussos2,4,11,12, Filip K. Swirski1,3, Cameron S. McAlpine1,2,3,*

Background
Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS). While CNS-resident glial cells and infiltrating immune cells contribute to MS pathogenesis, the networks that govern peripheral-central immune crosstalk and coordinate functionality among these ontologically distinct populations remain unclear.

Methods
To explore the function of interleukin-3 (IL-3) during MS-like neuro-inflammation and -degeneration, we adopted the murine model of MS, experimental autoimmune encephalomyelitis (EAE), in which mice are injected with myelin oligodendrocyte glycoprotein suspended in complete Freund's adjuvant (MOG35-55/CFA) and pertussis toxin (PTX) causing spinal cord inflammation, impaired neuromuscular and sensory function, demyelination, and paralysis. In humans, we measured IL-3 in the cerebrospinal fluid (CSF) of 36 patients with clinically diagnosed relapsing remitting MS (RRMS) and 35 age-matched unaffected controls. For an in-depth regional analysis of cell dynamics in the CNS of MS patients, we performed single-nuclei RNA sequencing (snRNAseq) on dissected regions of human brain tissue.

Results
We show in mice and humans, that astrocyte- and CD44hiCD4+ T cell-sourced IL-3 programs microglia and infiltrating myeloid cells to exacerbate neuroinflammation by inciting a cellular recruitment program that drives the accrual of immune cells in the CNS thereby worsening MS and its preclinical model EAE. We find that CNS-resident astrocytes and peripherally-derived CD44hiCD4+ T cells generate IL-3 while resident microglia and infiltrating monocytes, macrophages, and dendritic cells respond to the cytokine by expressing IL-3Rα, IL-3's specific receptor. Astrocytic and T cell IL-3 elicit an immune migratory, recruitment, and chemotactic program by IL-3Rα+ myeloid cells that enhances immune cell infiltration into the CNS leading to exacerbated neuroinflammation, demyelination, and clinical disease. Multiregional snRNAseq of human CNS tissue from unaffected controls and MS patients reveals the appearance of a subset of IL3RA-expressing myeloid cells in MS plaques with unique recruitment, migratory, and chemotactic programing and function. In humans with MS, IL3RA expression by plaque myeloid cells and IL-3 levels in the CSF predict myeloid and T cell abundance and recruitment into the CNS.

Conclusion:
Our findings establish IL-3:IL-3RA signaling as a bidirectional glial-peripheral immune crosstalk network that promotes neuroinflammation, prompts immune cell recruitment to the CNS, and worsens MS.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Cassidy Kohler
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Lab	Tristan Shuman
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Optogenetic manipulation of theta phase locking and its effect on cognition in temporal lobe epilepsy.

Cassidy Kohler, Zoe Christenson Wick, Paul A Philipsberg, Sophia I Lamsifer, Elizabeth Katanov, Keziah Diego, Susie Yu Feng, Tristan Shuman

BACKGROUND: Network-wide oscillations, such as theta, orchestrate and organize the spiking of individual neurons in a phenomenon known as phase locking. Phase locking has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. We've recently found altered theta phase locking of inhibitory neurons in the dentate gyrus of epileptic mice with spontaneous seizures and cognitive deficits. While phase locking has been widely studied in a variety of contexts using correlational methods, the direct, causal influence of this phenomenon has never been determined. Thus, we aimed to directly test the hypothesis that inhibitory theta phase locking can bidirectionally control cognitive performance in control and epileptic mice.

METHODS: To test these hypotheses, we developed a low-latency closed-loop optogenetic system to bidirectionally control inhibitory phase locking to theta in head-fixed control and pilocarpine-treated epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of parvalbumin (PV)+ and somatostatin (SOM)+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring accuracy in navigating a virtual environment.

RESULTS: Using our closed-loop optogenetic system in awake behaving mice, we have succeeded in precisely altering the phase locking of hippocampal interneurons and we have preliminary evidence that precise theta phase locking of dentate gyrus inhibitory neurons may influence performance on a demanding dentate-dependent virtual navigation task, particularly that mis-aligning inhibitory spike timing produces navigation deficits in control mice.

CONCLUSIONS: Theta phase locking of inhibitory spiking likely plays an important and causal role in two of the most concerning elements of epilepsy: hyperexcitability and cognitive deficits. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal the potential of oscillation-driven stimulation as an effective epilepsy therapeutic.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Maria Koromina
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Department	Psychiatry

Title: Statistical and functional fine-mapping as a powerful tool to unravel the genetic etiology of bipolar disorder

Authors: Maria Koromina, Ashvin Ravi, Brian M. Schilder, Benjamin Muller, Jonathan Coleman, Towfique Raj, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Niamh Mullins

Background:
The Psychiatric Genomics Consortium has published the largest GWAS of bipolar disorder (BD) (41,917 cases and 371,549 controls) which identified 64 BD risk loci. GWAS studies have helped toward identifying a plethora of genetic loci associated with BD. However, each one of these loci encompasses many associated genetic variants and genes, and those causal for BD remain largely unknown.

Methods:
Here, we prioritized BD causal genes and genetic variants using statistical and functional fine-mapping, namely SuSiE, FINEMAP, Polyfun-SuSiE and Polyfun+FINEMAP. Each fine-mapping method will generate a posterior probability (PP) of causality for each SNP in the GWS locus, and a 95% credible set, which can be interpreted as the minimum subset of SNPs that have ≥95% probability of containing the causal SNP(s). Consensus SNPs will be defined as the SNPs that have a PP greater than 0.8 in at least two methods.

Results:
We identified 25 genetic variants with a >50% probability of being causal for BD (PIP > 0.50), based on convergence of evidence across fine-mapping methods. The size of credible sets was assessed across different fine-mapping methods, LD panels and fine-mapping 'windows'.
Of these variants, 3 were missense variants within the SCN2A, FKBP2 and TRPT1 genes, and 12 overlapped with promoters or enhancers of gene expression in specific brain cell-types. Using expression quantitative trait loci (eQTLs) from PsychENCODE (prefrontal cortex) and brain single-cell eQTL data, we detected eQTLs which colocalized with BD loci at the FURIN, FKBP2, SYNE1, THRA, SRPK2 and RPL13 genes.
Convergent evidence from fine-mapping, colocalization and overlap with epigenomic peaks revealed FURIN, SCN2A, FKBP2, THSD7A, THRA, LINC02033 genes as potentially causal genes for BD. Finally, we demonstrated that leveraging fine-mapping can improve cross-population from polygenic risk scores (PRS), as fine-mapping improved the R2 variance explained (liability scale) of PRS by up to 2%.

Conclusions:
This comprehensive pipeline, implemented through Snakemake, will be made publicly available for the rapid, reproducible, and scalable fine-mapping of GWAS risk loci across psychiatric disorders, hence prioritizing genetic variants and genes for experimental validation.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Margaret Krassner
Job Title	Lab Manager and Associate Researcher
Lab	Crary Lab
Department	Pathology, Molecular and Cell-Based Medicine

TITLE: Time is of the Essence: Examining How Post-Mortem Interval Impacts Brain Cell Morphology and Mechanisms of Decomposition

AUTHORS: Margaret M. Krassner (1,2), Justin Kauffman (1,2), Samantha Walsh (3), Kurt Farrell (1,2), Andrew T. McKenzie (1,2,4), John F. Crary (1,2)

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Background: When assessing autopsy brains in research and clinical contexts, the post-mortem interval (PMI) has a significant impact on multiple factors, including the integrity of macromolecules. However, the changes to brain cell morphology are less understood.

Methods: We screened 2119 abstracts, 361 manuscripts, and selected 172 studies to investigate the effect of PMI on brain cell structure using a qualitative meta-analysis. For each publication, cellular degradation outcomes were extracted and rated by multiple reviewers on a 0-3 scale (absent/minimal, partial, severe, or near-total decomposition). We then examined how cellular features, such as membrane quality, are influenced by the PMI.

Results: Mechanistically, fluid accumulation causes volume changes at earlier time points, while complete disintegration of the cell membrane occurs later. Other common decomposition mechanisms include oncotic cell death, subcellular vacuolization, and biomolecule redistribution and degradation. Conditions such as storage temperature and premortem pathology further influence post-mortem decomposition rate. Certain visualization methods (e.g., immunohistochemistry) are especially sensitive to PMI because some antigens degrade rapidly. The intraclass correlation (ICC), a measure of inter-rater reliability, was 0.72 (moderate reliability, $p = 7.9 \times 10\text{-}43$), reflecting limitations in both the clarity of the categories we defined and the precision by which the observations were described. There is a wide range of PMIs after which histology reaches different decomposition severities across studies, experimental designs, and structural features. We identified a significant positive rank correlation between the PMI and decomposition severity score when pooling observations ($\rho = 0.29$, $p = 4.0 \times 10\text{-}7$).

Conclusions: We conclude that there may be advantages to examining some cellular features in biopsies, rapid autopsies, or in vivo animal models as they are influenced by the PMI. More investigation will further clarify the impact of PMI on brain cell structure.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Department	Department of psychiatry

Therapeutic deep brain stimulation in obsessive-compulsive disorder: effects on choice-behavior in a reversal-learning task

Rupak Krishnamurthy Vijayaalaksmi*, Sonia Olsen*, Andrew Smith*, Martijn Figee*, Vincenzo G. Fiore*

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BACKGROUND: Obsessive-Compulsive Disorder (OCD) is characterized by intrusive thoughts (obsessions) that lead to repetitive behavior (compulsions). Half of the correctly diagnosed and treated patients experience continuing disabling symptoms even after pharmacological or cognitive behavioral therapy. This motivated the investigation into the use of Deep brain stimulation (DBS) for OCD treatment. This relies on electrical impulses in the ventral capsule to interfere with the neural dynamics in cortico-thalamo-striatal circuits, a key neural structure in OCD. Here we study DBS treatment efficacy by examining task-related choice behavior of OCD patients, tested before and after surgery.

METHODS: Participants play a 3-options reversal learning task, with 1 or 2 reversals over each of 4 blocks of 20 trials. Three slot machines are presented on screen and in each trial, after selection, they yield an immediate probabilistic outcome of high, low, or no reward (probability distribution: 80%-10%10%). Participants are instructed to find the machine with the high reward and adjust their decisions after reversals. Data is collected from participants during an fMRI scan before the surgery (baseline, n=6). The task is then repeated at the onset of therapeutic stimulation (T0, n=6), under two stimulation settings, termed Off stimulation and therapeutic. We carried out both classic (model-agnostic) and model-based behavioral analyses, using a Rescorla-Wagner reinforcement-learning algorithm.

RESULTS: In a comparison between baseline and T0, the severity of OCD symptoms were significantly reduced (YBOCS scores, baseline: mean=33.67±3.99; T0: mean=30.17±4.5; within subjects ttest: t(6)=4.9, p=.0046). Task-related behavior also showed improvements in relation with choice selections. The percentage of changes of choice in both the trial, before the reversal and after the reversal, show therapeutic at T0 is characterized by reduced “switching” (mean=0.13±0.15, 0.2±0.12), compared to baseline (mean=0.3±0.19, 0.37±0.13; within subjects ttest: t(6)=2.7, 2.7, p=.042, .042). However, model-based analysis did not reveal a significant difference in the comparison of estimated learning rates before and after surgery.

CONCLUSIONS: This preliminary analysis shows DBS might be a viable treatment for severe OCD cases and highlights significant changes in ability to adapt to changes in a task-related environment even at a currently small sample size. Future analyses will reveal in more detail how the alteration of information processing in CSC can become an effective tool for precision treatments.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Francesco La Rosa
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Relationship between brain T1 relaxation time and aging: a 7T MRI multi-center analysis

Francesco La Rosa, Jonadab Dos Santos Silva, Gaurav Verma, Priti Balchandani, Erin S Beck

Background: Brain age is an imaging biomarker used to detect deviations from healthy aging. Atrophy is the main marker currently being analyzed for brain age models, and thus these models do not consider brain microstructural integrity. T1 relaxation time (T1-RT) is a sensitive MRI measure of microstructural properties of brain tissue, including water, myelin, and iron content, whose concentrations vary with aging. The Magnetization-Prepared 2-Rapid Acquisition Gradient Echo (MP2RAGE) is an MRI sequence that provides accurate T1-RT maps. In this work, first, we investigate how T1-RT varies due to different acquisition parameters. Second, we study the relationship between MP2RAGE-derived T1-RT and chronological age in a large, multi-center cohort of subjects imaged with high-resolution 7T MRI.

Methods: We analyzed 398 7T MP2RAGE scans of healthy subjects retrieved from 6 public and 2 private datasets (139 males, 153 females; age range: 19-75 years, mean: 32 years). The MP2RAGE structural (uniform) images were skull-stripped with HD-BET and brain parcellation was obtained with SAMSEG. Tissue masks were eroded by one-voxel to account for segmentation errors. The median T1-RT for white matter (WM), putamen, caudate nucleus, and thalamus was computed. Finally, linear and quadratic polynomial regression models were fitted to analyze the T1-RT relationship with age.

Results: The majority of the scans analyzed had an MP2RAGE protocol with a repetition time (TR) of either 5s (N=103) or 6s (N=154). In individuals between 20 and 30 years old (the most represented 10-year age interval), significant differences were observed in T1-RT between these two protocols for WM (TR=5s: median=1259ms, std=37ms; TR=6s: median=1179ms, std=36ms), putamen (TR=5s: median=1668ms, std=63ms; TR=6s: median=1549ms, std=44ms), and other deep GM structures (all p-values <0.001). T1-RT was correlated with age for both WM ($p<0.001$) and putamen ($p<0.005$). Considering scans acquired with the TR=6s protocol, a quadratic regression analysis showed a higher correlation coefficient compared to a linear model for both WM ($r2=0.20$ vs $r2=0.01$) and putamen ($r2=0.30$ vs $r2=0.01$).

Conclusions: At 7T, the T1-RT provided by the MP2RAGE is highly dependent on its acquisition parameters. A standardized protocol should be implemented to compare T1-RT across centers. As previously shown, the T1-RT in the WM and subcortical GM structures has a significant correlation with age. This age-dependency is better explained by a quadratic model, with minimum values at ages 35-45, rather than a linear correlation. Future work might include integrating T1-RT in a brain age model to better track deviations from healthy aging.

2023 Neuroscience Retreat

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Full Name	Anthony Lacagnina
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Hippocampal somatostatin interneurons govern switching between memories of threat and safety

Anthony F Lacagnina, Saqib Khan, Mazen Mohammed, Roger L Clem

Background: Fearful experiences create enduring negative associations with the surrounding context. Emotional responses to these contextual cues normally subside in the absence of threat, a process known as extinction. Fear and extinction memories appear to be represented by competing neural ensembles. However, very little is known about the mechanisms governing the switching between these conflicting memories. Understanding neural circuits underlying the gating of emotional memory expression can provide crucial insights for developing novel therapeutics for treating disorders of pathological fear.

Methods: Brain-wide c-Fos mapping, contextual fear conditioning, optogenetics, activity-dependent ensemble tagging, intersectional cell-type specific manipulations.

Results: We identified activity of somatostatin interneurons (SST-INs) in the ventral hippocampal area CA1 (vCA1) as uniquely correlated with extinction retrieval. An extinction-specific recruitment of vCA1 SST-INs was confirmed using an intersectional genetic tagging strategy. Optogenetically silencing vCA1 SST-INs impaired extinction retrieval, while stimulating these cells, either broadly or in an activity-dependent manner, prevented fear relapse. In contrast, manipulations of vCA1 parvalbumin-expressing INs did not affect expression of contextual fear or extinction, but did alter anxiety-like behavior. We confirmed that fear and extinction retrieval reactivate orthogonal vCA1 excitatory ensembles and, additionally, silencing excitatory projections from vCA1 to the prefrontal cortex specifically impairs extinction retrieval.

Conclusion: Our results suggest that retrieval of conflicting memories is mediated by vCA1 SST-INs. We hypothesize the vCA1 SST-INs gate the activity of orthogonal excitatory ensembles to suppress the activity of the ensemble associated with the initial contextual memory and promote the retrieval of the extinction-related ensemble.

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SINGLE NUCLEUS TRANSCRIPTOMICS REVEALS PERVASIVE GLIAL ACTIVATION IN OPIOID OVERDOSE CASES

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BACKGROUND: Opioid use disorder (OUD) is a growing public health issue and opioid overdose (OD) is now the leading cause of accidental deaths in the United States, with ~70,000 deaths annually. To date, no knowledge exists about genome-scale dysregulation associated with chronic opioid exposure and overdose. Ventral midbrain (VM), including glial and other non-neuronal cell populations, is important for mediating habitual behaviors and salience of cues associated with drug use, as well as withdrawal-related anhedonia and dysphoria. Despite intriguing mechanistic studies in animal models, the functional and clinical significance of VM glial populations in subjects diagnosed with substance use disorder remains unexplored. Here, we used cell-specific transcriptomic profiling of VM dissected from human post-mortem brain to identify molecular pathways associated with OUD.

METHODS: Case and control brains were collected from both the greater Detroit and Miami metropolitan areas, and sample processing for next generation sequencing of both brain cohorts was performed in New York. Brains were processed in pools of N=3-4 unique brains (donors). From each unique brain, a tissue aliquot containing ventral midbrain from the area of the substantia nigra and portions of the adjacent ventral tegmental area was homogenized, and nuclei were isolated, sorted using a BD FACSAria Cell Sorter, and processed using the 10x genomics single nuclei RNAseq platform. Data was analyzed using various established pipelines, including demuxlet, Seurat R package, and DeSeq2.

RESULTS: We studied gene expression in 212,713 VM single nuclei from 95 human opioid overdose cases and drug-free controls. Chronic exposure to opioids broadly affected glial transcriptomes, involving 9.5 - 6.2% of expressed genes within microglia, oligodendrocytes, and astrocytes, with prominent activation of the immune response including interferon, NFkB signaling, and cell motility pathways. Conversely, in VM non-dopaminergic neurons there was down-regulated expression of synaptic signaling and plasticity genes. VM transcriptomic reprogramming in the context of opioid exposure and overdose included 325 genes with genetic variation linked to substance use traits in the broader population, thereby pointing to heritable risk architectures in the genomic organization of the brain's reward circuitry.

CONCLUSIONS: These findings further support the emerging hypothesis that opioid exposure and addiction are associated with a coordinated transcriptional dysregulation in various neuronal and non-neuronal subpopulations residing in specific nodes of addiction circuitry.

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Full Name	You-Kyung Lee
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Title: Autophagy controls specific PKA signaling pathway and neuronal activity through autophagy receptor AKAP11

Authors: You-Kyung Lee, Xiaoting Zhou, Henry Kim, Xianting Li, Xian Han, Junmin Peng, Nan Yang, and Zhenyu Yue

Background: AKAP11 is an autophagy receptor that mediates the selective degradation of the RI subunit (not RII) and activate PKA pathway in tumor cells. However, the function of AKAP11 in neurons is unclear.

Methods: We performed systemic investigation of autophagy cargos and adaptors to understand autophagy pathways in ATG7 or ATG14-deficient human or mouse neurons. Both autophagy-deficient human induced neurons (iNeurons) and mouse brains were used for validating pathways of interest identified from quantitative proteomics.

Results: Our integrated proteomics and LC3-interactome analysis suggest that the components of the cAMP-PKA pathway are significant targets of autophagy in human and mouse. PRKAR1A (RIα), PRKAR1B (RIβ) and catalytic subunit of PKA complex are significantly enriched in autophagy-deficient iNeurons and mouse brains. the loss of autophagy disrupts PKA signaling in neurons and impairs neuronal activity. Our study of AKAP11 KD iNeurons supports a role of AKAP11 as a selective autophagy receptor in mediating RIα degradation in human neurons. A remarkable AKAP11 and RIα aggregation were colocalized with p62, in neurons at multiple brain regions, including the CA3 and DG regions of the hippocampus, layer IV of the cortex, amygdaloid, and thalamic nucleus from Atg7 cKO mice.

Conclusions: Our study suggests a particularly important role of autophagy in clearing RIα proteins and maintaining the homeostasis of PKA activity in neurons. Our findings help explain the mechanism whereby neuronal autophagy controls learning and memory.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Guanidinium, Amide and rNOE weighted imaging of the human brain using 3D graspCEST MRI

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Background:
Chemical exchange saturation transfer (CEST) MRI is a molecular imaging technique that allows the detection of proteins and certain metabolites through their exchange properties with tissue water. In this study, we propose a 3D steady-state CEST MRI technique to achieve Guanidinium, Amide and protein (relayed nuclear Overhauser effect, rNOE) weighted images of the human brain.

Methods:
3 brain scans were acquired on a 3T Siemens MAGNETOM Skyra scanner using a 3D-graspCEST sequence. Steady-state CEST saturation was achieved by a train of RF pulses interleaved with a stack-of-stars radial acquisition. Following each saturation pulse, the trajectory of the radial stacks was rotated by the golden angle. The rotation continued between each RF pulses and frequency offset. A navigator stack at zero rotation angle was acquired every 24 stacks.
To reconstruct the dynamic images, an offline image reconstruction tool (GRASP-Pro) implemented in Matlab was used. The temporal basis needed for subspace reconstruction was generated from the navigator stacks. Two regions of interest were drawn on a transversal slice, one in a grey matter region (GM) in the occipital lobe and one in a periventricular white matter region (WM).
Z-spectra were calculated for these two ROIs after $\Delta B0$ correction using a linear interpolation between acquired offsets. Amide, Guanidium and rNOE contrast maps were generated by taking the integrated signal of the difference (ΔZ) between the Z-spectra and Single-Lorentzian fitted background for each voxel.

Results:
From the ΔZ curves between the fitted background and the average Z-spectra, three peaks could be observed for both GM and WM. Two relatively distinct peaks, between 2-3 ppm and about 3.5 ppm, which could be attributed to Guanidinium and Amide protons, respectively, and one broad peak around -3.5 ppm, corresponding to rNOE signal.
Guanidinium and Amide weighted maps showed poor contrast between GM and WM, according to the ΔZ curves. Conversely, the rNOE-weighted maps showed visible contrast between GM and WM.

Conclusions:
We have shown that a 3D steady-state graspCEST imaging technique can be applied to detect in vivo Guanidinium, Amide and protein contrasts in the brain, with low B1 power. This technique provides a fast, low-SAR, 3D whole-brain motion robust, multi-parametric CEST imaging method.

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Full Name	Michael Leventhal
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Aberrant social experience after juvenile social isolation impairs recruitment of corticothalamic neurons necessary for sociability

Leventhal M, Lidoski A, Okamura K, Janis M, Waltrip L, Morishita H

Background: Juvenile social isolation (JSI) is known to disrupt social behavior in adulthood, but little is known about the neural mechanisms of social experience-dependent brain maturation that are disrupted by JSI. Previous studies suggest that, in male mice, there is a critical period between postnatal day (p) 21 and p35 when isolation will reduce adult sociability and induce prefrontal cortex (PFC) abnormalities, such as dampened excitability in medial PFC neurons projecting to the posterior paraventricular thalamus (mPFC□pPVT neurons). Interestingly, these circuit abnormalities were not present at the end of the isolation period (p35), raising the question of when and how JSI-induced social deficits emerge over the course of development.

Methods: To investigate the developmental progression of JSI-induced social dysfunction, we assessed sociability at multiple timepoints using the three-chamber test and free reciprocal interaction. During the post-isolation developmental period, we conducted tests of affiliative behavior and aggression among cage mates and used patch clamp electrophysiology to examine the excitability of mPFC□pPVT neurons.

Results: We unexpectedly found that JSI-induced sociability deficits in the three-chamber test (where subjects interact with novel mice) and associated dysregulation of mPFC□pPVT neurons were not present at the end of isolation. Instead, deficits emerge during the first 2 weeks of the adolescent rehousing period (p36-p50). Detailed examination of the first week after rehousing revealed a dynamic transition of cagemate interaction from aggression at p35 to social withdrawal by p42. Of note, chronic social isolation (p21-p50) without rehousing did not induce sociability deficits or mPFC□PVT neuron deficits at p50, suggesting that developmental mismatch during the post-rehousing period plays a key role in driving the dysregulation induced by JSI.

Conclusions: These results suggest that JSI may disrupt adult social behavior not only by impairing social development during the isolation period, but also by impairing subsequent development during the post-isolation developmental period. We propose that the prevailing “social deprivation model”, where adult social deficits are attributed to disruption of developmental processes occurring during the isolation period, should be supplemented by the “developmental mismatch model”, where social deficits are attributed to disruption of developmental processes occurring after the isolation period. An important implication of the developmental mismatch model is that social deficits induced by aberrant juvenile social experience may be treated by intervening during adolescence.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Exploring the VTA Circuitry of Anhedonia in Major Depressive Disorder using Ultra-High Field 7T MRI

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Background: A primary symptom and diagnostic criterion of major depressive disorder (MDD) is a loss of interest and motivation, known as anhedonia1. Animal models of depression suggest that ventral tegmental area (VTA) hyperactivity underlies depressive symptoms and anhedonia2. However, due to the limited resolution of 3-Tesla (3T) MRI, the VTA circuitry related to motivation in human patients with MDD has not been adequately studied. Fortunately, ultra-high field 7-Tesla (7T) MRI is more sensitive and can reveal subtle differences in functional connectivity that cannot be observed with 3T MRI3. Therefore, we used 7T resting-state MRI to explore the correlation between different levels of anhedonia and VTA with whole-brain functional connectivity across MDD patients and healthy controls, in order to investigate the relevant VTA circuitry.

Methods: We scanned MDD (n = 31) and healthy subjects (n = 26) using ultra-high field 7T resting-state MRI and assessed the level of anhedonia using two dimensions of the Temporal Experience of Pleasure Scale (TEPS): TEPS Anticipatory Subscale (TEPSA) and TEPS Consummatory Subscale (TEPSC)4. We analyzed VTA-whole brain functional connectivity across both groups, with TEPSA and TEPSC scores as covariates. We performed a voxel-wise analysis with a threshold of $p < 0.005$, and cluster-level family-wise error correction was applied.

Results: Across MDD and healthy controls, higher anticipatory anhedonia was associated with higher VTA connectivity with the left thalamus, right inferior frontal gyrus and medial prefrontal cortex. Higher consummatory anhedonia was associated with higher VTA connectivity with the left inferior frontal gyrus, right medial frontal gyrus, and right thalamus.

Conclusions: Higher anhedonia was associated with higher functional connectivity between VTA and various clusters in the brain. This aligns with animal studies showing hyper-connectivity in the VTA circuit in depressive phenotypes. Additionally, the findings suggest that higher levels of anticipatory anhedonia are associated with stronger functional connectivity between VTA and mPFC, replicating our previous findings. Our study is ongoing, and we plan to compare the VTA circuitry differences between MDD patients and healthy controls for the next step.

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Full Name	Marianna Liang
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Lab	Zhenyu Yue
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Single-cell transcriptomic atlas of the human substantia nigra in Parkinson's disease

Marianna Liang, Qian Wang, Minghui Wang, Insup Choi, Lily Sarrafha, Lap Ho, Kurt Farrell, Kristin G. Beaumont, Robert Sebra, John F Crary, Tim Ahfeldt, Joel Blanchard, David A. Davis, Xiaoyan Sun, Bin Zhang, and Zhenyu Yue

Parkinson's disease (PD) is the second leading neurodegenerative disorder characterized by degeneration of neuromelanin-containing dopaminergic (DA) neurons in the substantia nigra (SN). The cause of PD remains unclear however single-nucleus RNA sequencing (snRNAseq) has significantly advanced our understanding of neurodegenerative diseases but limited progress has been made in PD. We have generated snRNAseq data from human SN including 9 healthy controls and 23 idiopathic PD cases across different Braak stages. A combination of immunostaining and validation against datasets from independent cohorts resulted in the identification of three molecularly distinct subtypes of DA-related neurons, including a RIT2-enriched population in aged human SN. RIT2 variants are linked to PD. All DA neuron subtypes degenerated in PD. Analysis of the DA neurons of the three subtypes from PD demonstrated alterations of common gene sets associated with neuroprotection. Validation in mouse, midbrain organoids, and human tissue identifies a RIT2 population that partially overlaps with TH in the ventral substantia nigra. Our result highlights the heterogeneity of DA neurons in the human SN and suggest a molecular basis for vulnerability and resilience of human DA neurons in PD.

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Mutations in the autism risk gene DDX3X alter neuronal morphogenesis and synaptogenesis in a sex-specific manner

Jeronimo Lukin1,2,3,4, Adele Mossa1,2,3,4, Yeaji Park1,2,3,4, Zeynep Akpinar1,2,3,4, Silvia De Rubeis1,2,3,4

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BACKGROUND: Mutations in the X-linked RNA helicase DDX3X cause a neurodevelopmental condition (DDX3X syndrome) often presenting with autism spectrum disorder. DDX3X escapes X chromosome inactivation in human and mice, resulting in higher expression in female brains when compared with male brains. Further, mutations in the DDX3X gene affect primarily females. DDX3X regulates mRNA translation, but the mechanisms of action in neurons, the impact of clinical mutations, and the influence of sex have not been studied yet.

METHODS: Using a Ddx3x flox mouse line generated at the Seaver Autism Center, we developed a cellular model to examine the impact of Ddx3x mutations in male and female neurons. We cultured primary cortical neurons from male embryos (Ddx3x +/y or Ddx3x flox/y) or female embryos (Ddx3x +/+, Ddx3x flox/+, or Ddx3x flox/flox). We transfected them with a construct carrying Cre and mCherry to model male control (Ddx3x +/y) or null (Ddx3x -/y) neurons, as well as female control (Ddx3x +/+), haploinsufficient (Ddx3x +/-) or null (Ddx3x -/-) neurons. We also introduced DDX3X pathogenic mutations found in male and female patients. We then examined dendritic arborizations and synapse number and morphology and compared sexes and genotypes. We also performed unbiased quantitative proteomics.

RESULTS: We found that Ddx3x is critical for both dendritogenesis and synaptogenesis, and its role is dependent on both sex and gene dosage. The observed changes in neuronal morphogenesis are accompanied by changes in the neuronal proteome affecting the expression of proteins important for neuronal migration and neurite outgrowth, as well as proteins encoded by risk genes for neurodevelopmental disorders. We also found that mutations identified in female patients are more deleterious than mutations identified in male patients.

CONCLUSIONS: Our findings support a sex-specific role of Ddx3x in neuronal development and lay the bases to understand the sex biases in the prevalence and severity of DDX3X syndrome.

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Department	NEU

Profiling the Neurobiology Underlying Brain Structure in Living Human Subjects

Anina N Lund, Alexander W Charney MD, PhD, Noam D Beckmann PhD

BACKGROUND: A singular goal of neuroscience is to advance knowledge of the processes whereby neurobiology gives rise to human brain function. The anatomical structure of the human brain is believed to be a critical component of these processes, but surprisingly to date there have been no large-scale studies of the relationship between neurobiology and brain structure in living humans. Such studies have not been performed due to the inability to obtain brain tissue samples from living human cohorts.

METHODS: The Living Brain Project (LBP) was designed to overcome this limitation of human brain research by obtaining tissue samples from the dorsolateral prefrontal cortex (dlPFC) for molecular research in a large cohort of living subjects who undergo multimodal neuroimaging as deep brain stimulation (DBS) patients. Through having access to both brain tissue and neuroimaging we can look at the molecular profiles of brain structure in living human subjects. The following was done for samples from 171 individuals in the LBP. Structural MRI (sMRI) images were taken as part of patient's clinical work up. Those images were then taken and processed using freesurfer for metrics including thickness, volume and area. Tissue from the dlPFC was collected during DBS surgeries. RNA sequencing (RNAseq) was performed on these samples. For each imaging feature differential expression (DE) was performed using dream.

RESULTS: Integration of RNAseq with sMRI data from the same individuals identified genes whose levels of expression associated with imaging metrics of the dlPFC including cortical thickness, volume and area

CONCLUSIONS: This study represents the first attempt to connect genomics with brain structure in living people, and marks an important step towards gaining a more complete picture of the molecular processes underlying human brain function. This analysis significantly contributes to the body of work that attempt to generate a complete picture of the molecular properties that play a role in brain anatomy. Utilizing the LBP, we provide what is, to our knowledge, the most extensive characterization of the molecular profiles of brain structure.

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Investigating the cholinergic basis of cognitive deficits in Lrrk2G2019S mice

Alexandra Magee, Alexander Tielemans, KG Montes, Deanna Benson, George Huntley

Mild cognitive impairment is a prevalent non-motor symptom of both hereditary and idiopathic Parkinson's. Young adult male mice carrying the G2019S mutation in the kinase domain of leucine-rich repeat kinase 2 (LRRK2), the most frequent cause of hereditary PD, exhibit increased kinase activity, leading to impairments in divided attention and information processing speed, reflective of deficient cholinergic function and innervation anatomy in the mPFC. We seek to understand the region- and layer-specificity of the cholinergic innervation deficit in Lrrk2G2019S mice, and how this may differ in young adult females. Additionally, Lrrk2G2019S mice display mPFC-specific reduction in nerve growth factor (NGF), supporting our hypothesis that Lrrk2 may inhibit primary cilia formation, and therefore may impact survival, of NGF-releasing cells. Therefore, we also will test the hypothesis that a Lrrk2G2019S-driven deficiency in trophic support underlies sparse cholinergic innervation of mPFC.

mPFC tissue from male and female Lrrk2WT and Lrrk2G2019S knockin mice perfused at postnatal day 60 were immunofluorescently labeled for vesicular acetylcholine transporter (VAChT), a marker of cholinergic terminal fibers. Fiber density was quantified across mPFC regions and cortical layers, and compared between genotypes and sex. To assess whether Lrrk2G2019S NGF-releasing cells exhibit impaired primary cilia formation, mPFC tissue will also be immunofluorescently labeled for GABAergic neurons, the primary NGF-releasing cells in the mPFC, and adenylyl cyclase 3 (AC3), marker of neuronal primary cilia. The percentage of ciliated GABAergic neurons and the morphological features of the cilia will be quantified and compared between genotypes and sex.

Our results show that young adult Lrrk2G2019S mice exhibit sex-specific changes in cholinergic innervation density in all layers and regions of the mPFC. Compared to sex-matched Lrrk2WT mice, male Lrrk2G2019S mice display a sparser cholinergic terminal fiber density, whereas female Lrrk2G2019S mice demonstrate denser cholinergic fiber density.

While elevated Lrrk2 kinase activity is a common driver of changes in the cholinergic innervation of the mPFC of Lrrk2G2019S mice, more research is needed to determine the sexually-dimorphic mechanisms underlying the differential anatomical outcomes. Our results emphasize the need to investigate whether Lrrk2G2019S females display similar deficits in divided attention and information processing speed as Lrrk2G2019S males, despite a dissimilar cholinergic innervation density. Lastly, future investigation of the developmental timing underlying the deficits in cholinergic innervation of mPFC observed in Lrrk2G2019S mice will guide appropriate targets for future mechanistic intervention.

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Neural signatures of Attention-weighted reinforcement learning in humans

C Maher, I Saez, A Radulescu

Background: The human brain's ability to support flexible behavior depends on representation learning: the process of mapping high-dimensional observations to states to achieve a goal. For example, when deciding what to order on a menu, each item can be classified along multiple dimensions (e.g., size, price, flavor, spiciness), but only some predict whether we enjoy the meal. Efficient representation learning involves selective attention for relevant dimensions. For instance, we may only attend to flavor and spiciness when ordering from a different menu. Previous work has primarily used fMRI to study the role of different prefrontal regions in human representation learning (Niv et al., 2015; Leong & Radulescu et al., 2017; Niv 2019). However, how activity in these discrete regions is integrated to support the learning and maintenance of state representations remains an open question.

Methods: We recorded local field potentials (LFP) using stereotactic EEG electrodes implanted in neurosurgical patients (n=4) while they played an adapted multidimensional decision-making task ('Gem Hunters'). This approach provides high temporal and spatial resolution previously unavailable through human neuroimaging methods. In the 'Gem Hunters' task, participants choose between 3 'gem' options that vary in shape and color. Within each block, one target feature (e.g., red) within the relevant dimension (e.g., color) predicts reward with 80% probability, while all other features predict reward with 20% probability. Participants either received instructions that revealed the relevant dimension or no instruction regarding the relevant dimension (50% blocks were instructed; 50% blocks were not instructed). Participants maximize reward by selectively attending to the relevant dimension and choosing the option containing the target feature.

Results: Using BIC scores for reinforcement learning models fit to participants' behavior on instructed blocks, we confirmed that a model in which choice and learning were biased by attention to the relevant dimension (Niv et al., 2015; Leong & Radulescu et al., 2017) explained participants' behavior best. This finding confirms that participants deploy selective attention in service of representation learning. To determine how this attentional selection process is executed by the brain, we implemented a cluster-based permutation testing method to identify electrodes that displayed significant task-related power modulation (89 electrodes, 55% of total). We regressed power in the high-frequency domain (70-200 Hz) against model-relevant parameters (including relevant dimension, attention-weighted expected value of the chosen stimulus, and reward outcome), and found region-specific encoding of model-relevant parameters in the OFC, lPFC, ACC, and insula.

Conclusion: Several distinct regions play an integrated role in deploying selective attention to maintain compact state representations.

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The Relationship Between Eating Attitudes, Self-Esteem, Resilience, and Agency

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BACKGROUND: Relationships between eating behaviors and self-esteem and between self-esteem and agency are well documented. A sense of agency refers to the belief of a direct relationship between action and outcome. Overwhelmingly, the current literature supports that a higher sense of agency- or an internal locus of control- denotes a healthy understanding of oneself, which can shape individual's experience of resilience. Resilience, or the ability to bounce back, is a key protective factor against the development of psychiatric disorders. Higher levels of self-esteem are associated with a stronger sense of agency and better psychological adjustment. In this study, we examine the relationships between eating attitudes, self-esteem, resilience, and agency in a representation of the general population.

METHODS: In an online sample (N=251), we conducted a cognitive task measuring reward- and punishment-related agency (Self Agency Task, SAT). Participants were asked to score their level of agency on a 5-point Likert scale (1=self, 5=computer) after every trial. We also collected self-report data assessing self-esteem, measures of eating attitudes (Eating Attitudes Test 26, EAT-26), and measures of resilience (Connor-Davidson Resilience Scale, CD-RISC). Pearson's correlations were conducted to investigate these relationships.

RESULTS: There was a significant correlation between self-esteem and resilience scores ($r=.498$, $p<.001$). There was a significant negative correlation between self-esteem and EAT-26 scores ($r=-.182$, $p=.004$), and between resilience and EAT-26 scores ($r=-.187$, $p=.003$). There was a significant negative correlation between self-esteem scores and agency in reward trials ($r=-.127$, $p=.045$) and punishment trials ($r= -.130$, $p=.040$). Trends between agency in punishment trials and EAT-26 scores ($r=.112$, $p=.076$) and resilience ($r=-.112$, $p=.054$) were found. There were no significant associations between agency in reward trials and the EAT-26 or resilience scores.

CONCLUSIONS: In line with previous research, our exploratory analysis suggests significant relationships between eating attitudes, self-esteem, agency, and resilience. Higher self-esteem is correlated with a higher internal locus of control across trials and these individuals show higher resilience and lower instances of aberrations in eating attitudes. Future analysis will be conducted to determine the extent of these relationships.

2023 Neuroscience Retreat

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Full Name	Alice Min
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A Chimeric Mouse Model with Human iPSC-Derived Microglia Xenograft for Investigating CNS HIV-1 Infection

Alice K. Min, Behnam Javidfar, Roy Missall, Donald Doanman, Madel Durens, Samantha St Vil, Zahra Masih, Mara Graziani, Annika Mordelt, Samuele Marro, Lotje de Witte, Benjamin K. Chen, Talia H. Swartz, Schahram Akbarian

Background: Human immunodeficiency virus type-1 (HIV-1) is an incurable disease due to the persistence of latent viral reservoirs. The central nervous system (CNS) is seeded within the first two weeks of acute infection and serves as a major reservoir. In the CNS, HIV-1 predominantly targets microglia. The mechanisms governing HIV-1 latency in vivo remain unknown, and extensive studies on CNS HIV-1 disease have been limited due to the difficulty in distinguishing latently infected cells, which are transcriptionally silent.

Method: We developed a novel chimeric mouse model where human induced pluripotent stem cell (iPSC)-derived microglia (iMG) are xenografted into mouse brains. We genetically engineered the iPSCs to harbor Cre-recombinase-dependent dual fluorescent reporter cassette, which allows us to permanently mark cells that have ever been infected with HIV-1 expressing Cre. The mice were also engrafted with human peripheral blood mononuclear cells (PBMC) to initiate infections in the peripheral immune cells, which then spread to the CNS microglia xenograft. Hence our model mimics the physiological route of acute HIV-1 infection in humans.

Result: We confirmed engraftment of dsRed-expressing human iMGs in the mice cerebral cortex at 2 months. Cortical sections demonstrated dsRed+ cells that were validated with microglia-specific antibodies, IBA1 and P2RY12, and a human nuclear antibody staining. We confirmed HIV-1 infection of xenografted iMGs with Gag p24 expression. Moreover, we performed HIV-1 specific RNAscope in situ hybridization that clearly demonstrated HIV-1 infection of iMGs. We also performed parallel in vitro assays of iMGs that were successfully infected with HIV-1.

Conclusion: Our mouse model enables us to track the frequency and kinetics of infected microglial cells in the mouse brain. It is a powerful tool for investigating the mechanisms governing CNS HIV-1 infection as well as latency in the CNS at the single-cell level. Our lineage tracing of HIV-1 infected iMGs will be highly useful for downstream single cell profiling. Our model could also be used for quantitative testing of therapeutic interventions aimed at reducing the CNS HIV-1 reservoir, ultimately to find a sterilizing cure.

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Full Name	Alexandra Munch
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Department	Neuroscience

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

Authors: Alexandra Münch, Anastasia Efthymiou, Sarah Neuner, Edoardo Marcora, Anne Schaefer, Alison Goate

Background: As the global burden of Alzheimer's Disease (AD) continues to rise, so does the unmet need for disease-modifying therapies. Accumulating evidence from genome wide association studies (GWAS) posit that the brain's innate immune system plays a central role in AD etiology. As the central nervous system's resident immune cells, microglia have thus emerged as attractive cells to target therapeutically. Such drug targets may lie within the MS4A locus, a region associated with protection from AD, later age-at-onset, and increased levels of soluble TREM2, a biomarker of microglial activity. This region contains multiple genes within the membrane-spanning 4-domain subfamily A (MS4A) gene cluster, which encode structurally related transmembrane proteins primarily expressed by immune cells whose exact functions are not yet understood. We previously nominated a candidate causal variant within this locus, rs636317, in which the risk allele is predicted to disrupt an anchor binding site for the chromatin remodeling protein CTCF and is associated with increased expression of MS4A4A and MS4A6A in human myeloid cells.

Methods: Using CRISPR-edited human induced pluripotent stem cell (iPSC)-derived microglia (iMGL) we directly test the hypothesis that by modulating MS4A4A and MS4A6A, variant rs636317 alters microglial functions. Given known interactions between MS4A proteins and other immune receptors implicated in AD, such as TREM2 and CLEC7A, we perform targeted functional assays related to immune signaling in MS4A4A/MS4A6A knockout and rs636317-edited isogenic iMGLs. We then employ a novel xenotransplantation model involving direct injection of human microglia precursor cells into the mouse brain to evaluate the effect of this variant on cell function in vivo and in the context of disease using 5xFAD chimeric mice.

Results: As predicted, we observe decreased CTCF binding and increased MS4A4A and MS4A6A expression in iMGLs homozygous for the rs636317 risk alleles. rs636317 protective iMGLs mimic MS4A4A/MS4A6A knockout iMGLs, affecting TREM2 shedding, signaling and phagocytosis.

Conclusions: We hypothesize that decreased expression of MS4A4A and MS4A6A in human microglia promotes protective microglial responses related to TREM2 signaling, ameliorating plaque containment and subsequent cognitive decline. Elucidating the function of this gene family and the specific role it plays in AD progression has the potential to greatly impact public health.

2023 Neuroscience Retreat

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Full Name	Ha Nguyen
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FUNCTIONAL CHARACTERIZATION OF A NOVEL PIP2-INDEPENDENT GIRK2 CHANNEL GATING MECHANISM

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BACKGROUND: G protein-gated inwardly rectifying potassium (GIRK) channels regulate cellular excitability in the heart and brain. GIRK channels have emerged as a candidate drug target for modulating activity in the brain and treating diseases such as epilepsy or alcoholism. However, molecular and structural determinants of the gating regulation of GIRK channels by various ligands are not fully understood. Two regions have been identified as important molecular determinants of PIP2 and G$\beta\gamma$ gating: the inner helix bundle crossing (HBC) formed by the M2 TM domain, and the G loop in the cytoplasmic terminal domain (CTD). Previously, we determined the cryoEM structure of GIRK2 in complex with PIP2 and the cholesterol analog CHS. This structure identified the interaction of one residue, R92, with both cholesterol and PIP2, suggesting an important role in channel gating. To further investigate the role of R92 in channel gating, we introduced aromatic residues at this locus. Substitution with aromatic residues (i.e., Y and F) showed elevated basal activity in electrophysiological studies.

METHODS: Channels containing mutations R92Y and R92F were purified, reconstituted into proteoliposomes, and functionally characterized using a fluorescence-based flux assay. Secondly, R92Y and R92F GIRK channels are co-expressed with phosphatase Dr-Vsp in HEK cells and are subjected to whole-cell patch-clamp electrophysiology. Activation of Dr-Vsp by applying a depolarizing pulse (+100mV) at varying duration depletes the PIP2 level in the membrane and reduces the basal current of GIRK channels.

RESULTS: We found that both mutations increased basal flux, even in the absence of PIP2. The R92Y channels had an increase in PIP2 affinity while the R92F channel was completely PIP2-insensitive. PIP2 depletion caused by Dr-Vsp activation decreases the R92Y channels' current amplitude up to 50% but had no effect on R92F channels.

CONCLUSIONS: These results suggest a PIP2-independent gating mode introduced via mutation of this critical residue, R92 to aromatic residues. Further structural and functional characterization of these GIRK2 mutants will provide clarity on GIRK2 channel gating and a potential framework for rational drug design of GIRK channels.

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Title: Cholinergic modulation of frontal sensory cortical projections is associated with post-error attention adjustment

Authors: Tadaaki Nishioka, Samuel Allen, April Serratelli, Kevin Norman, Priscilla Maccario, Yulong Li, Hirofumi Morishita

Background: The frontal cortex, especially the anterior cingulate cortex area (ACA), is essential for exerting cognitive control after errors, but the mechanisms that modulate ACA neurons to improved performance after errors are poorly understood. Among neurons in ACA, our recent study found that top-down frontal sensory cortical projections to the visual cortex (ACAvis) causally contribute to post-error attentional enhancement (Norman et al Neuron 2021). However, little is known about the inputs that activate the ACAvis neurons and how they contribute to post-error attentional adjustment. Given that lesioning of cholinergic projection neurons in the basal forebrain (BF) causes attention deficits and that cholinergic neurons are activated by punishment, we hypothesized that cholinergic inputs may play a key role in modulating ACAvis neurons for post-error attentional adjustment.

Methods: To investigate the neural mechanisms of ACAvis neurons contributing to attentional adjustment, we employed an intersectional viral approach to selectively express the calcium sensor jGCaMP8s in the ACAvis neurons and performed calcium imaging via fiber photometry recording from mice performing the 5-choice serial reaction time task (5-CSRTT). To assess cholinergic input onto ACAvis neurons, we virally expressed the ACh sensor GRAB-ACh3.5 in ACAvis neurons and performed fiber photometry imaging. To examine the causal role of BF cholinergic projection to the ACA in attentional control, we optogenetically suppressed NpHR3.0 expressing BF ChAT+ projection terminals in the ACA of ChAT-cre mice performing the 5-CSRTT.

Results: ACh sensor imaging in ACAvis neurons showed that ACh signaling is preferentially elevated toward the end of the anticipatory period immediately before an animal makes correct choices after error trials. Consistently, calcium imaging showed ACAvis neurons are also activated at the same timing during post-error correct trials. Of note, optogenetic suppression of BF cholinergic projection terminals in ACA during this late anticipatory period resulted in selectively reduced performance accuracy on trials following the incorrect error, which suggests the causal contribution of cholinergic modulation of ACA neurons for post-error attention adjustment.

Conclusions: Our study demonstrates a key role of BF cholinergic inputs onto ACA neurons for cognitive control by improving attentional performance after errors. Our findings will also highlight ACh receptors expressed in frontal sensory projection neurons as promising therapeutic targets for ameliorating cognitive control deficits in neuropsychiatric disorders.

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Leveraging opportunities for invasive cognitive research in a clinical neurosurgical setting

Lizbeth Nunez Martinez, Ignacio Saez

Background: Neuromodulation therapies and intracranial surgical approaches are powerful treatment options for a variety of neurological and psychiatric diseases: patients with intractable epilepsy can be candidates for stereoelectroencephalography (sEEG) for diagnosis and long term Responsive Neurostimulator (RNS device) implantation for treatment and patients who suffer from movement disorders like Parkinson's disease and dystonia can be candidates for deep brain stimulation (DBS). DBS implantation also shows promise for treatment of psychiatric disorders (depression, obsessive-compulsive disorder). These surgeries involve the implantation of invasive depth electrodes to record intracranial electrophysiological data, which has high spatial and temporal resolution and signal-to-noise ratio compared to standard non-invasive techniques common in human (EEG, fMRI). Combined with behavioral tasks, they present a unique opportunity to study the neurobiological basis of human cognition.

However, research in a clinical setting presents unique challenges, such as the need to coordinate around patients' clinical schedule, to communicate with patients and their families and not to interfere with clinical care while facilitating the needs of the research effort such as the use of specialized equipment, handling of the resulting data, etc. Here, we describe the development of an integrated approach to leverage research opportunities present at a functional neurosurgical setting (Mount Sinai West) and maximize the opportunities to conduct invasive cognitive research in human patients without compromising the quality of clinical care.

Methods: Patient populations are recruited from referrals from the clinical team. We obtain informed consent obtained from patients undergoing sEEG or DBS surgeries prior to their surgeries. We carry out electrophysiological recordings using clinical or research-dedicated systems, including local field potentials, single unit activity (microelectrode) recordings and electrochemical detection of neurotransmitter concentration. Patients completed cognitive tasks either in the Epilepsy Monitoring Unit, the operating room or a dedicated behavioral lab. Post-testing, we collected and organized a variety of data include electrophysiological recordings, non-invasive images, clinical histories, demographic information, neuropsychological testing and behavior for subsequent analysis.

Results: We successfully recorded from 25 EMU patients, 20 DBS patients, and 7 RNS patients at the MSW site. We recorded from various regions of the brain, including the orbitofrontal cortex, hippocampus, amygdala, substantia nigra while patients carried out tasks designed to test their decision-making, memory, social behavior, abstract reasoning and other cognitive functions.

Conclusions: This integrated clinical-research approach allows us to investigate anatomically precise neurophysiological activity underlying a broad range of cognitive processes, which will provide new insights into the neurobiological basis of human cognitive processes valuable for both basic and translational neuroscience.

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A whole genome based transcriptomic approach to identify time dependent biomarkers of clinical relevance in cocaine use disorder

Chinwe Nwaneshiudu, Kiran Girdhar, Rita Z. Goldstein, Eduardo Butelman, Nelly Alia-Klein, Panagiotis Roussos

Background- Over half of individuals in treatment for cocaine use disorder (CUD) will relapse into regular use with higher drop-out in moderate and heavy users (51.8-66.7%) (Lappan et al., 2020). Using clinical and molecular biomarkers that identify vulnerabilities toward cocaine relapse is a focus of recent investigations (Goldstein, 2022; Poireau et al., 2022). Applying genome-wide transcriptomics to track dynamics of recovery is important. However, it is challenging due to sparsely available techniques for analyzing longitudinal transcriptomics. Here we created an analytic approach geared towards examining dynamic changes in behavioral and gene expression markers over several months in individuals with CUD.

Methods- A longitudinal study of 12 individuals (mean age, 53 years; male:female ratio, 9:3) with CUD, treatment-seeking and abstinent from cocaine at the first session. We conducted computational genomics on plasma collected repeatedly over 9 months (baseline, 3, 6, 9 months) with clinical phenotyping. Our goal was to test for time fluctuations in gene co-expression concomitant with recovery outcomes. Our analytical pipeline included cell deconvolution using CIBERSORT to estimate cell type heterogeneity in gene expression. We optimized a generalized linear model for differential gene expression with time comparisons using multivariate information criteria (mVIC) and dream software. These accounted for repeated measurements using random effects and quantified gene expression as a function of time across two groups (mostly abstainers n=6, relapsers n=6: Gene expression ~ 1|subject + group*time). We used weighted gene co-expression network analysis (WCGNA) to identify modules of co-expressed genes that depict changes in expression over time. Spline curves were fit to observe significant modules that show differences across subjects with varying number of abstinence days from cocaine use.

Results-. Our analysis showed major gene co-expression networks (modules) with highly co-expressed genes. Using functional enrichment analysis, we identified the biological functions of the modular genes. The mostly abstaining group showed time-dependent patterns of gene expression variation of significant networks involved with immune processes, cell cycle and death and RNA-protein synthesis. There is also immune cell-specificity in driving gene expression changes over time that discriminated between the groups. These results suggest an immunological mechanism in CUD that can be used to discriminate abstinence status.

Conclusion- We demonstrate a robust feasible pipeline for a whole genome-based longitudinal study in CUD. This pilot study may lead to larger studies into whole genome-based blood biomarker approaches for monitoring abstinence, relapse, and other dynamic fluctuations in addiction recovery.

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Functional connectivity networks associate with both perceived stress and atherosclerotic burden in a PTSD cohort

David O'Connor, Charbel Gharios, Mandy van Leent, Helena L Chang, Shady Abohashem, Michael Osborne, Cheuk Y Tang, Audrey E Kaufman, Philip Robson, Sarayu Ramachandran, Claudia Calcagno, Venkatesh Mani, Maria Giovanna Trivieri, Antonia Seligowski, Sharon Dekel, Willem Mulder, James Murrough, Lisa Shin, Ahmed Tawakol, Zahi Fayad.

Background: Chronic stress is associated with increased levels of cardiovascular disease (CVD). This is typified in individuals with post-traumatic stress disorder (PTSD). PTSD symptoms include increased emotional distress and recurrent negative memories, and individuals with PTSD have also been observed to have increased levels of atherosclerotic burden and negative cardiac events. The etiology of PTSD, and its downstream effects, is still poorly understood, and more research into the whole-body effects of PTSD, and the interaction between systems is required.

Methods: MR and PET imaging of the brain and vasculature were performed in 70 subjects (19 PTSD, 35 Trauma Control, and 16 Healthy Controls). In addition to imaging, cognitive assessments were collected to assess symptoms of chronic stress, including the Perceived Stress Scale (PSS). Data were analyzed in python. Connectome Predictive Modelling (CPM) was used to identify brain functional connectivity (FC) networks from the fMRI scans, which were associated with cognitive and vascular indicators of PTSD and CVD respectively. A 10-fold cross validation method was used to generate feature sets and assess the performance of the models.

Results: Using CPM, FC networks which could predict PSS were identified. A positive network, i.e., higher connectivity = higher PSS, with 3986 edges, was found which had a positive correlation with PSS ($R = 0.255$, $p = 0.033$). An additional negative network, i.e., lower connectivity = higher PSS, of 103 edges, was found which had a negative correlation with PSS ($R = -0.328$, $p = 0.005$). The positive network primary encompassed regions from the frontoparietal (FP), medial frontal (MF), and motor networks, with both stronger within network connectivity, and stronger FP-MF connections being associated with higher PSS. The negative network also encompassed edges from the MF and motor networks, as well as subcortical regions, whose connections were diminished with increased PSS. Predicted PSS values from each network showed associations with the standard deviation of left common carotid wall thickness ($R = 0.252$, $p = 0.047$ for positive, $R = -0.283$, $p = 0.025$ for negative), which is an indicator of atherosclerotic burden.

Conclusions: Modeling PSS using fMRI can reveal brain wide connections which underpin traditional PTSD symptoms, and which are also associated with increased atherosclerotic burden.

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Full Name	Emerald Obie
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EXPLORING THE POTENTIAL OF ACTIVE VTA NEUROFEEDBACK IN TREATING MAJOR DEPRESSIVE DISORDER WITH 7-TESLA MRI

E Obie, JM Beltrán, G Butler, Y Jacob, LS Morris

BACKGROUND: Major depressive disorder (MDD) is a prevalent mental health condition that can significantly impact a person's daily life. Noninvasive treatment methods are critical, especially for those with treatment-resistant depression. One of the most common symptoms of MDD is a lack of motivation, which has been linked to impaired activity in the mesolimbic dopamine system stemming from the ventral tegmental area (VTA). Neurofeedback, a noninvasive technique that aims to regulate brain activity, is a promising approach to treating MDD.
METHODS: In an ongoing Sham-controlled clinical trial, 17 participants with MDD have been randomized to either Active VTA or Sham neurofeedback in a single-blind 1:1 manner. The neurofeedback sessions consist of a pre-training run, three training runs, and a post-training 'test' run, including rest, count, and motivate trials. During motivate trials, participants are encouraged to identify strategies to regulate their own VTA activity and can simultaneously monitor their efficacy through a progress bar representing VTA activity. For the Active group, the progress bar is updated to represent the level of VTA signal activation during motivate trials relative to previous count trials, while the Sham group's feedback represents another participant's VTA signal from a prior session. The participants complete self-report and clinically administered assessments before and after the neurofeedback training and during a follow-up visit 24 hours post-training, including the Montgomery-Asberg Depression Rating Scale (MADRS) and Profile of Mood States—Bipolar scale (POMS), with a focus on the depressed-elated score. Mixed, repeated-measures Analysis of Variance (ANOVA) was used to assess the effects of time (pre- and post-training) and treatment group (Active and Sham feedback) and any interactions. We hypothesized that Active VTA neurofeedback leads to a more significant decrease in symptoms over time than Sham feedback.
RESULTS: Results from the repeated-measures ANOVA for MADRS showed a main effect of time ($p=0.01$), whereby MADRS scores reduced from pre- to post-training across all subjects. There was no main effect of treatment group ($p=0.92$) and no time x treatment group interaction ($F(1)=3.30$, $p=0.09$). For the POMS depressed-elated score, there was also a main effect of time ($p=0.02$) and no effect of treatment group ($p=0.96$) or interaction ($F(1) = 0.31$, $p=0.59$).
CONCLUSIONS: This is a preliminary analysis of an ongoing clinical trial. Our early findings identify promising trends in the improved ability of MDD patients to train themselves in VTA self-activation through subjective motivational strategies. Further work will elucidate the role of Active versus Sham feedback.

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Full Name	Kazuya Okamura
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Juvenile window for preventing deficits in frontal-thalamic social circuit caused by syndromic autism genes

K.Okamura, L.Waltrip, A.Lidoski, M.Leventhal, L.Bicks, B.Stevens, S.Akbarian, H.Morishita

BACKGROUND: Impaired social processing is one of hallmarks of autism spectrum disorder (ASD), yet little is known about the links between genetic risks and the circuit maturation underlying social processing. Here, we aimed to identify the developmental windows when circuits responsible for social processing are sensitive to genetic risk of ASD. Genetic and transcriptomic studies have shown that ASD risk genes are enriched in maturing prefrontal cortical (PFC) deep layer projection neurons. Based on our recent finding that deep layer projections from medial prefrontal cortex (mPFC) to paraventricular nucleus of thalamus (PVT) (mPFC→pPVT) are necessary for proper sociability, but dysregulated by juvenile social isolation (Yamamuro et al, Nat. Neurosci 2020), we examined the impact of ASD risk genes on the maturation of mPFC→pPVT neurons and social processing.

METHODS: We employed whole-cell patch clamp recording to characterize mPFC→pPVT neuron function in Fmr1KO and Tsc2 Het mice. Fiber photometry imaging and circuit-selective transcriptomics were used to interrogate the effects of the Fmr1KO genotype on mPFC→pPVT neurons. To explore potential therapeutic strategies, pharmacological and optogenetic approaches were combined with social behavior characterization of Fmr1KO mice.

RESULTS: In two mouse models of ASD, we found that mPFC→pPVT neurons show reduced excitability and increased inhibitory drive in adulthood. Fmr1KO mice showed blunted recruitment of mPFC→pPVT neurons during social contact, and optogenetic stimulation of mPFC→pPVT neurons was sufficient to acutely reverse social dysfunction in adulthood. Characterization of developing mPFC→pPVT neurons revealed that deficits emerge during the juvenile period between p21 and p35, and persist until adulthood. Given that a transcriptomic analysis of mPFC→pPVT neurons revealed a dysregulation of □catenin/GSK3□ pathways, we examined the impact of modulating GSK3 with lithium administration during the juvenile vulnerability window in Fmr1KO mice. Strikingly, a single dose of lithium at p30 was sufficient to prevent deficits in adult sociability deficits and intrinsic excitability while enhancing excitatory synaptic transmission onto mPFC→pPVT neurons.

CONCLUSIONS: These findings support that altered maturation of frontal projections to the pPVT mediates social processing deficits associated with genetic risks of ASD. Identification of the specific PFC circuits and developmental windows that modulate social behavior and whose functions are affected by mutations in ASD risk genes will point toward potential therapeutic targets that allow for circuit-based amelioration of social processing challenges in ASD.

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Dietary polyphenols drive behavioral, transcriptional regulation, and commensal microbiota alterations in models of opioid use

Aya Osman, Rebecca S. Hofford, Katherine R. Meckel , Kyle J Trageser, Tatsunori Oguchi, Drew D. Kiraly, Giulio M. Pasinetti.

Background

Opioid Use Disorder (OUD) is a neuropsychiatric condition associated with substantial medical and social consequences. Despite this, current pharmacotherapies for OUD are ineffective or intolerable for many patients. As such, interventions aimed at promoting resilience against OUD are of importance. Recently, treatment with a Bioactive Dietary Polyphenol Preparation (BDPP) was shown to promote behavioral resilience and adaptive neuroplasticity in several models of neuropsychiatric disease. Here, we assess effects of BDPP treatment on behavioral and molecular responses to repeated morphine treatment.

Methods

7 weeks old male C57BL6/J mice were treated with either BDPP comprised of grape seed extract, Concord grape juice and resveratrol, or drinking water containing matched concentrations of sucrose for 2 weeks. Mice were subsequently behaviorally tested using locomotor sensitization and conditioned place preference (CPP) to a range of morphine doses (2.5 - 15mg/kg given subcutaneously). As polyphenols are known enhancers of Sirtuin-1 (Sirt-1) histone deacetylase activity, an additional cohort of mice received microinjections of the Sirt-1 inhibitor EX527 into nucleus accumbens (NAc) daily during CPP training. To assess if BDPP effects are driven by two metabolites previously reported as mediators of BDPP behavioral effects: a subset of mice were pretreated with dihydrocaffeic acid (DHCA) and malvidin-3'-O-glucoside (Mal-gluc) for 2 weeks. For molecular analyses, NAc was dissected for qPCR analysis and RNA sequencing. As polyphenols are metabolized by the microbiome and have prebiotic properties, cecal samples were collected for 16S sequencing.

Results

BDPP pre-treatment reduced CPP at low dose (5mg/kg) morphine but enhanced it at high dose (15mg/kg). Parallel transcriptomic profiling of NAc, again showed dose x BDPP interaction, where at high dose, BDPP potentiated morphine induced expression of synaptic function related genes. 16S shows BDPP pre-treatment markedly altered microbiome composition and function at low dose morphine, alterations which significantly correlated with CPP score. qPCR data revealed a significant main effect of BDPP treatment on EGR4, Sirt1 and HDAC1 levels at low dose morphine. Interestingly treatment with EX527 or DHCA and MAL-gluc did not alter BDPP effect on reducing low dose morphine CPP, suggesting other mechanisms driving behavioral effects of BDPP.

Conclusions

These results demonstrate BDPP has robust dose-dependent effects on behavioral and physiological responses to morphine and lay the foundation for future mechanistic and translational work.

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Department	Neuroscience

Title: Brain-Heart-Body Connections in Mental Health: Intracranial Electrophysiological Measures of Interoceptive Processing in the Insula

Authors: Jacqueline Overton, Elisa Xu, Ignacio Saez, Fedor Panov, Lizbeth Nuñez, Samantha Pitts, Jacob Dahill-Fuchel, Martijn Figee, Joohi Shahed, Helen Mayberg, Allison Waters

Background: Abnormal interoceptive processing is observed across psychiatric and neurological conditions wherein core symptoms arise from a bodily sensation: pervasive negative mood and psychic pain in Major Depression, compulsive urge in Obsessive Compulsive Disorder, urge to tic in Tourette Syndrome, increased arousal and agitation in Anxiety and Panic Disorders, craving in addiction, etc. Despite this prevalence, interoceptive processing and abnormality is understudied in clinical populations. A candidate neural measure is the heartbeat evoked potential (HEP), a brain electrophysiological signal that is time-locked to the heartbeat and thought to index baroreceptor activity in the chest cavity. While promising, basic characteristics of this signal are not established or agreed upon. Cortical sources of the HEP have been identified in the insula, the primary interoceptive cortex. However, the spatial and temporal characteristics of the HEP on the scalp surface diverge widely across paradigms. This suggests that there are multiple cortical sources in addition to the insula as well as a range of functional correlates that have yet to be delineated. Additional challenges are that the insula may be too deep for precise measurement and localization using traditional scalp electroencephalography. To address these challenges, we record invasive stereoencephalography (sEEG) and simultaneous scalp surface EEG in neurosurgery patients while they perform a battery of interoceptive tasks.

Methods: Patients with medication resistant epilepsy who are undergoing clinical invasive electrophysiological monitoring are recruited for participation in research studies prior to surgery. Electrode placement is determined by their clinical care team, and routinely includes the insular cortex, cingulate gyrus, and other areas of interest. During their stay in the epilepsy monitoring unit (EMU), we collect a battery of tasks that manipulate interoceptive attention, arousal, and anticipation. These include: heartbeat counting with eyes opened, controlled breathing, affective pictures, and gambling. In addition to standard neuropsychiatric testing, we administer self-report depression and anxiety scales in the EMU.

Results: We have collected simultaneous sEEG, scalp EEG, EKG, and respiration data for 7 patients in the EMU and are currently developing analytical pipelines.

Conclusions: Understanding interoceptive processing in a range of psychiatric disorders is a critical need and a promising avenue for further research. Beginning with epilepsy patients with comorbid depression and anxiety, we are developing pipelines for interoceptive biomarker discovery with the broader goal of developing novel biofeedback and personalized neuromodulatory treatments.

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Department	Department of Psychiatry

Relating Speech-based Emotional Tags to Psychiatric Symptoms during the COVID-19 Pandemic

Siddhartha Peri; Agrima Srivastava; Riaz Shaik; Varshini Balasubramanian; Karmiella Ferster, Guillermo Cecchi; Cheryl Corcoran; Muhammad Parvaz

Abstract

The COVID-19 pandemic was an emotional stressor for many people; however, it is unclear if such emotional distress, assessed objectively, was associated with psychiatric symptoms. Therefore, in this online survey study, conducted between 07/2020 to 07/2021 (during the first and the second waves of the COVID-19 pandemic), we obtained validated behavioral questionnaire data (encompassing 30 behavioral measures) and video recordings (1 min, each) on the positives and negatives of the COVID pandemic from 28 participants (25.0% males; 57.1% 18 – 25 years of age). To extract the relative weights of 27 emotions from the speech transcripts, we used the Bidirectional Encoder Representations from Transformers (BERT) base model which was trained using the GoEmotions dataset. We conducted multiple linear regression models between behavior and emotion sentiments, and FDR correction was used for multiple comparisons. The results show that greater speech-assessed anger and remorse were associated with higher alexithymia symptoms (β_{anger} = 0.51, SE_{anger} = 0.16, p_{anger} = 0.003, $\beta_{remorse}$ = 0.40, $SE_{remorse}$ = 0.18, $p_{remorse}$ = 0.003), which is consistent with the existing literature, but never shown before using short 1-min speech. Moreover, we also found greater sentiments of disgust, disapproval, and anger to be associated with higher obsessive compulsive symptoms ($\beta_{hoarding,disgust}$ = 0.72, $SE_{hoarding,disgust}$ = 0.15, $p_{hoarding, disgust}$ = 0.007, $\beta_{checking,disgust}$ = 0.70, $SE_{checking,disgust}$ = 0.16, $p_{checking, disgust}$ = 0.018). As the pandemic severely worsened the mental health landscape for millions of individuals, fast and reliable measures such as short (< 1min) speech segments as well as an investigation into sex differences can pave the way towards objective and specific detection of psychiatric symptoms.

Funding: ISMMS

2023 Neuroscience Retreat

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APOE4 alters the plasma proteome to confer changes in brain phenotypes

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The strongest genetic risk factor for Alzheimer’s disease (AD) is the apolipoprotein E (APOE) ε4 allele. Compared to the common ε3 allele, the ε4 allele markedly increases AD risk by 3- to 12-fold, depending on number of alleles. Recent work exploring age-related cognitive decline identified changes in blood-CNS communication across aging. Youth-associated blood-borne proteins were sufficient to revitalize the aged brain in terms of hippocampal function, adult neurogenesis, and dendritic spine plasticity. Characterizing plasma proteomic changes in a variety of contexts may thus be critical for development of novel therapeutic strategies to combat AD. We hypothesized that the plasma proteome differs between APOE4 and APOE3 individuals, and these systemic changes account for differences in brain function according to APOE genotype. Using an aptamer-based profile of ~1300 proteins in plasma from APOE4/4 and APOE3/3 human subjects, we identified differentially abundant proteins and associated canonical pathways linked to CNS functions and processes. We next compared the plasma proteome in APOE-knock-in mice expressing APOE3 or APOE4 and found pathways conserved across species related to the extracellular matrix (ECM) and inflammation. To examine molecular mechanisms within the brain potentially perturbed by blood-CNS communication in APOE4 mice, we assessed transcriptomic changes in bulk hippocampal RNA-seq in parabiosis experiments in which APOE4 and APOE3 mice shared blood. Pathways related to cholesterol metabolism, myelination, ECM, synapse remodeling, and inflammation were altered as a result of sharing blood from the opposing APOE genotype. Ongoing experiments focus on investigating the protective impact of APOE3 relative to APOE4 on blood-brain communication mechanisms broadly, and in the context of AD pathology, which may ultimately inform our understanding of increased AD risk in APOE4 subjects.

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Full Name	Paul Philipsberg
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Title: PhaSER: An open-source tool for real-time, phase-targeted manipulations of endogenous oscillations

Authors: Paul A Philipsberg*, Zoé Christenson Wick*, Sophia I Lamsifer, Cassidy Kohler, Elizabeth Katanov, Yu Feng, Corin Humphrey, Tristan Shuman

Background: The coordination of neural activity relative to ongoing oscillations, (e.g., in the form of spike-phase coupling, phase-phase coupling, and phase amplitude coupling), has long been hypothesized to play a crucial role in both in facilitating the flow of information in cognitive processing, and in maintain excitatory- inhibitory balance. Causal investigations into these relationships, however, have thus far been limited by the significant technical challenges associated with specifically and precisely manipulating activity relative to endogenous oscillations. In order to address this, we have developed a closed-loop optogenetic system for cell-type specific stimulation phase-locked to endogenous oscillations.

Methods: Our closed-loop system, PhaSER (Phase-locked Stimulation to Endogenous Rhythms), uses low-latency signal processing and auto-regressive forward prediction to enable real-time phase estimation and temporally precise manipulations. Here, we evaluate the phase-targeting performance of this tool and test its ability to manipulate the phase-locking properties of somatostatin-expressing (SOM) interneurons relative to hippocampal theta oscillations.

Results: We show that PhaSER is able to accurately target specific phases of theta in real-time across a range of physiological theta powers in awake, behaving mice. Additionally, we show that our tool is able to shift the preferred firing phase of hippocampal SOM interneurons without altering the referenced theta power or phase.

Conclusions: The tool we have developed here is highly flexible and can be used to target cell-type specific manipulations to any phase of an endogenous oscillation. We have released PhaSER as an open-source tool to facilitate its use in future research. Phase specific manipulations will be vital for probing the mechanisms underlying seizures and cognitive impairments in neurological diseases in which neural synchrony is altered, including epilepsy, Alzheimer’s disease, and autism spectrum disorders.

2023 Neuroscience Retreat

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Full Name	Samantha Pitts
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Design Principles for using Heartbeat Evoked Potentials as a Neurofeedback Parameter in Interoceptive-Attention Tasks

Samantha Pitts, Elisa Xu, Sara Scherrer, Jacob Dahill-Fuchel, Jacqueline Overton, Allison C. Waters

BACKGROUND: Heartbeat-evoked potentials (HEPs), a direct electrophysiological measure of interoceptive processing, are sensitive to changes in attention to bodily sensation and anxiety. In personalized medicine, HEPs may provide a biofeedback parameter to augment behavioral intervention on bodily distress in likeness to heart rate variability (HRV). While the conventional averaging of HEPs enhances the signal-to-noise ratio, reliance on this strategy is an obstacle to the real-time demands of biofeedback.

METHODS: A community sample of adults (n=40) were recruited using broad inclusion criteria (e.g., 25% anxious). Participants were administered self-questionnaires (BAI, MAIA-II) to record psychometrics. EEG and ECG were recorded (256-array) in mind-wandering and heartbeat counting conditions. Averaged HEP magnitude and SDNN were compared across conditions using repeated measures Analysis of Variance and compared to psychometrics using Spearman's rank correlation. Trial-level signal fidelity and sensitivity to attention manipulation was assessed for applicability to a biofeedback design (n=33) in HEP magnitude.

RESULTS: HEP magnitude was enhanced with attention to interoceptive sensation, F(1,38)=7.9, p=.008, η_p^2=.172, and most sensitive to conditions. In single trials, HEPs in 7 of 22 normally distributed subjects showed an effect of attention (p<0.05). Variance in single trials was greater during mind-wandering (M=37.7, SD=57.1 vs. M=28.9, SD=30.2). The logarithm of the variance of HEP magnitudes during heartbeat counting was correlated with MAIA noticing and trusting subscales (r(1,38)=.33, p=.049, r(1,38)=.40, p=.01, respectively).

CONCLUSIONS: Results demonstrate an enhancement of HEP magnitude with attention to bodily sensation, consistent with the proposal of HEP biofeedback to augment intervention on interoceptive distress (e.g., exposure, meditation). In single trials, two of three subjects exhibited signal stability, and variance (not magnitude) of the HEP was sensitive to attention manipulation. Magnitude variance during attention to bodily sensation was more effective than HEP magnitude at achieving significant indicators of interoceptive awareness, in likeness of HRV to heart rate. Findings suggest that more complex HEP features such as variance may uncover a generalizable interoceptive biomarker that meets the demands of real-time biofeedback-enhanced intervention.

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Full Name	Gabrielle Price
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Diffuse midline glioma harbors alterations that are attenuated by MEK inhibitors and 5-aminolevulinic acid-photodynamic therapy

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Background: Diffuse midline glioma (DMG) is the leading cause of brain cancer-related mortality in children. There is a desperate need for therapeutic models that abrogate tumor cell invasion processes since standard radiation therapy is associated with transitory benefit and therapeutic resistance. 5-aminolevulinic acid-photodynamic therapy (5-ALA-PDT) is a photo-therapy that preferentially ablates tumor cells when 5-ALA is delivered with 635 nm light by metabolizing to protoporphyrin IX (5-ALA metabolite). The RAS/MEK signaling pathway has been implicated in tumorigenesis and has been shown to synergize with 5-ALA-PDT in various carcinoma models. Therefore, the objective of this study is to investigate the use of 5-ALA-PDT and MEK inhibitors as an approach for DMG treatment.

Methods: Five DMG lines were treated with 5-ALA-PDT and MEK inhibitor trametinib to evaluate effects on proliferation, invasion, live cell dynamics, and cell death in vitro. Apoptotic effects and changes in the tumor microenvironment were evaluated in vivo using a patient-derived xenograft model.

Results: Functional screens demonstrate sensitivity to 5-ALA-PDT and trametinib (5-ALA-PDT IC50=0.25- 0.41 μM; trametinib IC50=0.03 μM- 0.03 mM). An increase in cleaved-caspase3 ($p=0.0006$) and reactive oxygen species concentration ($p<0.0001$) was characteristic in DMG cell lines post-treatment. Immunofluorescence stainings showed a decrease in PDGFRa ($p=0.007$) and increase in Hsp70 ($p<0.0001$) expression. Trametinib and 5-ALA-PDT dampened cell invasion (invasive/total cells: 1.30, 0.20, 0.26, 0.05 for control, trametinib, 5-ALA-PDT, and combination, respectively). For in vivo studies, there were changes in cleaved-caspase3 (>4-fold difference) and glioma-associated neovascularization in tumor bearing mice.

Conclusion: This study proposes a promising, novel combinatorial strategy involving the use of 5-ALA-PDT and MEK inhibitors for DMG treatment and can be implemented for other CNS tumors.

2023 Neuroscience Retreat

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Perceptual memorability and reward valuation make parallel contributions to successful recognition memory.

Salman E. Qasim, Ignacio Saez, Xiaosi Gu

Background: Our experiences can be memorable for different reasons. Prior research has identified the importance of intrinsic perceptual features to memorability. However, recent work suggests that value-driven learning (i.e. via reward prediction errors [RPEs]) also influences memorability.

Methods: Here, we examined the joint contribution of perceptual memorability and value-based computations in influencing memory strength. Participants performed a two-arm bandit reversal learning task, in which they learned the value associated with images with different levels of baseline perceptual memorability. Next, participants performed a recognition memory task.

Results: Importantly, both the model-estimated RPEs and the perceptual memorability associated with images contributed to recognition memory. Value-driven individuals, who earned more rewards on the learning task, also prioritized these extrinsic RPEs over intrinsic perceptual features during recognition memory. Over-reliance on RPE was advantageous to memory performance in individuals with low trait anxiety, with this advantage diminishing in highly anxious individuals.

Conclusions: Together, these findings reveal a parallel relationship between intrinsic (perceptual memorability) and extrinsic (learned association with RPE) sources of information that both contribute to recognition memory; this relationship is dynamically modulated by both individual decision making and mental health traits.

2023 Neuroscience Retreat

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Full Name	Tanni Rahman
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Icer Dysregulation in the Nucleus Accumbens Core Mediates Impulsivity and Heroin Self-Administration Vulnerability in an Animal Model of Depression

Tanni Rahman, Joseph Landry, Randall J. Ellis, Jacqueline M. Ferland, Yanhua Ren, Yasmin L. Hurd

Background: Impulsive behavior, mediated partly by the nucleus accumbens core (NAcC) and shell (NAcS), is a risk factor for substance use disorder (SUD). Impulsivity may also mediate the relationship between depression and SUD. For instance, individuals with high impulsivity and major depression have a stronger trajectory for developing SUD. Furthermore, less is known about the neurobiological mechanisms underlying impulsivity as a risk factor for SUD in the context of depression-like behavior. Previously, we linked the cAMP Response Element Modulator (Crem) transcription factor to impulsivity and heroin addiction. Additionally, an earlier investigation found that Inducible Camp Early Repressor (Icer), an isoform of Crem, mediated depression-like behavior. This study investigates the molecular function of Crem isoforms, Icer and CremT, on impulsive behavior and heroin self-administration in an animal model of depression.

Methods: We studied adult male Wistar Kyoto rats (WKYs), an animal model of depression. Impulsive choice and action behaviors were measured by the intolerance to delay (ITD) task. Depression-like behavior and anhedonia were measured by the forced swim test and sucrose preference, respectively. Gene expression differences of Crem isoforms were assessed by qPCR and lentiviral over-expression was conducted in the NAcC. Downstream molecular effects were assessed by bulk RNA sequencing, differential gene expression analysis at the gene and transcript levels, in-silico single cell deconvolution, and multiscale gene co-expression network analysis.

Results: WKYs were dichotomized into high or low impulsive action groups. Icer mRNA was specifically reduced in the NAcC of WKYs with high impulsive action. Moreover, Icer in the NAcC, but not NAcS, negatively correlated with impulsive action. Additionally, heroin self-administration (SA) tended to reduce Icer mRNA in the NAcC of WKYs. Over-expression of Icer in the NAcC neurons of WKYs reduced impulsive action, heroin SA, and depression-like behavior. However, over-expression of Icer increased anhedonia. RNA-sequencing and in-silico single cell deconvolution of the NAcC revealed affected pathways related to interneurons, dopaminergic function, and neuroplasticity.

Conclusions: The results indicate that Icer may play a role in mediating impulsivity, heroin SA, and depression-like behavior by modulating interneuron and dopaminergic cell function in the NAcC. Future studies will investigate Icer's role in regulating specific cell populations in the NAcC relevant to heroin SA and depression-like phenotypes.

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2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Susana Isabel Ramos
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Department	Pathology, Molecular, and Cell Based Medicine

Implicating astrocyte progenitors from the developing human neocortex in glioma genesis and progression

Authors: Susana I. Ramos, Balagopal Pai, Thenzing Silva Hortado, and Nadejda M. Tsankova

Background: While astrocyte-like progenitors have been put forward as the glioblastoma (GBM) cell of origin, the origins of human neocortical astrocytes are poorly understood. This highlights a need for a better understanding of the transcriptomic drivers that initiate astrogenesis during the third trimester of gestation. Using computational lineage trajectory analyses, we previously reconstructed prenatal astrocyte lineages converging from two astrogenic populations, an EGFR+ gliogenic intermediate progenitor cell (gIPC) and a PDGFRβ+ astrogenesis-committed radial glia (RG-A). We have, however, yet to identify the transcription factors (TFs) that drive this divergence prenatally followed by lineage maturation postnatally. As malignant cells are known to co-opt neurodevelopmental pathways, the exploitation of TF driver vulnerabilities in malignant cells could bring novel therapeutic strategies to hinder GBM progression or recurrence.

Methods: To identify candidate TF drivers of astrogenesis, we generated single nucleus RNA- (snRNA-seq) and ATAC-sequencing (snATAC-seq) datasets from 1) surgically resected IDH-wildtype GBMs, 2) the subventricular zone and outer cortex from non-pathological adult neocortices, and 3) the germinal matrix and cortical plate of non-pathological neocortices collected at 17 to 41 gestational weeks (n = 17) and 3 to 6 postnatal weeks (n = 2). To bolster the power of our analysis and map entire astrocyte lineages, we integrated our datasets with recently published snRNA-seq (n = 6) and snATAC-seq datasets (n = 4) that include samples collected from 1 to 10 postnatal months. Next, we annotated non-malignant cell types and projected their signatures onto malignant cells in search for gIPC- and RG-A-like tumor cells. Finally, we leveraged our data to identify drivers of astrogenesis in both normal and malignant tissues.

Results: We found high correspondence between pre- and postnatal, but not adult, cell types and our malignant cell states. Notably, we observed high proportions of prenatal gIPC-like cells in EGFR amplified tumours and postnatal RG-A-like cells in tumours with PFGFRα or FGFR3 amplification. Moreover, we found that gIPC-like cells were highly heterogeneous and exhibited a range of cellular states (astrocyte-, oligodendrocyte progenitor cell-, and neuronal progenitor cell-like), while RG-A-like cells were mesenchymal-like.

Conclusions: Malignant cells exhibited gIPC- and RG-A-like signatures. By applying our knowledge of normal astrocyte lineage maturation, we might differentiate these malignant cells into less proliferative, terminally differentiated astrocytes. As recurrent tumours often transition to a mesenchymal-like state, this strategy holds enormous potential for the development of, not only therapeutic, but also preventative treatments against GBM.

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Full Name	Shawn Rhoads
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Lab	Gu
Department	Psychiatry

TITLE: Assessing social forward planning reliably across in-person, web-based, and mobile app-based platforms

AUTHORS: Shawn A. Rhoads, Matthew Schafer, Soojung Na, Matthew Heflin, Daniela Schiller, & Xiaosi Gu

BACKGROUND: It is estimated that over 6 billion people in the world currently use smartphones. This provides an unparalleled opportunity for scientists to conduct large-scale research on mobile platforms, which has revolutionized the cognitive and behavioral sciences (Brown et al., 2014; Gillan et al., 2016; Teki et al., 2016; Palan and Schitter, 2018). However, due to lack of monetary incentives or user engagement tracking, it remains elusive how reliable mobile-based data collection is, especially for the study of complex, higher-order social cognition.

METHODS: In the present study, we examined a particular form of complex social cognition—social forward planning—across three different data collection platforms: in-person during neuroimaging (N=48), online via web-interface (i.e., Prolific.co; N=1342), and online via novel mobile application (i.e., Social Brain App; N=762, data collection ongoing). These participants completed a social controllability task (Na, Chung et al., 2021) in which they could influence partners' proposals of monetary offers in the future (Controllable) or not (Uncontrollable).

RESULTS: Across platforms, participants successfully influenced their partners' offers in the Controllable condition on average (In-person: $t(47)=3.42$, $p=.001$; Web-based: $t(1341)=20.29$, $p<.0001$; Mobile app: $t(761)=91.40$, $p<.001$). Behavior in the Controllable condition was also consistently best characterized by computational models that captured participants' forward planning of future actions to affect subsequent offers from partners. Key model parameter estimates also did not significantly differ on average, including a parameter indexing participants' expected controllability, which reflects participants' estimate of how much the next offer will change if they reject or accept the current offer (δ; $F(2, 2360)=.24$, $p=0.78$).

CONCLUSIONS: Across three different platforms, we replicated that individuals were able to exert influence on others when given the opportunity by simulating how current choices might affect subsequent social interactions. These findings demonstrate that mobile apps can be leveraged to collect high quality, reliable behavioral data even in complex social contexts, which can eventually enable large-scale investigation of the mental health relevance and socioeconomic correlates of these behaviors.

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Full Name Miguel Rodriguez de los Santos

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Lab Michael Breen

Department Psychiatry

Divergent landscapes of A-to-I editing in postmortem and living human brain

Miguel Rodriguez de los Santos, Ariela Buxbaum Grice, Gauri Ganesh, Andy Yang, Eric Park, Pardis Amini, Sarah Zipkowitz, Lora Larkin, Eric Vornholt, Donjing Liu, Panos Roussos, the Living Brain Project Team, Alexander Charney, Michael S. Breen

Background: Adenosine to inosine (A-to-I) editing represents one of the most abundant RNA modifications catalogued in the human brain and is catalyzed by adenosine deaminases acting on RNA (ADAR) enzymes. Postmortem tissues have been critical for investigating adenosine to inosine (A-to-I) editing in the brain, yet ischemic exposures profoundly impact normal neurophysiology. The current project aimed to quantify the extent to which our view of RNA editing biology may be confounded by post-mortem-induced mechanisms to facilitate accurate physiological and biological interpretation.

Methods: The current study is anchored around state-of-the-art Living Brain Project (LBP) data comprised of paired whole-genome and bulk-tissue RNA sequencing (RNA-seq) of the prefrontal cortex from hundreds of living human biopsies (n=275) and matched postmortem tissues (n=243). A subset of living (n=22) and postmortem (n=21) cortical samples also underwent single-nuclei RNA-sequencing (snRNA-seq). By combining these data with mechanistically related in vitro models and complementary RNA-seq data from across neuronal and non-neuronal cell populations isolated from five cortical areas, we provide a systematic analysis and validation of the fundamental effects of organismal death on A-to-I editing in the human cortex.

Results: Global Alu editing significantly increases after death, including 72,356 dynamically regulated A-to-I sites. This shift is concordant with profound post-mortem-induced activation of innate immunity, inflammation and hypoxia. Further, we fully decode the cellular resolution of A-to-I editing across multiple cortical areas, uncovering profound Alu editing increases in microglia and non-neuronal cells after death. Importantly, in living cortical tissue, A-to-I sites with high editing levels are evolutionarily conserved, neuronal-specific, physiologically essential and are consistent with sites reported to be dynamically regulated in brain development and disease.

Conclusions: This work offers an unobstructed view of RNA editing with deep cellular resolution, promoting a greater understanding of A-to-I modifications in the living human cortex and their dysregulation in disease.

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Understanding the role of the mitochondrial AD risk gene LACTB in myeloid cells.
Carmen Romero-Molina, Wen Yi See, Tulsi Patel, Yiyuan Liu, Edoardo Marcora, Alison Goate.
Background: Although powerful evidence points out the importance of myeloid cells in Alzheimer's Disease (AD), the relevance of immunometabolism requires further exploration. Our analysis integrating AD genetics and myeloid cell genomics reported that lower LACTB expression is protective for AD, and proteomics studies have confirmed it (Wingo et al., 2021). LACTB is a mitochondrial serin protein that may influence mitochondrial morphology and bioenergetics. LACTB levels are associated with succinyl-carnitine levels (Ghazalpour et al., 2014, Suhre et al., 2011), a metabolite that has been linked to AD risk (unpublished). LACTB has also been nominated as a tumor-related and an obesity gene, but its function is not well defined.
Methods: THP1 cells were treated for 6 days with small-interfering RNA to reduce LACTB expression. iPS cells were CRISPR-edited to obtain LACTB knock-out (KO) lines and differentiated into microglial cells (iMGLs). Functional experiments were performed. Collected samples were outsourced for RNAseq, metabolomic and lipidomic analysis.
Results: we characterized, for the first time, the role of LACTB in myeloid cells. We observed that LACTB expression is increased upon differentiation (in iMGLs compared to iPSC, and in THP1 macrophages compared to monocytes) and LPS stimulation. The downregulation of LACTB in THP1 led to an increase in succinyl-carnitine (predicted to be protective for AD), and in histone succinylation, which may modify the cell epigenetics. Transcriptomics revealed an increase in the oxidative phosphorylation, which was validated by Seahorse experiments, and in the immune response to interferon and virus. In addition, LACTB knock-down polarized THP1 macrophages towards a DAM-like state. Lipidomics reported significant changes in specific lipid classes and a decrease in chain saturation. These experiments will be repeated in iMGLs.
Conclusion: LACTB may play a role in cell differentiation and response to stimulus in myeloid cells by modifying mitochondrial respiration and lipid metabolism. As future directions, iMGLs will be xenotransplanted in WT and 5xFAD mice to study LACTB role in vivo. Unlike other AD risk genes, LACTB encodes an enzyme, reduced expression is protective, and succinyl-carnitine can be used as a biomarker, which highlights it as a promising AD therapeutic target.

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Full Name	Bryce Rowan
Job Title	PhD Student
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Department	Neuroscience, Psychiatry, Genomic Genetic Sciences

Title: Large-scale analysis of patient-derived induced neurons discover early developmental changes in schizophrenia

Authors: Bryce Rowan, Xuran Wang, Michael Breen, Joe Friedman, Elodie Drapeau, Kristen Brennand, Tom Rusielewicz, Daniel Paull, and Joseph D. Buxbaum

Background: Schizophrenia is one of the most costly and debilitating psychiatric disorders with an incidence of 1% worldwide along with limited advances in therapeutic development in decades. Schizophrenia shows high heritability from both common and rare variants. These genetic variants and their mechanisms are poorly understood. Potential differences in ancestry have also not been explored, largely due to lack of collecting enough samples from non-European ancestral populations. Differences by sex also warrant further attention, since multiple studies point to differences in prevalence and potential treatments for schizophrenia by sex. We propose to address these issues by looking at gene expression in over 120 donors, some of admixed ancestry, with either idiopathic or 22q11-associated schizophrenia. We will look at differential expression and differential networks in cases and controls and stratify by ancestry and sex effects.

Methods: Donor induced pluripotent stem cells (iPSCs) were induced into glutamatergic and GABAergic neurons, followed by RNAseq. In idiopathic cases, we performed differential gene expression via limma voom, with a weighted least square linear regression model for GABAergic neurons and a linear mixed model was used for glutamatergic neurons due to cloning. We performed enrichment analysis, and then compared results to Common Mind results in bulk and single cell datasets. We performed weighted gene coexpression analysis (WGCNA) in cases and controls separately and then compared differential expression of modules detected in each one. We also performed WGCNA in a combined case-control dataset.

Results: Differential gene expression analyses were negative for both derived cell types. However, we found statistically significant by multiple correction enrichment for similar genes differentially expressed in Common Mind bulk data and Molecular Signature Database (MSigDB) known schizophrenia risk genes. WGCNA detected some sets of genes more expressed in cases than controls and vice versa. In the combined case-control results, WGCNA detected 2 modules that were statistically significant (> 0.05) without multiple testing corrections. One of these modules was also statistically significant for sex differences after multiple test corrections.

Discussion: We found network module differences in gene expression between cases and controls via WGCNA as well as enrichment for differentially expressed in Common Mind bulk tissue. We will repeat these analyses in stratified groups of sex, ancestry, and ancestry by sex. Then, we will perform eQTL, local ancestry eQTL, secondary RNA analyses, and compare 22q11 to idiopathic schizophrenia cell lines, resulting in potentially novel therapeutics.

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Full Name	Sharna Saha
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Title: Targeting metabolic genes with RNAi and drugs to delay Alzheimer's pathology using the model organism Caenorhabditis elegans.
Genetic and pharmacological screen to inhibit metabolic genes to delay Alzheimer's disease using the model organism Caenorhabditis elegans.

Authors:Sharna Saha, Kun-Hyung Roh, Ojee Sharma, Brandon Clarke, Damian Gonzalez, Rachel Litke, Charles Mobbs

Introduction: Alzheimer's disease (AD) is a devastating neurodegenerative disease with no cure as of today. The importance of new potential mechanisms in the pathophysiology of AD has become increasingly clear, among which, possible therapeutic targets such as mitochondrial dysfunction and metabolism dysregulations.We hypothesize that modulation of metabolic gene expression could delay Alzheimer's pathology. To approach this, we are using a Caenorhabditis elegans muscle model of AD with amyloid-beta-induced-paralysis.
Methods: First, we conducted an RNAi screen of 32 metabolic genes reported to extend lifespan in C.elegans and assessed their ability to delay paralysis in an AD model of C. elegans. As genetic manipulation is not a feasible option in humans, we searched for drugs that could modulate the expression of these protective metabolic genes. Then, using bioinformatic analysis of the scREAD and CMap databases, we selected drugs that inhibit metabolic genes found to be protective in vivo. Finally, we tested the selected drugs in our model of AD for their ability to delay paralysis in a liquid medium. Worms were filmed every 2-3 days and videos were analyzed to score worms as alive, paralyzed, or dead. Statistical analysis was conducted using a Kaplan-Meier survival curve.
Results: Interestingly, down regulation of 4 of the 32 metabolic genes (atp-1, tkt-1, mrps-30, and daf-2) significantly delayed worm paralysis in our model of AD($p<0.001$). The bioinformatic analysis identified 10 drugs that inhibit all 4 metabolic genes. Three of the drugs tested diminazene aceturate, epirubucin, and amsacrine showed a significant delay in paralysis compared to the control ($p<0.05$).
Discussion: Three drugs were identified as a potential therapeutic option to treat Alzheimer's disease in humans. By conducting research exploring possible mechanisms of AD and finding commonalities, the pertinent information can be used to develop novel therapies for AD. Further research still needs to be conducted to study how inhibiting genes in specific metabolic processes delay AD.

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Structural and Oxygen Metabolic Magnetic Resonance Imaging of long-COVID and ME/CFS

Sera Saju, Michelle Blate, Tiffany Soto, Benjamin Natelson, Xiang Xu

Background
A large and increasing number of patients who have been infected with SARS-CoV-2, continue to experience a constellation of symptoms long past the time that they have recovered from the initial illness (post-acute SARS CoV Infection or PASC). The most frequently reported symptoms were fatigue, post exertional malaise and cognitive dysfunction, which are the main symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Clinically, many of the PASC patients fulfill diagnostic criteria for ME/CFS. For both conditions, no specific neuroimaging biomarkers have been identified. In this project, we are conducting comprehensive brain magnetic resonance imaging (MRI) to determine similarities or differences in brain anatomy and metabolism between PASC and non-PASC ME/CFS patients, as well as healthy well individuals.

Methods: Multiparametric MRIs: (1) high resolution comprehensive brain structural imaging to quantify any lesions, hyper/hypointensities, brain volumes and atrophy; (2) in vivo measurement of venous oxygenation in the draining vessels of brain and global cerebral blood flow using MRI. Behavioral: A Likert scale questionnaire used in the diagnosis of ME/CFS was utilized for assessing the general symptom burden. An additional behavioral assessment specific to fatigue level was evaluated using the Multidimensional Fatigue Inventory and the physical functioning scale (PFS) of the Short Form 36. Patients' rating of their symptom burden and fatigue level determined by each behavioral assessment were correlated to the MRI derived parameters respectively.

Results: White matter hyperintensities (Fazekas scale 1) were identified in a few participants. No difference in oxygen saturation (SpO2) was observed among the three groups. A Significant difference in venous oxygen saturation level, Yv, was observed among the three groups (Kruskal-Wallis rank sum test, $p = 0.0074$). Pair-wise comparison showed that the PASC group had significant lower Yv than both the healthy control group and the classic CFS group (Wilcoxon rank sum test, $p = 0.004$ and 0.0173, respectively). The Yv of of the non-PASC CFS group did not differ significantly from healthy controls. A strong correlation ($r=0.61$) was found between the PFS and Yv.

Conclusion: This is an on-going study. Based on the current limited data size, we conclude that structural changes are unlikely specific to ME/CFS either with or without PASC. Oxygen extraction fraction, which is defined by the difference between SpO2 and Yv, is significant higher for PASC-ME/CFS patients as compared to non-PASC-ME/CFS or healthy controls. The oxygen extraction fraction is correlated with physical function.

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Full Name	Marcos Schaan Profes
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Department	Pathology

An optogenetic cellular system for high throughput analysis of tau aggregation and related drivers

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

BACKGROUND: Tauopathies are a category of neurodegenerative disorders characterized by abnormal tau accumulation in the brain with diverse movement and cognitive symptoms. Tauopathies can be subdivided depending on the dominant tau isoform, which may have three microtubule binding domain repeats (3R), four (4R), or a mixture of both (3R/4R). There is currently a gap in our understanding of the cellular mechanisms that lead to neuronal dysfunction and death in the tau proteinopathies reflecting the current lack of effective treatments. Therefore, there is a critical need for further studying the cellular and molecular etiology of tauopathies.

METHODS: Here, we developed an optogenetic inducible tau aggregation system (Opto-Tau) suitable for high-throughput analysis. CRY2 protein that changes conformation upon light activation was used as an optogenetic actuator to enable spatiotemporal control over protein aggregation in living cells. This Opto-Tau system was evaluated by biochemistry methods for the presence of aberrant tau aggregates in vitro. Live imaging and biochemistry will investigate tau aggregation kinetics and cellular burden due to imbalances in tau isoforms and known mutations. We will leverage Opto-Tau with overexpression and knockdown experiments to advance our knowledge to tauopathy-associated factors.

RESULTS: Our preliminary data showed mCherry fluorescent stable in SH-SY5Y transfected with the engineered constructs, indicating the presence of tau aggregates and supporting the feasibility of generating tau aggregates in our cellular system. We also engineered constructs of the 0N4R isoform with known tauopathy-related mutations: P301L, R406W and the V337M. All three mutations, upon transfection, also displayed stabled inclusions.

CONCLUSIONS: This research has the potential to enhance the screening process of possible tau aggregation drivers by creating a reliable, robust, but also flexible cellular tau aggregation model that will allow us not only to analyze in real time tau aggregation in a precise and spatiotemporal resolution, but also being compatible to be performed in parallel with many other biochemical assays to assess other burdened biological processes, such as protein aggregation, misfolding quality control pathways, oxidative stress, and other mechanisms. This model could also pose a new suitable model for drug screening.

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CONNECTIVITY MAPS OF ALIC DEEP BRAIN STIMULATION FOR OBSESSIVE-COMPULSIVE DISORDER

Alba Segura Amil (1,2,3), Ki Sueng Choi (1), Helen S Mayberg (1), Bryan H Koppell (1), Martijn Figee (1)

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BACKGROUND: Deep brain stimulation (DBS) is a surgical treatment option for patients with treatment-resistant obsessive-compulsive disorder (OCD). Although it can be an effective treatment, it is uncertain which brain networks must be stimulated for an optimal clinical response. The aim of the study was to build a tractography-based connectivity map of the implicated white matter tracts of anterior limb of the internal capsule (ALIC) DBS for OCD.

METHODS: 9 OCD patients were implanted with DBS leads in the ALIC at Mount Sinai in New York. 6 patients achieved clinical response after stimulation (>35% Y-BOCS improvement). DBS leads were localized with the Lead-DBS toolbox to generate the volumes of tissue activated (VTAs). Using the VTAs as seed, patient-specific tractography was generated to the rest of the brain using FSL Bedpostx. To obtain the first map, we averaged the generated streamlines of the 6 responder patients. For the second map, we weighted the streamlines of the 9 patients by the % of Y-BOCS improvement and then averaged them. In both cases, we obtained the connectivity of the averaged streamlines to the cortex.

RESULTS: Both connectivity maps reflected connections to the ventromedial prefrontal cortex, ventrolateral prefrontal cortex and to the midbrain.

CONCLUSION: Our tentative connectivity maps indicate that connectivity to the ventromedial prefrontal cortex, ventrolateral prefrontal cortex and to the midbrain could be related to good clinical outcomes. Future work will expand these maps to better understand which white matter tracts passing the ALIC should be activated for an optimal clinical response.

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Full Name	Jeremy Sherman
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RNA-Sequencing of the Dorsal Striatum Identifies PRC2 Complex as a Potential Epigenetic Regulator of Neuronal Morphology induced by Heroin Use

Jeremy Sherman, Randy Ellis PhD, Maria (Eli) Savoia, Adam Dawoud, Joseph Landry, James Callens, Yasmin L. Hurd PhD

BACKGROUND: Opioid use is an epidemic with overdoses claiming 80,000 lives annually. The dorsal striatum plays a critical role in the transition from drug taking to addiction, with subregions such as posterior dorsomedial (pDMS) and anterior dorsolateral (aDLS) mediating motivated and compulsive use respectively. RNA-sequencing is a powerful tool for characterizing alterations in the transcriptome that can help identify key regulatory biological processes associated with gene perturbations.

METHODS: The aDLS and pDMS of 10 rats that self-administered heroin and 10 saline controls were sequenced for bulk RNA while the remaining dorsal striatum tissue underwent single nuclei-RNA sequencing. Differential expression analysis examined the effect of heroin within each subregion, across all samples controlling for subregion, and heroin-by-subregion interactions, followed by ontological analysis. The results were compared to ATAC-sequencing and RNA-sequencing data obtained from post-mortem dorsal striatal samples from human heroin users and control individuals.

RESULTS: The greatest difference in gene expression was observed in the pDMS, though these changes were highly concordant with the expression pattern in aDLS, suggesting similar effects of heroin throughout the dorsal striatum. The upregulated genes in pDMS and across all samples were enriched for genes that regulate axon guidance through receptor tyrosine kinase signaling such as integrin, semaphorin, netrin, and ephrin systems. The epigenetic regulator most associated with the differentially expressed genes was the PRC2 complex. Furthermore, there was significant overlap between these two ontological networks, where the genes regulated by PRC2 were also involved in axon guidance. These results match those seen using a multiomic approach in post-mortem human samples, which showed heroin use increased chromatin accessibility and RNA transcripts from regions regulated by PRC2 and implicated in neuron morphology. Single-nuclei RNA-sequencing analyses are currently underway.

CONCLUSIONS: Increased expression of genes shown to be regulated by PRC2 appears to be a conserved feature of heroin use across humans and rats. PRC2 is an epigenetic regulator that deposits H3K27me3 repressive marks and has been implicated in neurodegeneration. Interestingly, our group has shown significant links between opioid use and neurocognitive disease and its pathological hallmarks. The heroin-related gene networks currently identified are strongly associated with neuron morphology, which is also disrupted in the striatum after heroin use. These functional networks regulated by PRC2 may provide critical insight into the pathophysiology of heroin use disorder and potential druggable targets for future therapeutic intervention.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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Dissecting the role of a brainstem cardiorespiratory circuit in fear regulation

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BACKGROUND: Post-traumatic stress disorder (PTSD) is characterized by persistent maladaptive fear responses after exposure to severe psychological trauma and is highly comorbid with cardiorespiratory dysfunction. Alterations in fear behaviors and cardiorespiratory functions are modulated by the sympathetic and parasympathetic nervous systems. However, the mechanisms underlying the association between PTSD and cardiorespiratory health are poorly understood. We examined the role of nucleus ambiguus (NA)- a brainstem region that projects to the heart and modulates parasympathetic signaling, as well as the role of preBötzinger complex (preBötC)- respiratory rhythm generator in the brainstem, in behavioral and cardiorespiratory dysfunctions. We investigated the role of the neuropeptide PACAP and its receptor PAC1 which play a role in central and peripheral stress responses and are highly expressed in the NA and preBötC. We hypothesized that NA to preBötC PACAPergic innervation may be important regulators of stress and cardiorespiratory outcomes.

METHODS: We injected either excitatory/inhibitory DREADDS receptors (hM3/hM4) expressing AAV /control AAV-GFP virus into the NA of PACAP-Cre mice. Separately, in the preBötC of PAC1-floxed mice, we injected the AAV-GFP-Cre virus for Cre-mediated deletion of PAC1 receptors. After three weeks of viral expression in both groups of mice, we had them go through the stress-enhanced fear learning (SEFL) protocol, a rodent model that recapitulates aspects of PTSD-like fear. We also performed an open-field light gradient task to measure anxiety-like phenotypes. We also paired the behavioral tasks with telemetry to capture real-time cardiorespiratory changes. Additionally, we measured changes in metabolism using indirect calorimetric measures. Finally, we sacrificed the mice and analyzed immune cell expression in blood, bone marrow, and heart using spectral flow cytometry.

RESULTS: We found that chemogenetic excitation of PACAPergic neurons in the NA, reduced heart rate, freezing behavior, and myeloid hematopoiesis in mice that went through SEFL. Chemogenetic inhibition of PACAPergic neurons in the NA reduced shock reactivity, increased heart rate, and immune markers in the periphery in mice that went through SEFL. Deletion of PAC1 receptor-expressing neurons in the preBötC led to disruption in breathing rhythms in mice that went through SEFL.

CONCLUSIONS: By studying the brain and body interactions of a molecularly defined pathway from the NA and preBötC to the heart/lungs, we are now able to ask questions about the link between PTSD and cardiorespiratory health. This has great advantages for translating our findings into personalized medicine to tailor the treatment and prevention of PTSD and PTSD-associated cardiorespiratory disorders.

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Social controllability and resilience to childhood trauma

Blair R. K. Shevlin, Xiaosi Gu

Background
Individual differences in stress responsivity to trauma can greatly affect psychological functioning, including sociability and susceptibility for mental health disorders. In this study, we explored how traumatic stress impacts the cognitive mechanisms needed to navigate proactive social interactions.

Methods
We recruited 1492 participants through the Prolific web-based platform. Participants completed a social decision-making task involving monetary exchanges, along with surveys assessing adverse childhood events, mental health, and demographics. Participants were filtered and grouped based on their endorsement of childhood trauma (ACE) and current psychological distress (SDS, STAI-S): healthy controls (ACE=0,SDS<50,STAI-S <40;n=211), distressed controls (ACE=0,SDS>50, STAI-S >40;n=35), resilient trauma-exposed (ACE>4,SDS<50, STAI-S <40;n=37), distressed trauma-exposed (ACE>4,SDS>50, STAI-S >40;n=184). We used computational modeling to assess decision-making parameters.

Results
In the social decision-making task, resilient trauma-exposed individuals received better offers than healthy controls ($p<.001$), distressed controls ($p<.001$), and distressed trauma-exposed ($p<.001$) groups. Computational modeling indicates that this improved performance was because these resilient individuals had elevated learning rates than both healthy controls ($p=.016$) and distressed trauma-exposed groups ($p=.011$), suggesting more proficient adaptation to task-relevant information. Comparing resilient trauma-exposed individuals to the distressed trauma-exposed group, the former were also better calibrated to the controllability of the task conditions ($p=.043$).

Conclusions
Our results suggest that trauma-exposed individuals with low psychological distress are remarkably proficient in proactive social decision-making. This proficiency was likely due to a combination of increased adaptation rates and well-calibrated beliefs about their ability to exert control over the task environment.

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Thenzing J. Silva-Hurtado. DVM, PhD. , Balagopal Pai. PhD., Susana Isabel Ramos. PhD., Dolores Hambardzumyan. PhD, MBA. Raymund L. Yong. MD, MS, FRCS (C) and Nadejda M. Tsankova. MD, PhD.

Abstract

Glioblastoma (GBM) is a deadly neoplasm with a median overall survival of 12-15 months. Recent studies have demonstrated new insights into the heterogeneity of this brain cancer. Nevertheless, most GBM subtypes share an infiltrating feature making it inevitable for a subset of tumor cells to avoid surgery resection and localized radiation therapies and representing a major difficulty for effective treatment. Most research done up to this point has been centered on treating the core of the tumor, which consists of irregular necrotic regions surrounded by dense accumulations of tumor cells. In this landscape, our research project opts to focus on GBM cell migratory properties at the intersection between tumoral borders and healthy tissue. We address this by utilizing the YAP-TEAD inhibitor verteporfin, which has been previously described to possess a decreasing effect on migration and invasion dynamics among different GBM types in vitro and in xenograft mouse models. Our goal is to validate this effect in human GBM ex vivo. Therefore, we are currently optimizing organotypic slice cultures obtained from patients undergoing tumor resection, focusing on the infiltrative margin. In this tissue cultures, we are performing confocal timelapse imaging after cell labeling with GFP to collect data about cell migration properties, such as speed and directionality. Henceforth, we will treat with YAP-TEAD inhibitors in order to determine if tumor migration is decreased after treatment. Furthermore, we will correlate tumor genomics to anti-migratory effects and will use immunohistochemistry to investigate treatment-related effects on the tumor microenvironment. Our preliminary data suggests that there is a beneficial effect on migratory neoplastic cells ex-vivo, which indicates that YAP-TEAD inhibitors could potentially be implemented as a therapeutic treatment along with current GBM treatments.

Key words: Glioblastoma, cell migration, YAP-TEAD inhibitors

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Anterior cingulate cortex neurons encode social but not nonsocial image identity during decision-making task.

Joseph Simon IV, Erin Rich

Background: Humans and nonhuman primates live in complex social environments that require them to process unique social information. Processing of this information has been linked to many brain regions including the anterior cingulate cortex (ACC), specifically the ACC gyrus. Here, we asked if this region more strongly encodes information from a social context, relative to a nonsocial, when the desired outcome is the same (i.e., when both predict reward target's location).

Methods: To test this, we targeted the ACC gyrus in two rhesus monkeys performing a reward localization task. Monkeys had to use social (i.e., eye gaze) or nonsocial (i.e., arrow direction) visual guides to locate the reward target. We recorded from neurons within the ACC and the frontal eye field (FEF), a region that hasn't reported any specificity for social information. We performed a regression using a sliding window to determine the effects of image type on neuron activity.

Results: We found that monkeys were able to locate the rewarding target above chance levels and were significantly better at nonsocial images compared to social. A binomial test found a significant difference between social and nonsocial in the ACC. More specifically, it found that the number of neurons that responded to social information in the ACC was significantly greater than nonsocial information.

Conclusions: Social information is an important contributor to decision-making. Here, we have found that during choice monkeys are able to use both (social and nonsocial) visual guides to make correct choices. How this information is interpreted in the ACC, seems to be separated with only social information showing significant encoding.

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Full Name	Ivan Soler
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Progression of entorhinal spatial coding deficits in a mouse model of temporal lobe epilepsy

I Soler, Y Feng, A Jurkowski, S Lamsifer, K Diego, N Khan, P Dong, Z Pennington, C Kentros, N Yang, T Shuman

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

METHODS: Our approach employs vector constructs for layer specific calcium indicator expression in MECII stellate cell and MECIII neuronal inputs to CA1 alongside in vivo calcium imaging with miniature microscopes in freely behaving mice as they perform a battery of spatial foraging or memory tasks.

RESULTS: Our preliminary data suggests pilocarpine induced TLE causes disruptions to the spatial coding of both MECII stellate cells and MECIII neurons, thus explaining -- at least in part -- the degradation of encoding functionally downstream in CA1. Specifically, epileptic mice have lower MECIII neuron information content while both MECII stellate cells and MECIII neurons trend toward progressive stability deficits.

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

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Tractography Analysis of Subcallosal Cingulate DBS for Treatment-Resistant Depression Using Normative Connectome Data

Ha Neul Song, Gavin Elias, Jurgen Germann, Alexandre Boutet, Andres Lozano, Helen S Mayberg, Ki Sueng Choi

BACKGROUND: SCC-DBS for treatment-resistant depression has demonstrated sustained response and remission rates. SCC-DBS targeting evolved from anatomy-based to connectome-based targeting, now stimulating convergence of three (forceps minor (FM), cingulum bundle (CB), and subcortical-junction (SJ)) white matter (WM) pathways, with improved clinical efficacy. However, there is response variability that might be explained by differences in WM activation pathways. We evaluated the relationship of WM activation pathways to clinical improvement in large number of patients using normative connectome data.

METHODS: Three different cohorts of SCC-DBS data were combined. Based on changes in HDRS-17 defined at 1 year (cohort1) or 2 year (cohort2&3) time point, one-hundred-forty-three patients were analyzed and divided into two groups: responders (n=84,HDRS$\geq$50%) and non-responders (n=59,HDRS<50%). After registering images of postoperative to preoperative MRI and reconstructing electrode trajectories in MNI space, volumes of tissue activated (VTA) and E-fields were estimated in all patients using Lead-DBS software. At the group level, three different analyses were conducted. First, each group's common WM activation pathways were generated using normative-connectome data and compared among two groups in each cohort. Second, probabilistic stimulation maps (PSMs) were calculated in each cohort to find optimal SCC target in MNI space. Finally, permutation-based linear regression was conducted between E-field and HDRS to find activation pathways explaining HDRS in each cohort.

RESULTS: We found WM activation differentiated among the two groups; Responders shared full activation of CB and FM pathways, but non-responders were missing one of pathways. Moreover, left VTA produced greater pathway activation in responders than non-responders. For PSM, although high value voxels indicating optimal DBS target regions were differed among three cohorts, when cohorts were combined, the voxels located in SCC WM at left (X=-12,Y=30,Z=-11) and SCC WM-GM boundary at right (X=6,Y=28,Z=-13). Finally, full activation CB and FM pathways were significantly correlated with HDRS improvement. Specifically, posterior FM connecting left and right SCC was more involved with HDRS than anterior FM reaching to frontal areas.

CONCLUSIONS: Current study first confirmed the importance of CB and FM activation using large data in normative connectome data. This suggests SCC targeting should maximize bilateral CB and FM for achieving maximal antidepressant benefit. Consistent methods for tractography-guided surgical targeting are likely required for optimal SCC-DBS outcomes.

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Full Name	Frederic Stoll
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Outcome preferences dynamically modulate representations of reward identity and probability in prefrontal-limbic circuits

Frederic M. Stoll & Peter H. Rudebeck

BACKGROUND: Deciding optimally requires the integration of multiple features, some of them extracted from the external world whereas others are solely based on our experiences and internal state. Parts of frontal cortex including orbitofrontal (OFC) and ventrolateral prefrontal cortex (vlPFC) are seen as central to how we combine, integrate, and use value information to guide decision-making. However, their specific roles are unclear. Here we aimed to identify the neural mechanisms by which prefrontal-limbic circuits dynamically encode the probability of receiving an outcome and its identity, and how these representations are modulated by the animal's internal state.

METHODS: We recorded the activity of thousands of neurons within multiple frontal structures including vlPFC, OFC, inferior frontal gyrus (IFG), and agranular insula (AI) as well as amygdala during tasks where the probability of receiving different outcomes was manipulated. Specifically, monkeys were free to choose between two visually distinct stimuli, each of them associated with a specific probability of receiving one of two outcomes (fruit juices) distinct by its identity. We investigated how individual neuron and population responses related to outcome probability and identity using a range of encoding/decoding analysis approaches. We finally assessed how animals' preferences for specific outcome identities, and changes in the animal internal state over time, impacted the strength of these representations in frontal cortex, both between and within sessions.

RESULTS: We found that neurons in OFC more strongly encoded the chosen outcome identity compared to neurons in other areas. Neurons in vlPFC and IFG, however, mainly encoded the chosen probability, whereas amygdala neurons represented both information well. The strength of monkeys' preference toward a particular identity not only correlated with the degree to which outcome identity was represented in all areas but also influenced outcome probability representations in vlPFC and OFC. Notably, in vlPFC, preferences altered the degree to which outcome probability for the least favored juice could be decoded. Finally, we found that local modulation of preference within a session had a ubiquitous influence on neurons in all areas, with stronger modulations in neurons that encoded probability and/or identity within the OFC and AI.

CONCLUSIONS: Our data provide new insight on how representation of outcome identity and probability are integrated, and dynamically modulated, within prefrontal-limbic circuits.

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Department	Neuroscience

Diabetes alters economically dissociable decision-making algorithms depending on the salience of reward scarcity in the environment

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BACKGROUND: Individuals with diabetes mellitus are at significantly higher risk of developing depression and other psychiatric disorders. Although diabetes is primarily characterized by chronic hyperglycemia, it remains unclear how impaired insulin function, which is known to have direct effects on neural activity, regulates motivated behavior.

METHODS: We characterized value-based decision-making of an insulin-deficient diabetic mouse model on a complex naturalistic neuroeconomic foraging paradigm. 40 8-week old CB57BL/6J male mice were injected with either vehicle (VEH) or streptozotocin (STZ), an antibiotic that ablates insulin producing beta cells in the pancreas, to induce hyperglycemia. Mice were then tested longitudinally across two months on the “Restaurant Row” task during which they foraged daily for their primary source of food while on a limited time budget. Mice learned to make serial decisions accepting or rejecting reward offers as a function of cost (delays cued by tone pitch) and subjective value (flavors cued by unique spatial contexts).

RESULTS: Mice were trained on two different schedules during which the economic landscape (i) drastically or (ii) gradually progressed into an increasingly reward-scarce environment. Overall, STZ-treated mice earned less food but shifted meal consumption patterns in complex ways based on the revealed preferences of various flavors. Vicarious trial and error behavior, a proxy of deliberation, revealed decreased decision conflict for less-preferred flavors in STZ-treated mice. These findings were divorced from individual differences in economic choice policies, which were uniquely modulated in STZ-treated mice depending on their prior training schedules. Interestingly, we found that groups of mice valued the passage of time differently based on the type of choice being made. During change-of-mind decisions, mice became sensitive to the magnitude of time spent waiting, or “sunk costs,” in altering the probability of earning a reward but only after transitioning into a reward-scarce environment - except STZ-treated mice trained on a gradual schedule, who surprisingly never developed sensitivity to sunk costs.

CONCLUSIONS: Deliberative and re-evaluative choice algorithms, which have been previously shown to be processed in physically separable circuits in the brain, may be differentially perturbed in a mouse model of insulin-deficient diabetes. These findings suggest that complex relationships between glycemic regulation, realized scarcity of the environment, and different types of opportunity costs interact to influence dissociable decision-making systems and fundamentally distinct behavioral computations underlying unique aspects of reward value.

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CHARACTERIZATION OF FOLLICLE STIMULATING HORMONE IN DOWN SYNDROME MOUSE MODEL Ts65Dn

Angel Tang, Jocelyn Widjaja, JoColl Burgess, Ki A. Goosens PhD

BACKGROUND

Down Syndrome (DS) is a congenital condition caused by trisomy 21, which can lead to mental and physical delays. Previous research has shown that patients with DS show a high prevalence of obesity, osteoporosis, and early-onset Alzheimer's disease. Recently, these diseases have been linked to high levels of follicle-stimulating hormone (FSH), a peptide hormone secreted by the pituitary gland into the bloodstream. It was reported that children and adolescents with DS have dysregulated levels of gonadal hormones and impaired sex development. Children with DS also showed elevated FSH levels. Hence, we sought to characterize FSH in the DS mouse model Ts65Dn and validate previous findings regarding developmental differences.

METHODS

We used enzyme-linked immunosorbent assay (ELISA) to measure circulating FSH levels in serum samples obtained from both female and male WT and Ts65Dn mice. We weighed the mice daily from birth until 21 days to observe growth differences. We measured fat and lean mass in WT and DS mice with quantitative magnetic resonance imaging (qMRI) and bone mineral density with Dual-energy X-ray absorptiometry (DEXA).

RESULTS

Our findings are consistent with previous clinical research on FSH in DS individuals. We found that male DS mice have significantly higher levels of FSH. Additionally, female and male DS displayed lower lean mass and bone mineral density in their tibia, femur, and whole body compared to WT mice. There is also a growth difference between DS and WT mice starting from when they are 7 days old.

CONCLUSIONS

Our findings suggest that Ts65Dn mice are a robust model for further investigating the link between development impairments such as osteoporosis and body mass linked to increased circulating FSH. These findings create an opportunity for a therapy targeting FSH to help with these conditions in DS patients.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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BACKGROUND: The ability to assign motivational value to a neutral stimulus is crucial for survival, and the reward circuitry is responsible for encoding this learning. Alcohol disrupts this circuitry by inducing uncontrolled dopamine (DA) elevations in the NAc, leading to altered reward processing. In this study, we investigated the dynamics of alcohol-induced alterations in the reward circuitry of D1-MSN mice using genetically-encoded DA and Ca2+ sensors.
METHODS: We infused AAV9 hsyn-DA2m (GRABDA) and AAV9 FLEX-jGCaMP7s into the NAc core of D1-cre mice using stereotaxic virus injection and cannula implantation. Fiber photometry was used to monitor DA release and D1-MSN activity, and conditioned place preference and two-bottle choice tests were used to measure alcohol preference.
RESULTS: We found that DA release and D1-MSN activity were synchronized across hemispheres and positively correlated, but disrupted by acute ethanol exposure. Ethanol induced burst-like inhibition on D1-MSN activity. Mice showed preference for ethanol, and a high DA-D1 correlation was observed during alcohol-specific behaviors. We also extended the study to other neuronal populations in the NAc core, such as D2-MSN and cholinergic interneurons. Furthermore, we investigated NAc core projections and found that Prelimbic Cortex and Baso-Lateral Amygdala are key projections to the NAc Core. Currently, we are collecting data using a similar strategy, maintaining the DA sensor in one hemisphere and studying activity with GCaMP in different populations, such as D2-MSN and cholinergic interneurons or NAc-PrL/BLA projections, in the other hemisphere.
CONCLUSIONS: Our results so far suggest that normal behavior is characterized by synchronized DA release and D1-MSN activity in the NAc core, which is disrupted by acute ethanol exposure. Ethanol induces burst-like inhibition of D1-MSN activity, potentially contributing to altered reward processing. Temporal dopamine activation and high DA-D1 correlation are observed during alcohol-specific behaviors, supporting the role of the reward circuitry in alcohol preference. These findings contribute to the understanding of the mechanisms underlying alcohol addiction and may inform the development of new treatments.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Emily Teichman
Job Title	PhD student
Lab	Dr. Ming-Hu Han (run by Dr. Carole Morel), Dr. Paul Slesinger, Dr. Jian Jin
Department	Pharmacological Sciences

Antidepressant drug discovery to target a midbrain dopaminergic HCN channelopathy

Emily M Teichman, Jianping Hu, Xiaoping Hu, Carole Morel, Jian Jin, Ming-Hu Han

Background: Depression is a devastating disease associated with profound neurophysiological alterations. Upregulation of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in ventral tegmental area (VTA) dopamine neurons is associated with depressive-like symptomology in mice. Alleviation of these symptoms occurs when HCN channels are inhibited by Cilobradine a blood brain barrier (BBB)-penetrant analog of Ivabradine, an FDA-approved drug to treat heart disease. Here, we aim to augment and refine the HCN-inhibiting, minimally BBB-penetrant features of Cilobradine so as to improve rapid-acting and long-lasting therapeutic effects.

Methods: Utilizing medicinal chemistry and drug design, we synthesized 11 analogs of Cilobradine and 1 analog of Zatebradine. We then combined ex vivo and in vivo electrophysiological approaches to investigate the effects of these analogs on VTA dopamine neuron Ih current and firing rate of C57Bl6J adult mice. We also determined the pharmacokinetic profile and brain plasma ratios (BPR) of the potent analogs. Using the chronic social defeat stress model to capture features of depressive behaviors in mice, we further characterized their antidepressant effects utilizing operant behavioral assays adapted from human studies.

Results: We demonstrated that the analogs have a variety of inhibitory effects on Ih currents in VTA dopamine neurons. Compounds 10 and 12 were chosen for further study based on their strong inhibition of both the Ih current and firing rate; Cilobradine reduced the firing rate of VTA dopamine neurons by 66%, while C10 and C12 led to 91.5% and 92.4% reductions, respectively. Pharmacokinetic analysis determined that the BPR of C10 and C12 are 0.28 and 0.57, respectively, greatly improved from the 0.076 BPR of parent compound Cilobradine. Continued exploration of C10 and C12 with in vivo electrophysiology demonstrated a potent decrease in firing rate and bursts at lower concentrations than Cilobradine, corroborating their ex vivo inhibitory effect in a more physiological system. Behavioral assays examining the effect of the compounds in vivo are ongoing.

Conclusions: We demonstrate that minimal changes to the Cilobradine scaffold can alter, and even improve, its inhibitory effect on VTA dopamine neurons. Furthermore, these minimal changes can drastically improve its BBB permeability. Ongoing studies will assess the antidepressant behavioral effects of compounds 10 and 12 in vivo. The compounds will also be sent to the NIMH PDSP to profile their effects on other molecular targets in the brain and body. Our results provide a new avenue of research for the development of novel therapeutics to alleviate psychiatric disorders associated with dopamine dysfunctions.

2023 Neuroscience Retreat

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Full Name	Shelly Teng
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Development and validation of machine learning models for prediction of post-operative delirium using preoperative EHR data

Authors: Shelly Teng, BSE, Ira Hofer, MD

BACKGROUND: Post-operative delirium (POD) is one of the most common adverse outcomes following surgery, particularly in older adults, and can lead to increased risk of readmission, all-cause mortality, and long-term cognitive and functional decline. Although 30-40% of POD cases are preventable, there are no reliable and scalable ways to identify high-risk patients. The use of machine learning models in predicting postoperative outcomes is an emerging area of promise, especially given the large volume of electronic health records (EHR) data. While some models have demonstrated robust performance in using EHR data to predict outcomes such as acute kidney injury or all-cause mortality, current literature for machine learning prediction of POD shows large variation in model performance.

This study aims to develop and validate several machine learning models to predict postoperative delirium within one week after surgery using preoperative features extracted from the EHR.

METHODS: A retrospective analysis of EHR data from 26,121 adult patients who underwent any type of surgery and had delirium assessed using the confusion assessment method (CAM) at Mount Sinai Health System hospitals between June 19, 2018 to November 10, 2022 was conducted. A total of 103 features were extracted from preoperative EHR data which included patient demographics, vitals, surgical information, labs, and medications. The data was randomly split into a training set (80%) and testing set (20%) to develop and evaluate two main machine learning algorithms, logistic regression and XGBoost.

RESULTS: The patient sample had an overall delirium incidence of 4.39%. The logistic regression (LR) model achieved an accuracy of 0.92 and an AUROC score of 0.74 with a specificity of 0.95 when adjusted for class imbalance and optimized with a threshold of 0.78. The XGBoost model performed similarly to the LR model with an accuracy of 0.93 and an AUROC score of 0.72 with a specificity of 0.96 when adjusted for class imbalance and optimized with a threshold of 0.62. Analysis of feature importance using random forest classifiers shows the top features are age, surgery length, BMI, and vitals.

CONCLUSIONS: This study demonstrates the potential use of ML models in predicting POD using preoperative EHR data as features. Overall performance of XGBoost and LR models suggests the inherent class imbalance introduced by delirium incidence may be important in further exploration and clinical implications of using machine learning to predict POD.

2023 Neuroscience Retreat

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Full Name	Alissa Valentine
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Department	CBIPM; Neuroscience?

Investigating the diagnostic bias of schizophrenia in Mount Sinai Health-System

Alissa A. Valentine, Alexander W. Charney, Isotta Landi

Schizophrenia (SCZ) is amongst the most disabling medical conditions due to its cognitive and social impairments. SCZ diagnoses are intersectional, such that Black people are diagnosed 2-4 times the rate of White people in the United States, and males are diagnosed 1.4 times the rate of females. These findings have yet to be replicated in Mount Sinai Health-System (MSHS), the largest health care system of New York City.

This project investigates the effect of race and gender on SCZ diagnosis in MSHS leveraging electronic health record (EHR) data from patients seen in emergency department, inpatient, or outpatient settings between March 2006 – January 2023. The SCZ cohort consists of patients with at least one F20-29 ICD diagnosis (N = 12,105; 62% Black; 56% male). Three control groups were used to understand SCZ in psychiatric and non-psychiatric contexts: 1) patients with no SCZ diagnosis (N=2,506,838; 28% Black; 44% male); 2) patients with no psychiatric diagnoses (N=2,312,440; 28% Black; 44% male); 3) patients with at least one psychiatric diagnosis and no SCZ diagnosis (N=194,398; 28% Black; 44% male).

A logistic regression was conducted with each control group to test the association between SCZ diagnosis and patient age, socioeconomic status (SES), the interaction of race and gender, and risk factors of SCZ including substance, or trauma/stress-related disorders. There is a significant interaction of race and gender ($p<0.001$) such that being Black and male has on average a 1.4x10-2 larger log odds of being diagnosed with SCZ than race or gender alone. Higher SES (R1: ß=-9.8x10-9, SE=1.3 x10-9; R2: ß=-1.1x10-8, SE=1.3x10-9; R3: ß=-1.8x10-7, SE=1.5x10-8; all $p<0.001$) and increased age (Mean=48-51 years; SD=20 years; R1: ß=-4.7x10-5, SE=2.5x10-6; R2: ß=-4.6x10-5, SE=2.5x10-6; R3: ß=-1.7x10-4, SE=2.7x10-5; all $p<0.001$) are negatively associated with SCZ diagnosis. Substance disorders (R1: ß=2.2x10-2, SE=3.9x10-4; R2: ß=7.8x10-1, SE=2.2x10-3; R3: ß=-7.7x10-2, SE=1.4x10-3; all $p<0.001$), and trauma/stress-related disorders (R1: ß=2.3x10-2, SE=3.9x10-4; R2: ß=7.8x10-1, SE=2.2x10-3; R3: ß=-6.0x10-2, SE=1.4x10-3; all $p<0.001$) are positively associated with SCZ diagnosis in the first and second regression but negatively associated with SCZ diagnosis in the third regression.

These results suggest that the SCZ diagnostic process at MSHS needs further investigation with an intersectional framework. Next steps should involve information extraction from unstructured EHR data (i.e., clinical notes) to uncover how diagnostic bias is driven by race and gender in SCZ.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Maya Verghese
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Department	Psychiatry

Trauma Exposures and Chronic PTSD in World Trade Center Rescue, Recovery and Clean-up Workers

Eden Astorino*, Maya Verghese*, Zoe Schreiber, Saren Seeley, Robert H. Pietrzak, Adriana Feder

BACKGROUND:
Tens of thousands of workers were involved in rescue, recovery and clean-up efforts following the 9/11/2001 World Trade Center (WTC) terrorist attacks. While several studies examined WTC-related trauma exposures and WTC-related posttraumatic stress disorder (PTSD), most employed self-report PTSD scales and assessed WTC workers a few years post-9/11. We aimed to identify specific WTC-related exposures associated with chronic PTSD persisting into the second decade post-9/11 in a sample of traditional (e.g., police) and non-traditional (e.g., construction workers) WTC responders.

METHODS:
WTC rescue, recovery and clean-up workers who completed at least three periodic health monitoring visits at the WTC Health Program (WTC-HP) were recruited from the WTC-HP General Responder Cohort from 2013 to 2017 [mean (SD)=13.0 (1.3) years post-9/11]. We employed stratified random sampling to recruit participants ranging in PTSD symptom severity from no/low to severe symptoms. Lifetime psychotic/bipolar I disorder, substance abuse/dependence or alcohol dependence in the prior three months, current pregnancy, unstable medical illness, or history of significant head injury/CNS disorder were exclusionary. Trained clinical interviewers administered the SCID-IV and past-month CAPS to establish presence/absence of current PTSD, defined as meeting DSM criteria for PTSD and past-month CAPS score$\geq$40, and an in-depth WTC Exposure Assessment Interview, which inquired about a range of trauma exposures (e.g., sustaining a severe injury at the WTC site, witnessing others' death or injury, encountering dead bodies/body parts, a loved one's death on 9/11). WTC exposures associated with current PTSD at the $p<0.10$ level in bivariate correlations were entered into a forward (Wald) logistic regression to predict current PTSD diagnosis.

RESULTS:
The sample included 370 eligible participants [Mean age (SD)=54.2 (8.4) years, 82% male, 59% traditional responders, 15% current PTSD]. WTC-related exposures associated with current PTSD included having encountered dead bodies/body parts (odds ratio [OR]=4.2, $p<0.001$); being present at the WTC site during the attacks (OR=3.3, $p=0.022$); and having suffered a serious physical injury on 9/11 or during the WTC recovery effort (OR=2.8, $p=0.040$). Non-traditional (OR=6.7, $p<0.001$) and female (OR=2.4, $p=0.043$) workers were also more likely to have PTSD.

CONCLUSION:
Specific WTC-related exposures are associated with chronic PTSD in WTC workers assessed in the second decade post-9/11. Results may help inform targeted assessment and treatment efforts for this disabling and chronic disorder in this population.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	James Vicari
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Validation of CRISPRa/i Microglia for Screening Targets of Alzheimer's Disease

James Vicari, Roman Kosoy, Zhiping Shao, John Fullard, Christopher Kellner, Panos Roussos

Background: Alzheimer's disease (AD) is a neurodegenerative disease that manifests as memory and language deficits due to neuronal death, accumulation of misfolded proteins and inflammation in the brain. Growing evidence has pointed to microglia, the brain's resident immune cells, as a key cell type in the progression of AD. Therefore, targeting microglia may be key in developing new therapeutics for AD. To address this question, we intend to use CRISPRa/i systems to screen genetic targets identified in human microglia isolated from AD cases and controls. In preparation for high throughput screening in HMC3 microglia, we confirmed microglial phenotypes and generated stable cell lines expressing the CRISPRa/i effectors dCas9-VPR and -KRAB.

Methods: Flow cytometry was used to observe microglia surface markers present on HMC3s and inflammatory activation was determined in lipopolysaccharide (LPS) and amyloid-beta (Aβ) stimulated cells. RNAseq was performed on stimulated HMC3s, primary human microglia (phMG) and induced-pluripotent stem cell (iPSC) derived microglia (iPSC-MG).

To generate stable CRISPRa/i lines, HMC3s were transduced with dCas9-VPR or -KRAB containing lentivirus under puromycin selection. dCas9 expression was determined by qPCR and effector activity evaluated using guide RNAs targeting IL6 followed by qPCR.

Results: HMC3s were positive for CD11b, Iba1 and TMEM119 but lowly expressed CD45. Both LPS and Aβ showed induction of IL1α and IL1β, while only LPS greatly increased TNFα and IL6 expression. Transcriptomic analysis showed iPSC-MGs were more similar to phMG compared to HMC3s and that Aβ treatment resulted in an upregulation of protein targeting and mitochondrial pathways seen in phMG-AD which were not induced with LPS treatment.

HMC3s transduced with lentivirus were positive for dCas9 by qPCR and guides targeting IL6 resulted in increased and decreased mRNA expression in the VPR (2480%) and KRAB (24.8%) lines respectively.

Conclusions: HMC3 microglia were confirmed to positively express microglia specific markers and are activated to an inflammatory state when stimulated with LPS but not Aβ. At baseline, HMC3 are transcriptionally distinct from phMG, however specific molecular pathways enriched by Aβ stimulation are similarly found in phMG isolated from Alzheimer's patients.

Finally, HMC3s were successfully transduced to stably express the CRISPRa/i effectors and demonstrated their functionality using guide RNAs targeting IL6. This stable line has been well characterized and will serve as a useful tool for high throughput CRISPR screens to identify potential therapeutic targets for AD.

2023 Neuroscience Retreat

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Full Name	Eric Vornholt
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Department	CBIPM

Expression differences between living and postmortem cortical tissue suggests systemic confounds in studying the human brain transcriptome postmortem.

Eric Vornholt, Brian Kopell, Ryan Thompson, Lora Liharska, Esther Cheng, Noam Beckmann, and Alexander Charney

Background: The molecular underpinnings of brain disorders remain unknown. This is in part due to the inability to study brain tissue from living people. Instead, the field has relied on postmortem human brain tissue, which may not be an accurate representation of living human brain tissue. The Living Brain Project (LBP) has allowed researchers to ethically biopsy living cortical tissue to study multi-omic differences between living and postmortem brains.

Methods: Single-nuclei RNAseq was generated from 31 living and 21 postmortem cortical samples and clustered/annotated into neural cell types. Differentially expressed genes (DEGs) were identified across cell types using a linear mixed model. Gene regulatory networks (regulons) were defined using SCENIC and then tested for differentially active regulons (DARs) between groups. The utility of the living vs postmortem expression signature was explored via elastic net to create a postmortem linear predictor score (PMlink) for postmortem bulk samples.

Results: After QC, the 52 samples yielded 362,390 quality cells (61% postmortem and 39% living) which were clustered into 10 cell types. Differential expression revealed massive signals across all cell types, with 64% of genes differentially expressed in at least one cell type (n = 16,759 genes). Neuronal markers are disproportionately upregulated in postmortem neurons and oligodendrocyte markers are upregulated in living across all cell types. In examining DARs, living cells show increased regulon activity associated with RNA processing, whereas postmortem cells display increased activity of regulons associated with neuronal signaling. Finally, the calculated PMlink score had strong predictive strength in determining LV vs PM classification in an external bulk cohort (ROC AUC = 0.84). When incorporated as the dependent variable in a linear mixed model containing only postmortem bulk samples the LV vs PM pseudo-bulk DE signal is replicated (r=0.65).

Conclusion: The combined DEG and DAR results reveal ubiquitous dysregulation of key biological systems throughout the postmortem brain that are not reflective of the living expression profile. These findings provide necessary context for interpreting postmortem gene expression as a snapshot of biological processes at death rather than a proxy for living brain function. Machine learning methods provide utility for creating correction algorithms that can help address this problem in past and future postmortem transcriptomic studies of the brain.

2023 Neuroscience Retreat

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Full Name	Allison C. Waters
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Lab	Waters Lab
Department	Psychiatry and Neuroscience

Title: Electrical perturbation of human cortex generates a reliable, individualized read-out of cortical excitability: what's the potential and is this just a phase?

Authors: Allison C. Waters, Andrew Smith, Ki Sueng Choi, Martijn Figee, Brian Kopell, Helen Mayberg

Introduction: Electrical perturbation mapping provides a read-out of electrocortical dynamics in response to single pulses of brain stimulation. The approach holds great promise for optimizing neuromodulation therapies according to individual differences in brain responsiveness to stimulation. Moreover, perturbation mapping reveals fundamental properties of cortical functioning, leading some to speculate that a human electrical connectome will soon be defined. This hype is both tempered and fueled by progress made in the applied domain of neuromodulation.

Method: A perturbation map is a spatiotemporal pattern of voltage fluctuations, often observed in the form of a stimulation evoked potential (EP). We characterize and compare DBS evoked potentials at two distinct white matter targets: the subcallosal cingulate (SCC) for treatment of depression and the anterior limb of the internal capsule (ALIC) for treatment of obsessive-compulsive disorder (OCD). EPs were recorded from each of 8 contacts (4 per hemisphere) and at varying doses. Patient-specific tractography models provided an estimate of white matter structure, which was then regressed on features of the evoked potential.

Results: Stimulation EPs are strikingly coherent and reliable on the level on individual patients. Results also demonstrate clear and reliable location sensitivity for the stimulation evoked potential. Features sensitive to stimulation location appear to be generated by phase alignment of endogenous oscillatory activity. Evidence of an association between evoked components and white matter architecture explain location specificity, only in part.

Discussion: While competing mechanistic assumptions have yet to be clarified, results support the application of perturbation mapping to optimize treatment with DBS, as well as to a novel characterization of individual differences in cortical dynamics. The need for such a read-out is particularly urgent in psychiatric deep brain stimulation (DBS), where device optimization occurs in the absence of an acute behavioral response, such as the cessation of motor tremor.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Yolanda Whitaker
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Department	Psychiatry

Exploring Locus Coeruleus Neuromelanin Content in Patients with Anxiety, PTSD & Healthy Controls.

Yolanda I. Whitaker, B.S., Philipp Neukam, PhD., Sarah Boukezzi, PhD., Yael Jacob. PhD., Priti Balchandani, PhD, James Murrough, MD, PhD, Laurel Morris, PhD.

Background:
Literature has explored the Locus Coeruleus (LC) and its role in stress and anxiety. This is because the LC is a major regulator of norepinephrine (NE) in the brain and extends projections throughout the CNS, controlling bodily arousal states (O'Donnell et al., 2012). The LC contains neuromelanin (NM), a dark pigment found in dopaminergic neurons in the brain, which has been found to play a role in the etiology of various neurodegenerative diseases, such as Parkinson's, as well as psychiatric illnesses like schizophrenia and depression (Haining & Mendes, 2017). Although there is a plethora of research investigating the functioning of the LC in relation to various psychiatric disorders, including anxiety disorders (Morris et al., 2020), there is limited research on how neuromelanin content is linked to clinical symptoms.

Methods:
Data used for this study derives from a 7T neuroimaging R01 NIH funded study at the Depression and Anxiety Center at Mount Sinai. The sample included patients with anxiety-related disorders (N=27), PTSD (N=22), and Health Controls (N=34). NM content was measured indirectly using a magnetization transfer (MT) contrast that measures the exchange between water protons and the protons associated with macromolecules. Clinical symptoms of anxiety, panic and phobia were measured using the Albany Panic and Phobia Questionnaire (APPQ) as well as the Generalized Anxiety Disorder 7-item (GAD-7) scale. Pearson's correlations were conducted to investigate relationships between each group's NM content in the LC and clinical symptoms.

Results:
Correlations between the ANX, PTSD and HC groups found a positive correlation between LC NM content and APPQ total score in the ANX group ($r=0.729$, $p=<0.001$, $N=20$) but not for the PTSD or HC group. Similarly, between-group correlations found a positive correlation between LC NM content and GAD-7 total score in the ANX group only ($r=0.482$, $p=0.031$, $N=20$).

Conclusion:
These findings suggest that higher neuromelanin content is associated with anxiety-related symptoms, such as general worry, panic, and phobic symptoms in patients with anxiety disorders. Interestingly, the fact that there are no significant correlations between LC NM content and anxiety symptoms within the PTSD group could suggest neurobiological variations in NM modulation in the LC within psychiatric disorders. Future research on this topic must be conducted in order to further determine whether there are LC NM differences in psychiatric patients to try design NM-targeted interventions that can mitigate clinical symptoms in those populations.

2023 Neuroscience Retreat

Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

Full Name	Kristen Whitney
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Investigating mechanisms of sporadic progressive supranuclear palsy in autopsy-validated human iPSC-derived midbrain organoids and human brain tissue

Kristen R. Whitney, Margaret M. Krassner, Sean Thomas Delica, SoongHo Kim, Kurt W. Farrell, Diana K. Dangoor, Abhijeet Sharma, Won-Min Song, Thomas D. Christie, Megan A. Iida, Hadley A. Walsh, Lily Sarrafha, Gustavo Parfitt, Ruth H. Walker, Giulietta Riboldi, Steve Frucht, Tim Ahfeldt, Bin Zhang, Ana C. Pereira, Sally Temple, John F. Crary

Background: Progressive supranuclear palsy (PSP) is the most common primary tauopathy, with a constellation of pathological features including 4R-tau positive neurofibrillary tangles and tufted astrocytes. Most PSP cases are sporadic and associated with common structural variation in the 17q21.31 MAPT locus as well as other risk loci, including EIF2AK3 which is critical for the unfolded protein response (UPR). Despite these known genetic risk associations, mechanisms underlying disease pathogenesis are unclear. To investigate candidate mechanisms, there is a critical need for model systems that better recapitulate the cellular complexity of the human brain. Human induced pluripotent stem cell (hiPSC) patient-derived organoid models have emerged as powerful tools to study molecular and cellular changes in a disease-relevant genomic context.

Methods: Fibroblasts grown from sporadic PSP patient skin cells were cultured in vitro and reprogrammed into hiPSCs. HiPSC-derived midbrain organoids were generated in suspension spinner flasks through pharmacological directed differentiation, processed and screened for patterning using qRT-PCR, immunohistochemistry (IHC), and quantitative immunoblot. Total tau, tau isoform, hyperphosphorylated tau (p-tau), and UPR activation markers were assessed in organoids and human brain tissue. Single-nucleus RNA sequencing (snRNA-seq) was performed on the subthalamic nucleus and adjacent structures in autopsy-validated PSP brain tissue and clinically normal controls.

Results: PSP and control organoids displayed a cytoarchitectural and gene expression pattern consistent with the developing neuroectoderm and midbrain. We observed disease-relevant differences between PSP and control organoids, including increased high molecular weight p-tau, a higher ratio of p-tau:total tau, and increased levels of 4R-tau in the PSP organoids. Human PSP brain snRNA-seq data showed dysregulation of the UPR in astrocytes and neuronal subpopulations. We also observed different UPR activation levels in PSP organoids. These findings were validated by neurohistological characterization of the UPR in autopsy brain tissue.

Conclusions: Single nucleus transcriptomic and neurohistological data reveals dysregulation of the UPR in key cell types affected in PSP. PSP patient-derived organoids develop a characteristic midbrain cellular composition and recapitulate key disease-relevant features, including elevation of toxic tau proteoforms and UPR dysregulation. This sporadic PSP organoid model will provide insight into cell-type specific drivers of neurodegeneration that underlie sporadic tauopathy.

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Lrrk2-G2019S Impact on Corticostriatal Signaling

Amelia Wieland, Chris Guevara, Kumayl Alloo, Deanna Benson, George Huntley

BACKGROUND: Parkinson's is associated with early-appearing cognitive non-motor symptoms including deficits in visuospatial attention. The latter is modulated by top-down attention circuits in mPFC mediated, in part, by L5 corticostriatal neurons. The lab has shown previously that young adult male mice carrying a G2019S knockin mutation of leucine- rich repeat kinase 2 (Lrrk2), one of the most prevalent hereditary risk factors for late-onset Parkinson's in humans, display significant deficits in visuospatial attention and slower information processing speed assessed by performance in the 5-CSRT task. To investigate the basis for this, prior and ongoing work in the lab using patch-clamp recordings from L5 corticostriatal neurons in area prelimbic cortex (PL) has shown that in adult male mutant mice, the excitatory/inhibitory (E/I) balance is shifted towards greater excitation due largely to less inhibition compared to wildtype male controls. In female mutants, the E/I balance is more-or-less similar to wild type female controls. Here, we probed for excitatory and inhibitory synaptic markers in L5 of area PL to investigate whether electrophysiological differences were accounted for by anatomical differences in synaptic markers.

METHODS: To address this we used immunofluorescent to localize vGlut1 (excitatory presynaptic marker) and GAD65 (inhibitory presynaptic marker) with high-resolution confocal microscopy.

RESULTS: We found no differences in density or sizes of excitatory or inhibitory immunofluorescent puncta in the layer V of cortical neurons between G2019S and WT neither in males nor in females.

CONCLUSION: These data suggest that the functional differences in inhibition seen in G2019S males is not due to overt differences in inhibitory synapse number or size, but rather likely reflects differences in cell-surface trafficking of postsynaptic receptors and/or differences in probability of neurotransmitter release. This conclusion is broadly in line with our previous work showing mutation-driven impairment of cell-surface trafficking of the GluA1 AMPAR
subunit in striatum. The current work suggests a cell-type and region-specific effect of the G2019S mutation on trafficking of particular neurotransmitter receptors, ion channels and other types of vesicular-bound cargo that impairs circuit function and constraints behavioral flexibility early in the course of Parkinson's.

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An efficient and scalable dissection protocol for human brain tissue banking

Emma L. Thorn, MA, Claudia De Sanctis, PhD, Adam M. Goldstein, MD, Megan A. Iida, Alicia Casella, Kurt Farrell, PhD, John F. Crary, MD, PhD

Departments of Pathology, Artificial Intelligence & Human Health, Nash Family Department of Neuroscience, Ronald M. Loeb Center for Alzheimer's Disease, Friedman Brain Institute, Neuropathology Brain Bank & Research CoRE, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

BACKGROUND: Access to high quality human post-mortem brain tissues is critical for translational research of brain diseases. Brain tissue biorepositories (“banks”) are essential conduits for enabling studies of the human brain in physiological and neuropathological contexts. Brain banking is challenging owing to complex pathoanatomical considerations at the time of processing and retrieval, which engenders operational delays and inefficiencies that negatively impact research programs. Among the barriers are the need to subdissect tissue fragments from frozen slabs or in some cases entire brains frozen en bloc. Some protocols involve pre-dissecting targeted brain regions prior to freezing, but these protocols are generally not feasible because of significant pathoanatomical knowledge required of staff prosectors. Here, we describe a novel, efficient, and scalable post-mortem human brain parcellation/dissection protocol for brain banking.

METHODS: Extensive photo documentation of every step is performed. Fresh brains are bisected sagittally, with one hemibrain frozen and the contralateral hemibrain immersion fixed in 10% neutral buffered formalin for two weeks. The hemibrain to be frozen is sectioned coronally (~0.5 cm thickness) entirely. Each resulting slab is sequentially photographed at high-resolution three times: in the intact state, following parcellation, and a final time with associated label/barcode which allows post-processing neuroanatomical annotation. Brainstem structures are sectioned horizontally. The resultant tissue specimens result in up to 150 2x2 cm blocks. Blocks are frozen between two cold plates over dry ice then stored at -80°C for distribution.

RESULTS: We have currently banked 202 brains using this protocol resulting in 29,986 unique specimens, of which 1,344 have been distributed. Diagnoses include Parkinson’s disease and atypical parkinsonism (n=35), COVID-19 (n=53), Alzheimer’s disease neuropathological changes/aging (n=57), and controls (n=92). Of the postmortem intervals of these cases, 61% are below 24 hours. Of the 136 fresh brains in which the data is available, the average processing time from the start of the dissection process to the time that all tissue is frozen is 79 min.

CONCLUSIONS: In conclusion, parcellation of dissected human autopsy brain tissue provides significant advantages over slab or en bloc freezing protocols, and can be efficiently deployed in brain bank settings.

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Enhancement of Neural Interoceptive Processing Observed in Responders to Deep Brain Stimulation for Treatment Resistant Depression

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Background: Change in interoceptive processing (i.e., bodily sensation) may be relevant to the mechanisms by which deep brain stimulation (DBS) to the subcallosal cingulate (SCC) affects depression. A measure of interoceptive processing is the heartbeat evoked potential (HEP), which is time-locked to the cardiac cycle. HEP is thought to reflect interoceptive processing of cardiac sensation and is suppressed in depression. Given evidence that SCC DBS impacts autonomic regulation, we predict that reduction of negative mood with DBS relates to change in interoception, indexed by the HEP.

Methods: Eight consecutive patients with treatment resistant depression were studied as part of an ongoing experimental trial of SCC DBS for depression (Clinical trials ID: NCT01984710). HEPs were extracted from resting EEG recordings (256-array) acquired with stimulation off in a laboratory setting before the initiation and after 6-months of therapeutic SCC DBS. We compared HEP magnitude and investigated correlations between change in HEP and symptom severity pre/post treatment.

Results: Compared to baseline, the HEP at 6-months was enhanced over frontal midline channels in treatment responders at the 420-432 ms latency ($Z=2.200$, $p=0.03$). Though below threshold for statistical significance, we observed a positive correlation of change in HEP amplitude and reduction in HDRS-17 scores ($r=0.47$, $p=0.23$). We note the clinical significance of this effect size despite low variance in clinical outcomes.

Conclusions: This study indicates that SCC DBS affects cortical mechanisms of interoceptive processing, which may be relevant to treatment efficacy. Understanding this relationships instructs new strategies for rehabilitation of treatment resistant depression with SCC DBS.

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A REFINED ATLAS OF CELL TYPE-SPECIFIC ISOFORMS IN THE HUMAN CORTEX

Andy Y. Yang & Michael S. Breen

BACKGROUND: Alternative splicing (AS) is highly prevalent and evolutionarily conserved in the vertebrate nervous system, serving as a crucial post-transcriptional regulatory mechanism that contributes to the functional complexity of the mammalian cortex. However, despite recent advances in isoform-level transcriptomic annotation, our understanding of AS mechanisms at the individual cell level in the brain remains limited. Here, we systematically characterize cell type-specific isoforms across the human cortex.

METHODS: We utilized fluorescence-activated nuclei sorting to purify five major cell types from the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC), including MGE-GABAergic neurons (NeuN+/SOX6+), glutamatergic neurons (NeuN+/SOX6-), oligodendrocytes (NeuN-/SOX10+), astrocytes (NeuN-/SOX10-/IRF5-) and microglia (NeuN-/SOX10-/IRF5+). For each cell type, we generated Illumina short-read RNA-sequencing and Pacific Biosciences long-read isoform sequencing (Iso-Seq). Data were subjected to a systematic computational analysis to reveal high-confidence cell-type specific isoforms.

RESULTS: We discovered extensive transcript diversity across neuronal and glial cell types in the DLPFC and OFC, with the majority of transcripts coding for proteins. Glial cells exhibit increased diversity of full-length transcript isoforms relative to neuronal cells in both DLPFC and OFC. Further, thousands of novel transcripts not present in existing genome annotations were identified, including those mapping to unannotated genes. Finally, we uncover changes in AS, with differential transcript usage between cell types and brain regions.

CONCLUSION: Our study provides new and valuable insights into the transcriptomic diversity of neuronal and glial cell populations in the DLPFC and OFC regions, significantly expanding the available reference transcriptomes for these brain cells.

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Role of the ventral hippocampus in regulating social behaviors

Yewon Yang, Long Li, Scott J. Russo

BACKGROUND: The significance of social interaction is reflected by a number of psychiatric disorders that bring about social impairment, including schizophrenia and depression. On this account, it is critical to understand the neural circuit mechanisms involved in regulating social behaviors. The ventral hippocampus (vHPC) has previously been implicated in playing an essential role in social interaction, especially in storing social memory. However, how the vHPC and its subcortical projections coordinate to modulate social behavior remains largely unknown.

METHODS: To validate that the vHPC responds to social behaviors, we used fiber photometry to record calcium signals in freely moving mice interacting with another mouse. We applied HSV-RPF for anterograde trans-synaptic tracing to reveal the downstream regions of the vHPC in mice. We then performed Fast 3D Clear, a three-day tissue clearing method to clear the brains, and imaged them with a light-sheet microscope. The images were aligned and compared to the Allen Brain Reference Atlas to identify the downstream regions, and the number of +RFP cells was counted using ClearMap.

RESULTS: Here, we found that the vHPC neurons showed increased activity to social interaction onset. Our images revealed that the vHPC projected to at least the following seven downstream targets: the entorhinal area (ENT), lateral septal nucleus (LSN), supramammillary nucleus (SuM), medial mammillary nucleus (MM), nucleus accumbens (NAc), olfactory tubercle (OT), and interpeduncular nucleus (IPN).

CONCLUSIONS: The vHPC-NAc has already been extensively reported to be involved in social behaviors. However, the rest of the projections (vHPC-LSN, vHPC-SuM, vHPC-MM, vHPC-OT, and vHPC-IPN) have not. Therefore, by manipulating these pathways during animal social interactions, we can better understand the function of vHPC in social behavior and gain a deeper insight into its role in neuropsychiatric disorders.

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Full Name	Abi Yates
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Lifestyle modulates hematopoiesis to influence neuroinflammation and the severity of experimental autoimmune encephalomyelitis

Abi G. Yates, Máté G. Kiss, Pacific Huynh, Jan Hoffmann, Walter Jacob, Sukanya Goswami & Cameron S. McAlpine

Multiple sclerosis (MS) is an autoimmune disease driven by neuroinflammation and immune cell infiltration of the central nervous system. Abundant clinical data has firmly established that MS severity and progression is influenced by lifestyle factors, including hyperlipidemia and exercise. However, the cellular mechanism that connect lifestyle to MS remain uncertain. In this study, we aimed to evaluate the contribution of hematopoiesis and its manipulation by lifestyle factors to disease severity in the murine model of MS. Using the experimental autoimmune encephalomyelitis (EAE) model of MS, we report that hematopoiesis and hematopoietic stem cell (HSC) abundance is increased in the vertebrae and femur bone marrow, and the spleen of EAE animals relative to healthy controls, leading to systemic monocytosis and neutrophilia and neuroinflammation. Hyperlipidemia induced by Apoe deletion and high fat diet feeding increased HSCs and immune cell generation in the BM and spleen, raised blood monocytes and neutrophils, augmented immune cell infiltration of the spinal cord, and worsened EAE clinical score. By contrast, suppression of hematopoiesis with voluntary exercise improved clinical scores in EAE mice. The contribution of lifestyle factors to EAE was independent of peripheral immune priming as the proliferation and generation of growth factors by CD4+ T cells in the spleen and cervical lymph nodes, was unchanged. Collectively, these data indicate that hematopoiesis promotes EAE progression and its manipulation by lifestyle factors modulates disease severity.

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The Human Affectome
Alessandra N. C. Yu, Daniela Schiller, & Leroy Lowe

BACKGROUND: The affective sciences seek to explain the mechanisms of affective phenomena, but this field's divergent metaphysical and methodological assumptions, as well as differing scholarly motivations, have led to divisions in theoretical frameworks with no clear consensus in sight. Given the heterogeneity in assumptions, a principled set of teleological premises—principles that explain why affective phenomena arise—are necessary to construct a parsimonious framework.

METHODS: In this special issue, "Towards an Integrated Understanding of the Human Affectome", 173 researchers from 28 countries have come together as a global, interdisciplinary taskforce. Following exploratory computational linguistic analyses and the production of twelve reviews on different areas of the affective sciences, we have performed a literature review across the existing metaphysical and methodological assumptions in the field in order to synthesize an integrative, algorithmic, enactive, and allostatic framework of affective phenomena in a principled manner.

RESULTS: We characterize affective phenomena as experiences that are grounded by algorithmic mechanisms with allostatic purpose. This allows us to organize affective phenomena by their algorithmic mechanisms. First, we consider mechanisms that address affective concerns, which indicate the allostatic relevance of a sensory objects by predictively suggesting actions to treat them. These mechanisms can organize affective phenomena along a hierarchy of sensorimotor planning, ranging from the most immediate and concrete concerns which are the least complex in actionability (i.e., bodily sensations) all the way to distal and abstract concerns with complex actionability (e.g., emotions). In addition, a separate set of mechanisms summarize across hierarchical affective concerns in order to globally and dynamically track them across time (i.e., mood). Finally, a fundamental set of mechanisms, those expressing affective features, gauge metrics on the status of the allostatic process in any given one moment (i.e., valence, arousal, and motivation). In discussing each of these mechanisms, we provide exemplars of existing affective research that describe affective phenomena within these algorithmic domains—as well as provide an overview of how this framework can further be implemented to characterize affective profiles using computational psychiatry methodology.

CONCLUSIONS: This teleological framework, the Human Affectome, synthesizes existing assumptions in the interdisciplinary field of affective sciences. This mechanistic approach not only bridges across theoretical divisions in the field, but frames, organizes, and founds a principled research program of testable scientific theories on affective phenomena.

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The effects of pre-reproductive stress in adolescent female rats on tRNA expression

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BACKGROUND: Pre-reproductive stress (PRS) to adolescent female rats alters anxiogenic behavior in first- and second-generation offspring in a sex-dependent manner. PRS also leads to corticotropin-releasing factor receptor 1 type 1 (CRF1) gene expression and microRNA changes in oocytes of exposed females and in offspring brains at birth and in adulthood, although mechanisms for stress-induced behavioral alterations and intergenerational transmission are still unknown. Recently, we've shown a role for transfer RNAs (tRNAs), small RNAs consisting of 70-90 nucleotides, in regulating adult brain function and behavior. Here, we investigated the potential role of tRNAs in pre-reproductive stress in adolescent females and their role in mediating the transgenerational effects of PRS.
METHODS: Adolescent female rats (F0) were exposed to a 7-day stress procedure, and the prefrontal cortex (PFC) was extracted from a subset of PRS and control rats at two different time points: 4 days after the stress and 2 weeks after the end of the stress procedure. The remaining female rats (F0) were mated two weeks after the stress, and their male and female offspring's (F1) PFC was extracted at birth. To measure tRNA expression in an unbiased manner, we used total RNA and prepared next-generation sequencing libraries for YAMATseq, followed by sequencing on the Illumina MiSeq and bioinformatic analysis.
RESULTS: Preliminary data show differential expression of tRNA isodecoders dependent on age and stress exposure.
CONCLUSIONS: Combined with our previous findings, these data raise the possibility that changes to regulatory tRNAs and translational mechanisms act in concert with psychosocial mechanisms to transfer the effect of stress from one generation to the other in a sex-dependent manner.

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Full Name	Xiaoting Zhou
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Title: The Landscape of Autophagy Degradation and Regulation in Human Neurons

Authors: Xiaoting Zhou, You-Kyung Lee, Henry Kim, Xianting Li, Xian Han, Carlos Sanchez-Priego, Junmin Peng, Nan Yang, and Zhenyu Yue

Background: Autophagy is a lysosomal degradation pathway and plays an important role in neuroprotection. It is often disrupted in neurodegeneration diseases and the impairment of autophagy has recently been linked to neurodevelopmental disorders. However, the precise process of autophagy in human neurons remains poorly defined. The mechanism for how autophagy is disrupted in human neurodevelopmental diseases remain unclear.

Methods: We performed systemic investigation of autophagy cargos and adaptors to understand autophagy pathways in neurons. We generated autophagy-deficient human induced glutamatergic neurons (iNs) from human pluripotent stem cells. To enrich autophagy cargos, we suspended autophagy in neurons using CRISPR-inhibition technology to knockdown ATG7 or ATG14. To validate our finding in vivo, we also established neuron-specific atg7 or atg14 conditional knockout (cKO) mice. To identify LC3-associated autophagy cargo, we generated ATG7 cKO mice expressing GFP-LC3, followed by affinity purification of LC3-interacting proteins. Quantitative proteomic analysis was performed to identify proteins with increased levels in ATG7 or ATG14-deficient human or mouse neurons. Both autophagy-deficient human iNs and mouse brains were used for validating pathways of interest identified from quantitative proteomics.

Results: Accumulations of known autophagy-associated proteins were observed in autophagy deficient neurons. We identified novel autophagy cargos and adaptors involved in pathways including ER-phagy, synaptic vesicle and PKA pathways. Calumenin was identified as an ER resident autophagy receptor.

Conclusions: Our work revealed the landscape of autophagy degradation and regulation in mouse and human neurons. We identified novel autophagy cargos and adaptors. Our study underscores the complexity of the autophagy functions in neurons and shed light on the mechanisms for neuroprotective function of autophagy.

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Presented by the Friedman Brain Institute, Neuroscience Graduate Program and the Charles Bronfman Institute for Personalized Medicine

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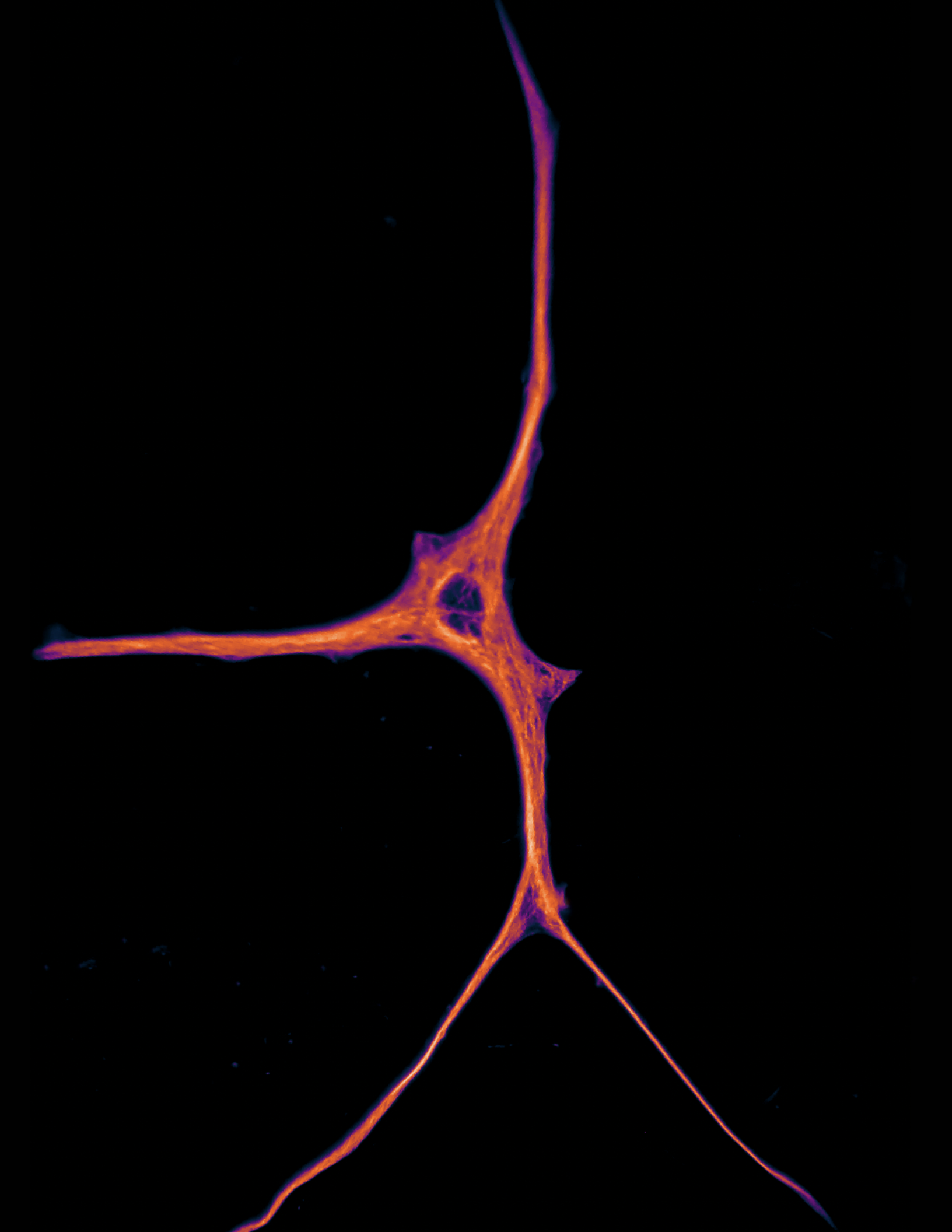
BACKGROUND: Of the 13 serotonin (5-hydroxytryptamine, 5-HT) receptors in humans, the 5-HT1E and 5-HT1F subtypes (1E and 1F, respectively), are understudied G protein-coupled receptors with high sequence identity among themselves, and to a lesser degree, the other 5-HT1 receptor subtypes. While 1F is a validated target for anti-migraine drugs, the physiological function of 1E remains unknown due to a lack of rodent orthologs and selective compounds.

METHODS: We screened a small library of medications and research compounds with known activities at various aminergic receptors using orthologous cyclic AMP accumulation and arrestin recruitment assays. Resulting hits were tested in a dose-response fashion. CryoEM structural studies were performed by complexing protein (1E receptor, engineered Gi1 heterotrimer, and stabilizing ScFv16) recombinantly produced from Sf9 insect cell culture. Imaging was conducted at the New York Structural Biology Center on a 300 keV Krios microscope, and processed with CryoSPARC. Model fitting was performed with WinCoot and Phenix.

RESULTS: The compound screen led us to discover that a series of clinically-used drugs featuring a tetracyclic scaffold are high-affinity agonists at 1E and 1F, while they have generally been reported as pan-aminergic antagonists. We subsequently determined structures of 5-HT1E complexed with Gi1 and bound by two of these drugs, mianserin and setiptiline, at 3.31 and 3.28Å.

CONCLUSIONS: These structures reveal unambiguous binding poses that demonstrate key interactions with binding pocket residues that confer high affinity in a ligand-specific fashion, and lay the stage for the generation of 1E-specific agonists for physiological studies. Additionally, our functional work offers a putative mechanism of action for the reported anti-migraine activities of the medications characterized in this study.



Neuroscience Graduate Training Program

It was a very good year for the Neuroscience graduate training program. With Covid mostly in the rear-view mirror, things *felt* largely back to normal, including classes, seminars, meetings, social interactions... all thankfully back to being in person. Speaking of being in person, I am happy to report that our Admissions this year was a tremendous success (perhaps a case of "*careful what you wish for*…"), I think due entirely to the fact that we returned to in-person, on-campus Admissions events. Having the applicants on our campus, interacting with our current students and outstanding faculty and seeing our Institutional resources up close is our big strength—the applicants can experience the strong, supportive, collaborative and nurturing research and training environment. We had a record number of applications (327), and in the end, we welcome 19 (yes, nineteen) new PhD students of varied research backgrounds, interests and experiences. As of this writing, the outcome of the MSTP admissions is not yet known, though typically 3-5 new MSTP students in each year's cohort are interested in NEU, so I'm anticipating the same. I am ever grateful for the hard work of *Peter Rudebeck, Betsy Cropper, Nan Yan, Silvia De Rubeis, Xiaosi Gu and Ki Goosens*—our Admissions screening team extraordinaire, and *Alie Fink*, who sacrificed an entire day to help me at the Institution-wide Admissions meeting. And of course, none of this would be possible without the dedication of the many faculty and students who met with, dined, interviewed and otherwise worked hard to recruit these outstanding students. Those applicants we lost were lost to the usual suspects—UPenn, Harvard, NYU, Columbia, Princeton, Yale, UCSD.

While welcoming our new students on the one hand, we simultaneously say goodbye to the many who successfully defended their outstanding thesis work in the interval between last year's and this year's retreat. Sixteen PhD or MSTP students defended their thesis work during this time, with a few more to follow later this summer. Best of luck to our newly-minted colleagues.

Curriculum-wise, we are in the process of re-tooling our biostatistics classes. Things were upended this past year with the departure of some key faculty, the postponement of one of the major first-year Stats classes, and other unfortunate but coincidental events. Our goal will be to design a new, stand-alone first year Biostats course for the NEU students, followed by an advanced second year course. Stay tuned.

George Huntley

Image by Tanvi Joshi

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Notes

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