We hope
you will
join us in
2021
for the
13th Annual
Neuroscience
Retreat

Image by Ni-ka Ford, Instructional Technology Group

THE FRIEDMAN BRAIN INSTITUTE and
NEUROSCIENCE GRADUATE PROGRAM

April 24, 2020

The 12th Annual Neuroscience Retreat

Icahn
School of
Medicine at
Mount
Sinai

THE FRIEDMAN BRAIN INSTITUTE
LEADERSHIP TEAM

Eric J. Nestler, MD, PhD
Director, Friedman Brain Institute

Schahram Akbarian, MD, PhD
Chief, Division of Psychiatric Epigenomics

Priti Balchandani, PhD
Director, Advanced Neuroimaging Research Program

Mark G. Baxter, PhD
Director, Lipschultz Center for Cognitive Neuroscience

Joshua B. Bederson, MD
Chair, Department of Neurosurgery

Kristen Brennand, PhD
Director, Alper Neural Stem Cell Center

Joseph Buxbaum, MSc, PhD
Director, Seaver Autism Center

John F Crary, MD, PhD
Professor, Pathology and Neuroscience

Samuel Gandy, MD, PhD
Director, Center for Cognitive Health

Alison M. Goate, D. Phil
Director, The Ronald M. Loeb Center for Alzheimer's Disease

René Kahn, MD, PhD
Chair, Department of Psychiatry

Patrick Hof, MD
Vice Chair, Department of Neuroscience

Yasmin Hurd, PhD
Director, Addiction Institute at Mount Sinai

Paul Kenny, PhD
Chair, Nash Family Department of Neuroscience
Director, Drug Discovery Institute

Helen S. Mayberg, MD
Director, Nash Family Center for Advanced Circuit Therapeutics

Scott J. Russo, PhD
Director, Center for Affective Neuroscience

Anne Schaefer, MD, PhD
Director, Center for Glial Biology of Mount Sinai/CUNY

Paul Slesinger, PhD
Director, Center for Neurotechnology and Behavior

Barbara G. Vickrey, MD, MPH
Chair, Department of Neurology

12th Annual Neuroscience Retreat Committee

Retreat Organizers:

Daniela Schaefer (Neuroscience)
Towfique Raj, PhD (Neuroscience)

Retreat Administrators:

Andrea Marie Nievera, Vena Persaud, Jenny Rivera, Danny Roldan and Veronica Szarejko

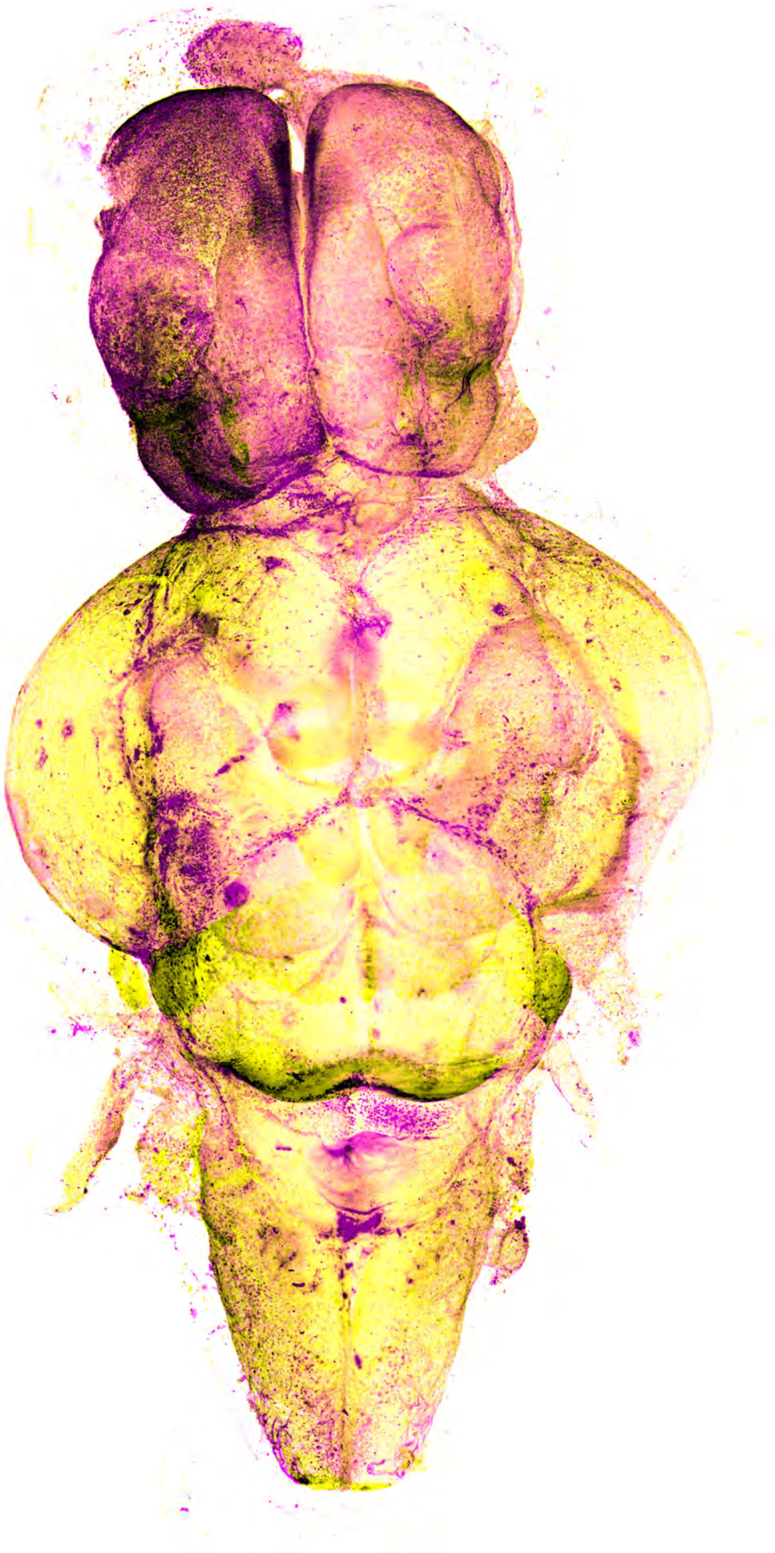


Image by Paloma Bravo, MS, Department of Cell, Developmental and Regenerative Biology

THE FRIEDMAN BRAIN INSTITUTE

CONTENTS

Image by Long Li, PhD, Nash Family Department of Neuroscience

THE FRIEDMAN BRAIN INSTITUTE

Agenda

9:00am – 10:00am

Opening Remarks and Announcements

Eric J. Nestler, MD, PhD
Paul Kenny, PhD
George W. Huntley, PhD

10:00am – 10:30am

Keynote Speaker – Mark G. Baxter, PhD, Neuroscience

Neuroscience, Cognition, and Anesthesia

10:30am – 10:50am

Student Abstracts

Ana Badimon, PhD (Schaefer Lab), Neuroscience

Negative feedback control of neuronal activity by microglia

Sarah King (NARC Research Program – Goldstein Lab), Psychiatry

Anatomical connectivity of the habenula and aggression in cocaine-addicted individuals

---

10:50am – 11:10am

Postdoc Abstract

Flurin Cathomas, MD (Russo Lab), Neuroscience

Interactions between peripheral monocytes and the brain in stress disorders

Ofer Perl, PhD (Gu Lab), Psychiatry

Belief About Nicotine Modulates Reward Signals in a Dose-dependent Fashion

---

11:10am – 11:30am

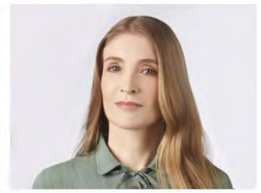
Awards Announcements

(AWARDS: Postdoc Award, Neuroscience Mentorship Distinction Award
"NMDA" Award, Most "Liked" Social Media Image)

Speakers

Eric J Nestler, MD, PhD
Director, Friedman Brain Institute

Paul J Kenny, PhD
Chairman, Nash Family Department of Neuroscience



Daniela Schiller, PhD
Retreat Organizer

Towfique Raj, PhD
Retreat Organizer

Allison C Waters, PhD
Moderator

Drew D Kiraly, MD, PhD
Moderator

George Huntley, PhD
Director, Neuroscience Graduate Program

Mark Baxter, PhD
Faculty Keynote Speaker

Ana Badimon, PhD
Speaker

Sarah King
Speaker

Ofer Perl, PhD
Speaker

Flurin Cathomas, MD
Speaker

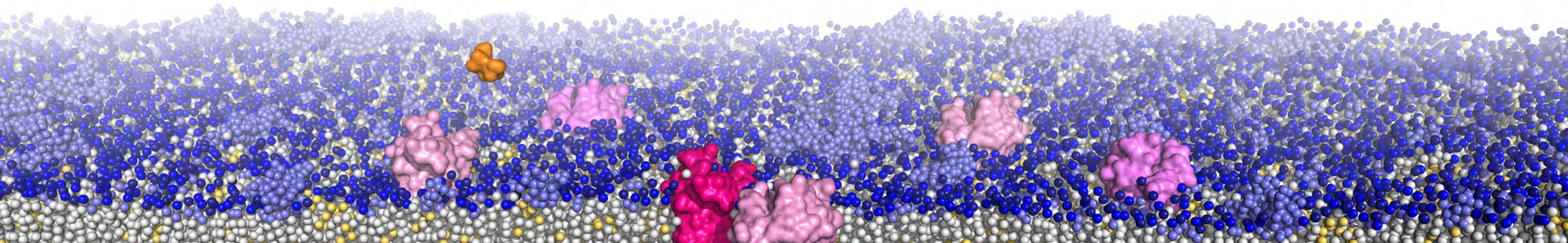


Image by Davide Provasi, PhD (Filizola lab), Department of Pharmacological Sciences

Ana Badimon
Nash Family Department of Neuroscience

Negative feedback control of neuronal activity by microglia

Microglia, the brain resident macrophages, play a key role in the regulation of brain function by removing dying neurons, pruning non-functional synapses, and producing ligands that support neuronal survival. We have identified a new function of microglia as modulators of neuronal activation. We show that microglia can respond to neuronal activation, and that ablation of microglia amplifies and synchronizes the activity of neurons, leading to seizures. The suppressive impact of microglia on neuronal activation depends on the ability of microglia to sense activity-induced metabolites produced by neurons. Microglia catabolize the metabolites to generate neurosuppressive molecules that dampen neuronal activity and prevent hyperexcitabiltiy. Our findings suggest that this microglia-driven, negative feedback mechanism operates in a fashion similar to inhibitory neurons and protects the brain from excessive activation.

NIH, NIMH

Sarah King
(NARC Research Program – Goldstein Lab)
Department of Psychiatry

Anatomical connectivity of the habenula and aggression in cocaine-addicted individuals

The lateral habenula (Hb) has emerged as a potentially critical structure in drug addiction due to its modulation of midbrain monoaminergic signaling and reward network activity. Functions of the Hb include the regulation of behaviors related to self-control such as aggression, which is often elevated in addiction. However, the neurocircuitry underlying this relationship has not been elucidated. This study aimed to detail Hb anatomical connectivity using diffusion MRI and assess the relationship between white matter microstructure and trait aggression scores in 33 individuals with cocaine use disorder (iCUD) and 35 healthy controls.

Probabilistic tractography analysis using the fiber orientation distribution function model identified Hb tracts to the rostral middle frontal gyrus (RMF), orbitofrontal cortex, insula, and nucleus accumbens in the whole sample. Although groups did not differ in the total number of Hb-to-whole brain streamlines per voxel ($p>.05$), mean fractional anisotropy (FA) of right-hemisphere tracts was reduced in iCUD ($p=.02$). The percentage of all identified Hb streamlines projecting to the right RMF was increased in iCUD ($p=.02$), and FA was reduced in this tract ($p=.05$). There was a significant interaction effect by which greater Hb-to-RMF connectivity predicted higher aggression scores in iCUD. ($p=.04$).

We successfully mapped anatomical connectivity profiles of the Hb noninvasively using diffusion tractography. Results highlight anatomical alterations in Hb-to-prefrontal cortex tracts reflecting a possible neurophysiological substrate of aggression in addicted individuals.

Funding: R21DA034954

Flurin Cathomas, MD
Nash Family Department of Neuroscience

Interactions between peripheral monocytes and the brain in stress disorders

Psychosocial stress is a risk factor for numerous neuro-psychiatric disorders, including major depressive disorder (MDD). Chronic stress leads to profound changes in the immune system causing behavioral alterations relevant to MDD. However, the detailed mechanisms of how the peripheral immune system acts on the brain remain to be elucidated.

In a murine model of social defeat stress, we performed cell-type specific RNA-sequencing of Ly6chigh and Ly6clow monocytes, B- and T-cells. We then used mass cytometry and single cell RNA-sequencing to characterize brain resident and infiltrating immune cells. Lastly, using a translational approach, we validated the murine findings in patients with MDD.

Ly6chigh monocytes from susceptible mice showed the most pronounced transcriptional changes. Several cytokine receptor genes were upregulated on monocytes in susceptible compared to resilient and control mice. Peripheral monocytes accumulated in brain-border regions. Transcriptional analysis of blood and brain identified increased expression of matrix metalloproteinase-8 (MMP8) produced by Ly6chigh monocytes in stress-susceptible versus resilient or control mice. Administration of recombinant MMP8 to mice was sufficient to increase behavioral susceptibility. Lastly, we showed that serum levels of MMP8 was positively correlated with symptom severity in patients with MDD.

Investigating the mechanisms underlying interactions between the immune system and brain provides important insights into the etio-pathophysiology of MDD leading to potential novel therapeutic targets.

NIH, SNSF

Ofer Perl, PhD
Department of Psychiatry

Belief About Nicotine Modulates Reward Signals in a Dose-dependent Fashion

Nicotine, the primary addictive substance in tobacco, stimulates neural pathways mediating reward processing. Mounting evidence suggest pivotal roles for cognitive factors like belief and expectation in addiction and intervention outcome which cannot be attributed solely to neurochemistry (Gu et al. 2015). Uncovering mechanisms by which belief overrides drug responses is therefore a crucial step towards treatment and management. Here, using computational modeling and model-based functional magnetic resonance imaging we investigated the impact of suggested belief on neural learning signals. Over three separate sessions, we engineered chronic smokers' (N=20, 7F, 41±12.8YO) prior beliefs about the amount of nicotine (low/medium/high) in e-cigarettes smoked before a sequential stock market investment task. Smokers' self-reported belief about nicotine content increased linearly with engineered belief (rmANOVA, $F(2,38) = 9.71$, $p<0.0005$). We observed responses for monetary signals in bilateral lateral-posterior thalamus increase as a function of belief in a dose-dependent fashion (Within-subject ANOVA, $p<0.005$, $k=100$ whole-brain corrected). A sychophysiological-interaction analysis with this ROI as seed uncovered belief-induced reduction in functional connectivity in a network comprised of parahippocampal gyri, insulae and ventral striatum. (Within-subject ANOVA, $p<0.05$, $k=50$ whole-brain corrected). Interestingly, modelling subjects' individual belief ratings uncovered similar dosedependent dynamics in caudal periaqueductal gray. Our findings suggest subjective belief can override physical presence of powerful neuroactive compounds like nicotine by modulating reward-related learning signals.

Funding: NIH

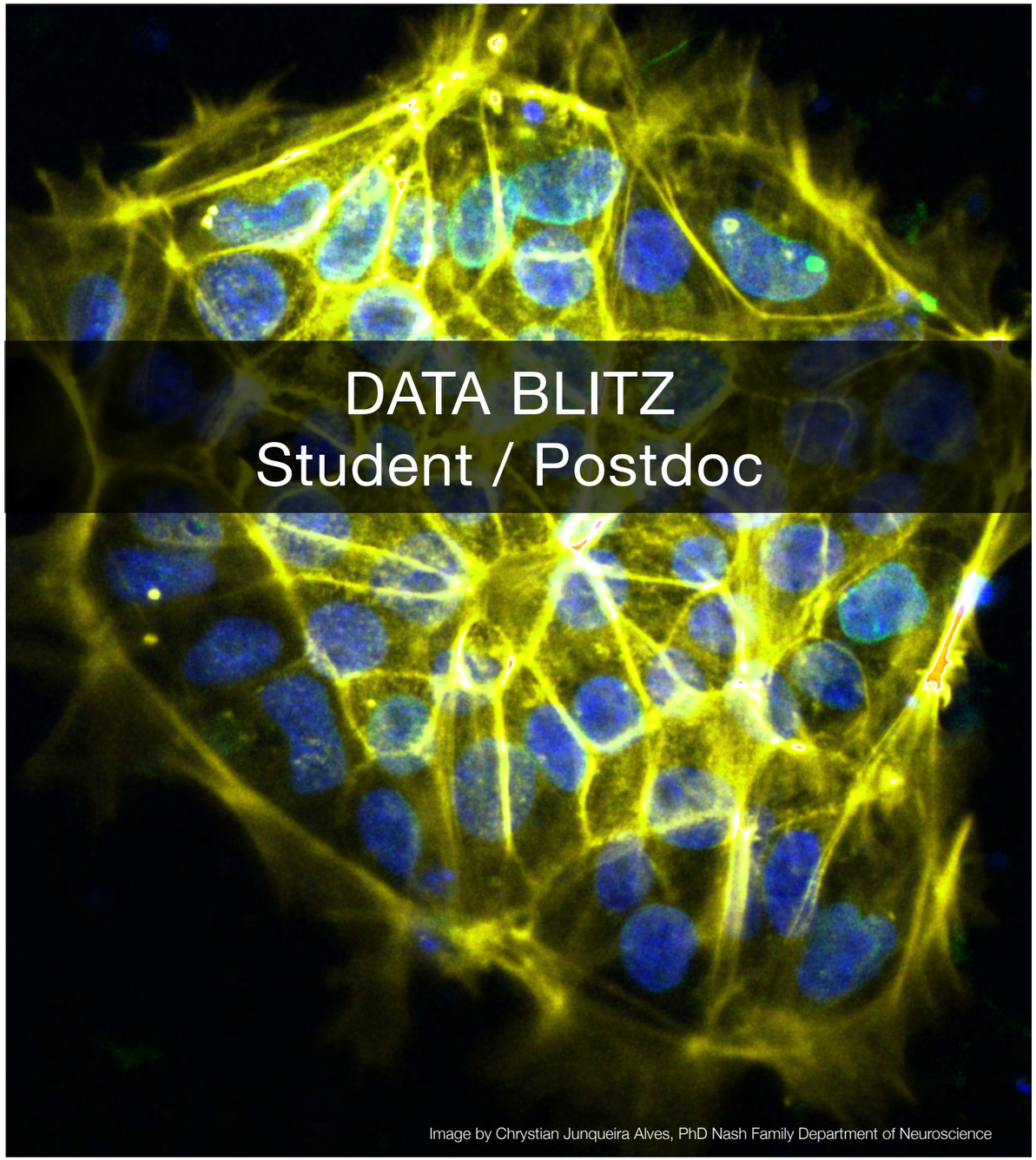


Image by Chrystian Junqueira Alves, PhD Nash Family Department of Neuroscience

1

GM-CSF regulates molecular and behavioral responses to cocaine

Lucerne,K.E., Kiraly,D.D.

Affiliations: Neuroscience & Psychiatry

Background: Recent work suggests that the gut microbiome has profound effects on brain and behavior in substance use disorders. Our group demonstrated that shifts in the microbiome alter the rewarding properties of cocaine. While the mechanisms underlying gut-brain communication are not fully understood, evidence points to the immune system as a promising gut-brain interface.

Methods: To investigate effects of gut-immune-brain signaling, we performed quantitative serum multiplex analysis on mice with intact or depleted gut microbiomes after chronic cocaine or saline. To assess the role of GM-CSF in gut-immune-brain signaling following cocaine, mice with intact or depleted microbiomes underwent a cocaine conditioned place preference (CPP) assay. Mice received daily injections of GM-CSF (10µg/kg) or vehicle throughout CPP. Nucleus accumbens of cocaine and GM-CSF treated animals was used for RNA-sequencing.

Results: The multiplex analysis identified granulocyte-macrophage colony-stimulating factor (GM-CSF) to be significantly increased by repeated cocaine only in animals with an intact gut microbiome. On the CPP test, microbiome-depleted animals injected with vehicle developed a robust place preference for low doses of cocaine as seen previously. However, injection of microbiome-depleted animals with GM-CSF returned place preference to control levels. Cocaine+GM-CSF animals showed robust regulation of synaptic plasticity pathways in the NAc.

Conclusions: Altogether, these data suggest that cocaine-induced GM-CSF signaling is dependent on the gut microbiome, and plays a key role in cocaine-induced behavioral and molecular plasticity. This introduces GM-CSF as a novel gut-immune-brain communication conduit.

Funding: NIDA/NARSAD

2

Systematic Identification and Characterization of Molecular Subtypes of Alzheimer's Disease

Neff RA, Wang M, Vatansever S, Guo L, Ming C, Wang Q, Wang E, Horgusluoglu-Moloch E, Song_W, Li A, Castranio E, TCW J, Ho L, Goate A, Gandy S, Ehrlich ME, Schadt E, Cai D, Brennand KJ, Haroutunian V, Zhang B*

GGS, ISMMS; Center for Transformative Disease Modeling, ISMMS; Icahn Institute for Data Sci.& Genomic Technology, ISMMS; MSTP, ISMMS; Nash Family Dept. Neuroscience, ISMMS; Friedman Brain Institute, ISMMS; Dept. Psychiatry, ISMMS; GSBS, ISMMS; Ronald Loeb Center for Alzheimer's Disease, ISMMS; Dept. Neurology, ISMMS; Alzheimer's Disease Research Center, ISMMS; Dept. Pediatrics, ISMMS; Neurology and Psychiatry Departments, JJ Peters VA Medical Center

Alzheimer's disease (AD) is one of the most devastating forms of dementia common in the elderly. Traditionally, a definitive diagnosis of AD is determined by the presence of amyloid-beta plaques and Tau neurofibrillary tangles on post-mortem brain tissue biopsy across the brain, but most importantly within the hippocampus. However, AD is now recognized as a heterogeneous disease caused by a variety of pathophysiologic mechanisms. In this study, we interrogate the molecular heterogeneity of AD by analyzing the transcriptomic data from 1543 samples of five brain regions in two cohorts. At least four molecular subtypes of AD are identified in each cohort, corresponding to different combinations of pathways with increased or decreased activity, such as synaptic signaling, immune system processes, mitochondrion organization, cell cycle, and neurogenesis. Additionally, each AD subtype shows distinct clinical and pathological features that are robust and reproducible. We demonstrate that subtypes can be accurately predicted across cohorts by a small number of genes. Multiscale network analysis reveals subtype-specific gene networks and drivers such as GABRB2, LRP10, MSN, PLP1, and ATP6V1A. Strikingly, we show that AD mouse models match only certain subtypes and that none of the models capture all features across all subtypes. This discrepancy may partially explain why a vast majority of AD drugs that are successfully tested in certain mouse models fail in human trials of AD. Therefore, the identification of AD subtypes and subtype-specific molecular signatures and drivers will not only help to dissect the complex molecular mechanisms of AD but also paves the way for developing more effective, targeted therapeutics against AD.

Data Blitz

3

GABAergic activation of basal forebrain promotes food consumption and hunting behaviors.

Ciorana Roman-Ortiz1, Jessica A Guevara2, Francesca A Cinque3, Roger L. Clem1

1Nash Family Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 2 St. Francis College, Department of Biological Sciences, Brooklyn, NY 3Fordham University, Neuroscience Department, New York, NY

Background: Overeating is one of the main causes of obesity. The intensification of obesity world-wide increase the necessity for the understanding the biological substrates of feeding disorders. Previous reports have shown that basal forebrain (BF) GABAergic neurons are important for food consumption but the precise contribution of this population is not fully understood. Here we sought to investigate the specific involvement of BF GABAergic neurons in feeding and hunting behaviors.

Method: To evaluate the effect of BF GAD2+ activation, we utilized optogenetic tools and a series of behavioral testing to assess food consumption and hunting behavior.

Results: In this study, we found that photoactivation of BF GAD2+ neurons increased food consumption and gnawing of non-edible materials. Moreover, activation increased time spent hunting and reduced latency to hunt in assays involving real as well as artificial prey.

Conclusion: Altogether, these findings demonstrate that BF GAD2+ activation increase consumption and hunting behaviors independent of caloric value.

Funding: NINDS and NIMH

4

The hippocampus encodes 2D social distances

Schafer M et al.

Icahn School of Medicine, Depts. of Psychiatry and Neuroscience

Social cognitive mapping may allow flexible social inferences: low-dimensional models of social spaces, anchored by dimensions such as power and affiliation, could permit quick computation of novel predictions. One way to infer similarity in such a system is to represent individuals as coordinates along relevant social axes and, as needed, compute distances between coordinates. Using fMRI, we sought to test whether the hippocampus, which performs similar functions in other spaces, shows evidence for distance signals in the social space.

In a naturalistic role-playing task in fMRI, participants interacted with various characters to achieve goals. Participant decisions were used to model the coordinates of the characters in a 2D 'social space' of power and affiliation. Using representational similarity analysis (RSA), we tested whether characters' coordinates in the 2D space were represented in hippocampal voxelwise patterns, assuming that trials with coordinates closer in the space (as measured by 2D euclidean distance) should elicit more correlated activity patterns.

Region of interest analyses (n=17) suggest that both left and right hippocampus represent 2D distances between social map coordinates (uncorrected p=.04 and p=.007, respectively). These preliminary results corroborate other reports of hippocampal distance representation in low-dimensional abstract spaces, and suggest further analyses and experiments. Additional subject recruitment is ongoing.

Funding: NIDA

5

Dopamine signaling as a cognate microglia-neuron interaction in the striatum

Hayley J. Strasburger, Pinar Ayata, Ana Badimon, et al… Anne Schaefer.

Microglia are the tissue resident macrophages in the brain that perform diverse functions to maintain brain homeostasis. Microglia phagocytose dying cells and debris, secrete growth factors, and prune afunctional synapses. In order for this homeostasis to be maintained, microglia need to sense cognate changes in neuronal activity. One exciting possible mechanism by which microglia sense changes in neural activity is by expressing receptors for the neurotransmitters present in their microenvironment. In this way, microglia could sample fluctuations in local neurotransmitter levels, infer changes in neural activity, and corresponding modify overall neural activity to maintain circuit homeostasis. Accordingly, we found that a subset of microglia in the striatum express the dopamine 1 receptor (D1R). Dopaminergic innervation is crucial for psychomotor functioning, and dysregulation is associated with neurological and neuropsychiatric disorders. We hypothesize that the unique subpopulation of D1R-expressing microglia in the striatum may actively sense changes in dopamine levels and relay these changes to striatal neurons by modulating their activity. In order to test the functional significance of this receptor on microglia, we deleted Drd1a selectively in microglia using a Cx3cr1CreErt2Drd1afl/fl mouse line. We will show changes in gene expression and behavior that occur as a consequence of ablating the microglial response to dopamine in the striatum. These findings highlight the important role of cognate microglia-neuron communication in regulating neuronal activity during homeostasis and in disease.

Funding: NIH

6

CREB-mediated activation of Zfp189 in the nucleus accumbens drives behavioral responses to psychostimulants, but not opiates

C. D. Teague1, C. J. Browne1, R. Futamura1, W. J. Wright2, F. J. Martinez1, P. Mews1, A. Minier-Toribio1, et al.

1Mount Sinai, New York, NY; 2Univ. of Pittsburgh, Pittsburgh, PA;

Background: Psychostimulants and opiates elevate cAMP-responsive element binding protein (CREB) expression in the nucleus accumbens (NAc), a major brain reward region. CREB overexpression in NAc reduces the rewarding effects of cocaine and opiates, suggesting CREB activation promotes drug tolerance. However, CREB overexpression or knockdown experiments induce transcriptional changes at hundreds of genes, limiting mechanistic insight.

Methods: Here, we use in vivo neuroepigenetic editing to causally link CREB binding to the promoter region of a single target gene, transcription factor Zfp189, with drug-induced behaviors and physiological adaptations.

Results: We observed that CREB-mediated Zfp189 activation attenuates the rewarding properties of cocaine, but increases cocaine self-administration and locomotor sensitization. Conversely, Zfp189 induction had no effects on the behavioral response to morphine. These data suggest a psychostimulant-specific mechanism by which CREB promotes drug tolerance through activation of Zfp189. This hypothesis is further supported by our data showing that Zfp189 activation mimics the same physiological adaptations in medium spiny neurons as animals with prior cocaine exposure.

Conclusion: This work is evidence that neuroepigenetic editing models a single drug-induced molecular interaction and identifies its causal contribution to the broader syndrome, which may reveal therapeutic targets for psychostimulant addiction.

Funding: Pathway to Independence Award, NIDA

Data Blitz

7

Single cell analysis of MAPT V337M organoids

KR Bowles1, DA Pugh1, S Goederie2, K Onanuga2, S Temple2, AM Goate1 & Tau Consortium Stem Cell Group

1Friedman Brain Institute, ISMMS

2Neural Stem Cell Institute, Rensselaer

Background: The MAPT V337M mutation is associated with an autosomal dominant form of Frontotemporal dementia, characterized by neurofibrillary tangles and Tau hyperphosphorylation. In order to determine the mechanism and impact of this mutation in human brain, we have generated iPSC-derived forebrain organoids derived from individuals heterozygous for this mutation and CRISPR-edited isogenic controls.

Methods: We have leveraged a single cell sequencing technology called Cell Hashing, which was used to label individual organoids from multiple isogenic cell lines. 349 individual organoids were sequenced, spanning seven iPSC lines across three batches and three differentiation time points, resulting in a unique dataset of ~380,000 cells. Read alignment and demultiplexing was carried out at the New York Genome center, and downstream data QC and analyses were carried out using Seurat, SingleR, Monocle and Ingenuity Pathway Analysis.

Results: We find that inter-organoid variability substantially increases with age, and organoids show increased glial cell proportions from 4-6 months as well as a reduction in the proportion of excitatory neurons at 6 months. We identify altered pathways associated with neural development and signaling in V337M neurons, such as synaptogenesis and branching, while V337M astrocytes suggest activation of neuroinflammatory and cytokine signaling pathways. We are in the process of comparing pseudotime trajectories between V337M and control organoids.

Funding: Tau Consortium

8

Title: Prefrontal tuning in mnemonic chunking in a spatial self-ordered search task

Feng-Kuei Chiang and Erin Rich

Nash Family Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai

Abstract: The capacity of working memory (WM) is limited to only a few items, but this constraint doesn't disrupt our cognitive performance because we implement mnemonic strategies, such as grouping items into "chunks". My previous study found that spatial tuning in lateral prefrontal cortex (LPFC) neurons was modulated by self-generated sequencing strategies, but it remains unclear how mnemonic chunking affects these neurons. To assess this, we trained two monkeys to perform a spatial self-ordered search task with six or eight identical visual targets. The subjects were required to saccade to each target, one at a time in any order, returning their eyes to the center after each selection. No reward delivered after revisited targets, so subjects had to use WM to track which targets had been visited. We defined chunks as groups of targets frequently selected together, and used graph theory approaches to quantify the degree of chunking in trial blocks. Preliminary data indicate that stronger chunking reduces error rates, consistent with the notion that chunking increases WM capacity. Using decoding approaches, we can reconstruct two-dimensional spatial locations of targets held in WM from populations of LPFC neurons. We hypothesize that chunking targets involves an efficient reorganization of this location information represented in LPFC neurons.

Funding: R01 MH121480, Schneider-Lesser Foundation, Whitehall Foundation, FBI Seed Funds.

9

Consequences of downregulation of X-linked Dystonia Parkinsonism (XDP) causative gene Taf1 in rodent brains

Maria-Daniela Cirnaru1, Jordi Creus Muncunill1, Shareen Nelson2, Travis Lewis2, Jaimie Watson2, Pedro Gonzalez-Alegre2, Michelle E. Ehrlich1

1.Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.

2.Raymond G. Perelman Center for Cellular & Molecular Therapeutics, CHOPS, Philadelphia, PA 19104, United States.

Background: XDP is an X-linked primary,progressive, late onset dystonia, described almost exclusively in males from Panay Island in Philippines. Unlike most genetic dystonias, XDP is characterized by neurodegeneration, beginning in the medium spiny neurons (MSNs) in the striosome compartment of the striatum. Genetic studies widely associate alteration of TATA-box binding protein-associated factor 1 (TAF1) gene sequence with XDP and some report decreased expression levels of the neuronal isoform, N-TAF1, characterized by inclusion of an addition 6bp intron, in the striosome neurons in XDP.

Methods: To understand the effect of the downregulation of TAF1 isoforms we specifically down-regulated Taf1 isoforms in mice and rats using P0 intraventricular or P21 intra-striatal injections of AAV miRNAs. Motor performance was evaluated 2 months post injection, followed by characterization of morphologic and molecular alterations.

Results: The miRNA sequences are able to specifically and efficiently downregulate Taf1 isoforms. In vivo, this induces motor deficits in both rats and mice that recapitulate a dystonic phenotype.

Conclusion: TAF1 downregulation mediated by specific miRNA AAVs in rodent brains provides the first in vivo model to study morphologic and molecular pathology related to XDP.

Funding: XDP, DMRF

10

Mitochondrial and proteasomal dysregulation in Parkinson's disease monocytes

Navarro E, Udine E, Parks M, Lopes K, Humphrey J, Riboldi G, Schilder B, Zhang M, Allan A, Sikder T, Argyrou C, Snijders G, De Witte L, Marcora E, Frucht S, Saunders Pullman R, Crary J, Raj T

Background: Genetic studies have identified over 90 loci associated with Parkinson's disease (PD), yet how they confer susceptibility is not understood. Our previous work suggests that some of these loci contain genes expressed in innate immune cells. We hypothesize that PD susceptibility genes modulate disease risk by affecting the innate immune cells.

Methods: We generated a large-scale (n=230) genomic, transcriptomic and functional dataset of human-derived CD14+ monocytes from disease and healthy donors. We performed independent validation in blood from AMP-PD (n=650) and in human primary microglia isolated from PD brains.

Results: Transcriptomic analysis shows up-regulation of mitochondrial oxidative-phosphorylation (OXPHOS) and down-regulation of proteasomal function. Although we identified many monocyte specific genes, this signature is conserved in blood. We observed a discordant direction of effect in OXPHOS genes in primary microglia. Unbiased network analysis corroborated these results. We further show that 14/78 PD loci have common variants that contribute to altered gene expression (eQTLs) in monocytes.

Conclusions: We have generated transcriptome profiles from PD monocytes that provide a resource for further mechanistic studies and biomarker discovery. Our findings suggest peripheral alteration of mitochondrial function-associated genes in sporadic PD, which will serve as novel therapeutic targets.

Funding: US NIH, MJFF and Ramon Areces Foundation.

11

Neuronal 3D Genome Regulation Across Human Cortical Development

Rahman et al

1 Department of Psychiatry, 2 Friedman Brain Institute, 3 Department of Genetics and Genomic Science and Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 4 Mental Illness Research, Education, and Clinical Center (VISN 2 South), James J. Peters VA Medical Center, Bronx, NY, USA.

Background: Genetic variants linked to psychiatric disease are mostly found in enhancers. Thus, it is imperative to elucidate the nuclear organization of the genome during brain development to understand how enhancers regulate neuronal genes.

Method: In situ HiC on human fetal cortical tissue from 18- and 24-weeks post-conception and on FANS sorted neurons and glia from the prefrontal cortices of young and old adult postmortem brains to investigate the spatiotemporal organization of the genome across the lifespan of human brain development.

Results: Adult neurons have weaker compartments than glia but have stronger TADs insulated within longer loops. Loops are enriched for active chromatin and cell type specific GO terms. At 24 weeks intra-TAD contacts increase along with increased TAD insulation. Neuronal TAD boundaries are stable across development, but intra and inter-TAD interactions are remodeled. Furthermore, super-long loops linking H3K27me3 enriched loci appear at 24 weeks and persist in adult neurons but are absent in glia, suggesting a repressive function implicated in neuronal identity.

Conclusion: The neuronal 3D genome differs considerably from glia, with key features established at 24 weeks of cortical development, showing subtle changes across adulthood.

Funding: NIH

12

Discovery of an alcohol-like activator (GiGA1) of GIRK channels

Zhao Y1, Ung PMU2, Zahoranszky-Kohalmi G3, Zakharov A3, Martinez N3, Simeonov A3, Glaaser IW1, Bantukallu G3, Schlessinger A2, Marugan JJ3, Slesinger PA1

1 Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

2Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

3 National Center for Advancing Translational Sciences (NCATS), Rockville, MD 20850, USA

G protein-gated inwardly rectifying K+ (GIRK) channels are essential effectors of inhibitory neurotransmission, controlling the resting membrane potential. GIRK channels have been implicated in diseases with abnormal neuronal excitability, including epilepsy. GIRK channels are tetramers composed of either the same subunit (e.g., homotetramers) or different subunits (e.g., heterotetramers). Compounds that specifically target subsets of GIRK channels in vivo are lacking. Previous studies have shown that alcohol directly activates GIRK channels through a binding pocket located in the cytoplasmic domain of the protein. Here, we report the identification and functional characterization of an alcohol-like GIRK1-selective activator, termed GiGA1, that targets the alcohol pocket. GiGA1 activates GIRK1/GIRK2 both in vitro and in vivo, and in turn, mitigates the effects of a convulsant in an acute epilepsy mouse model. These results shed light on the structure-based development of subunit-specific GIRK modulators that could provide potential treatments for brain disorders.

This work has been supported in part by the National Institutes of Health (R01AA018734) to PAS, (R01 GM108911) to A.S. and P.M.U.U.

13

Assessing the contribution of PRC2 dysregulation to Huntington's disease pathogenesis

Sahil Agrawal1, Melanie von Schimmelmann1, Sung-Wook Jang2, Anne Schaefer1

1Department of Neuroscience, ISMMS; 2CHDI Foundation

BACKGROUND: Huntington's disease (HD) is an autosomal dominant disorder characterized by progressive motor dysfunction, cognitive impairments, and behavioral changes. Although many neuronal subtypes are affected, D2 medium spiny neurons (MSNs) are the most vulnerable. RNA-sequencing studies of post-mortem HD brains and mouse models have identified significant changes in transcriptional programs essential for MSN function and identity. Our lab has previously identified that expression of these transcriptional networks are epigenetically regulated by the H3K27 methyltransferase, Polycomb Repressive Complex 2 (PRC2), raising the question whether PRC2 is dysregulated early and/or causally in HD.

METHODS: We performed striatal neuron-specific ChIP-sequencing analysis of H3K27me3 in a R6/2 model of HD prior to disease onset. We will repeat the ChIP-sequencing on mouse models of HD with different CAG repeat lengths and at different time points during disease. To determine a causal role, we will assess whether suppressing the H3K27me3 demethylases can offset changes in H3K27me3 and prevent disease progression.

RESULTS: ChIP-sequencing revealed that there is early redistribution of H3K27me3 in HD, which overlaps with gene expression changes. Notably, loci that lose H3K27me3 include transcription factors and cell death genes that are predicted to drive neuronal dysfunction.

CONCLUSION: Our preliminary data support our hypotheses that PRC2 dysregulation occurs early in HD and therefore contributes to alterations of transcriptional networks that lead to disease pathogenesis.

FUNDING: NIH, CHDI Foundation

14

Histone serotonylation in the developing and adult brain: novel mechanisms of neuroepigenetic plasticity and disease

Al-Kachak, A.

Department of Neuroscience, Icahn School of Medicine at Mount Sinai

The field of neuroepigenetics has grown rapidly over the past few decades and has recently implicated chromatin phenomena in the etiology of several psychiatric disorders including major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field still has only a limited understanding of the underlying mechanisms contributing to this disorder. New data from our laboratory suggest potential alternative mechanisms of action for monoamines–so-called histone monoaminylations–whereby, for example, the presence of serotonin in the nucleus of dorsal raphe (DRN) neurons may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood. Male C-57 mice were virally injected with either empty vector, wild-type H3.3, or modified H3.3Q5A, blocking any serotonylation. Mice were then repeatedly subjected to bouts of chronic social defeat stress by a larger CD-1 mouse screened for aggressive behavior and behavioral response was analyzed via social interaction testing. H3.3 Q5A injected animals (both control and defeated) had a significantly greater SI ratio than empty vector and H3.3 wild-type injected animals. Globally blocking serotonylation in DRN promotes a pro-adaptive resilient response in face of CSDS, which will be further explored in a more targeted, cell-type specific manner.

MQ Mental Health Research Charity and NIH

15

Mitochondrial DNA copy number is associated with dementia risk

Shea J Andrews; Alison Goate

Background: Increasing evidence has implicated mitochondrial dysfunction in the pathogenesis of Alzheimer's Disease. Mitochondria contain their own DNA outside of the nuclear genome, with every cell having between 100-10,000 copies of mtDNA. Mitochondrial DNA copy number (mtDNA-CN) has been used as a surrogate measure of mitochondrial function, with reduced mtDNA-CN associated with age-related diseases. The aim of this study was to evaluate the association of mtDNA-CN with dementia risk.

Methods: We evaluated the association of mtDNA-CN with dementia in the Mount Sinai Brain Bank (MSBB). mtDNA-CN was estimated using fastMitoCalc in 277 non-Hispanic white subjects using whole-genome sequencing data generated using DNA isolated from post-mortem frontal cortex or superior temporal gyrus brain tissue. The Clinical Dementia Rating scale was used for assessment of dementia - with controls scoring 0 or 0.5 (n = 60) and cases scoring ≥ 1 (n = 217). Logistic regression adjusting for age of death, sex, and APOE were used to evaluate the association of mtDNA-CN with dementia.

Results: A one standard deviation decrease (1 s.d. = 61) in mtDNA-CN was associated with increased risk of dementia (OR [95%CI] = 1.41 [1.05 – 1.89], p = 0.02; excluding CDR 0.5 (n = 27): 1.47 [1.0 – 2.13], p = 0.05).

Conclusion: Mitochondrial dysfunction as measured by mtDNA-CN is with an increased risk of dementia.

Funding: JPB Foundation

16

Myeloid Cells in Neurodegenerative Diseases (MyND): A longitudinal, clinical, genetic and multi-omic study

Allan A, Argyrou C, Zhang M, Navarro E, Udine E, Parks M, Riboldi G, Snijders G, De Witte L, Sikder T, Frucht S, Saunders Pullman R, Crary J, and Raj T

Departments of Neuroscience, and Genetics and Genomic Sciences, ISMMS.

BACKGROUND: The MyND initiative aims to build large cohorts of individuals with neurodegenerative diseases (NDDs) for collaborativetranslational research. Given the implication of the immune system on neurodegeneration we are collecting immune cells from subjects for biomarker and functional genomic studies with the potential to open up new diagnostics and uncover pathogenic immune mechanisms that can be targeted for therapeutic development.

METHOD: Subjects provide blood which is processed into plasma, peripheral blood mononuclear cells, and CD14+ monocytes. Microglia isolated from postmortem brain tissue for a subset of subjects is stored for further experimental use. Genotyping and multi-omic profiling is performed on all samples.

RESULTS: We have recruited 830 subjects including 380 PD, 100 AD and MCI, 280 Controls, and 70 with other neurological conditions from clinics across New York. We have isolated microglia from 24 donors from multiple brain regions. Various projects have been initiated from these cohorts for identifying disease specific expression signatures.

CONCLUSION: We have created a longitudinal cohort of diverse, sex-balanced, and extensively-phenotyped individuals with NDDs that will be critical for advancing knowledge of disease mechanisms, potentially leading to novel biomarkers and therapeutic candidates and genotype-based patient stratification.

FUNDING: NIH, MJFF.

17

Specialized functions of microglia in health and disease

Pinar Ayata, Ana Badimon, Hayley Strasburger, Brittany Hemmer, Sarah Montgomery, Andrew Chan, Eddie Loh, Bojan Losic, Anna Pimenova, Edoardo Marcora, Alison Goate, Anne Schaefer

Icahn School of Medicine at Mount Sinai

BACKGROUND : Microglia, the resident macrophages of the brain, perform homeostatic functions supporting neuronal health and function. They have recently been implicated in Alzheimer's disease (AD). Based on the complex structure of the brain in health and disease, we hypothesized that microglia have cue-dependent subtypes performing localized functions.

METHODS: TRAP-seq, ChIP-seq, immunoblotting, immunofluorescence, RNA ISH, behavior, single-cell sequencing

RESULTS: We identified cerebellar microglia as a subtype of microglia that specialize in the phagocytic clearance of apoptotic neurons. We uncovered an epigenetic mechanism underpinning microglial regional specialization, and showed that proper regulation of microglial functional state is necessary for normal brain function. Included in the cerebellar microglia signature is the reduced expression of myeloid transcription factor, Spi1, which is associated with delayed AD onset. We discovered that reduced microglial Spi1 levels alter microglial subpopulations in AD mouse models. They lead to increased numbers of microglia around extracellular plaques, as well as reduced cellular stress and increased homeostasis in microglia. These changes in microglia are associated with alleviation of AD-associated neurodegeneration.

CONCLUSION : Our studies provide a mechanistic insight into the cue-dependent specialization of microglia and its significance for normal brain function, as well as into the genetic association between microglia function and AD risk.

FUNDING: BBRF, NIMH, NIA

18

Social Decision-Making and Symptom Severity in Autism Spectrum Disorder

Sarah Banker et al.

Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY

Autism Spectrum Disorders (ASDs) are characterized by impairments in social functioning and repetitive behaviors/restricted interests. Perhaps due to deficits in socioemotional reciprocity and interpersonal exchange, ASD patients are thought to show alterations in social decision-making.

Herein, we examined associations between symptom severity and performance on two social decision-making tasks. ASD patients completed the ultimatum game, a neuroeconomic task in which they accepted or rejected proposed monetary offers from partners. Additionally, patients completed a role-playing game in which they simulated interactions with virtual characters to find a job and a home. Each interaction shifted a given character's position in a 2D 'social space' of power and affiliation. Computational modeling approaches extracted signals of interest based on the trajectory of decision-making in each task.

In the ultimatum game, ASD patients (n=8) showed higher initial offer expectations and increased sensitivity to norm violation than have been previously reported in healthy individuals (Na et al., 2019). Such maladaptive high expectations were associated with increased restricted/repetitive behaviors (SRS; r=.701). In the role-playing game, reduced social consistency (more variable character trajectories) correlated with increased autistic symptoms (ADOS; r=-.875).

Together, these results suggest that behavioral impairments in ASD influence social decision-making. Sophisticated computational modeling of behavior in two discrete tasks allowed for an improved understanding of how ASD symptoms relate to complex aspects of social decision-making.

Funding: Seaver Foundation

19

Motivational disturbances in adults with prenatal THC exposure relates to striatal epigenetic dysregulation

CV Morris, **A Bara**, RJ Ellis, AL Frick, E Loh, J Landry, TO Uzamere, P Rajarajan, A Ramakrishnan, L Shen, K Brennand, H Szutorisz and YL Hurd

Cannabis preparations are among the illicit drugs most widely abused by pregnant women in Western societies. Ingestion of cannabis and its principal psychoactive component, Δ9-tetrahydrocannabinol (THC), during the prenatal period can result in negative consequences for the offspring in adulthood, since cannabinoids cross the placenta barrier during gestation and thus can affect developmental processes. In this study, adult male progeny of rat dams exposed to THC during pregnancy exhibited increased motivation for food. To investigate the underlying biological mechanisms, we screened a panel of epigenetic regulators in the nucleus accumbens (NAc) of in utero THC-exposed offspring and identified a robust increase in the expression of Kmt2a, a histone H3 lysine 4 (H3K4me3) methyltransferase. Alterations in NAc gene expression and H3K4me3 enrichment were measured using RNA- and ChIP-sequencing. Given that an siRNA-mediated knockdown of Kmt2a in the NAc restored a normal motivational phenotype in prenatally THC-exposed rats, we developed a CRISPR-based in vitro overexpression model to directly investigate the causal relationship between Kmt2a upregulation and other molecular changes. Comparison of our sequencing data sets on prenatal THC-related mRNA and epigenetic alterations with the specific consequences of Kmt2a upregulation in the CRISPR model revealed robust alterations of genes and pathways related to neurotransmission, synaptic plasticity and cytoarchitecture integrity.

Funding: NIH, NIDA-Inserm

20

Probing the role of a prelimbic GABAergic ensemble in fear memory encoding

Kirstie Cummings, **Sabina Bayshtok**, Roger Clem

Research suggests that the rodent prelimbic cortex (PL) is required for fear expression. However, it remains unclear whether plasticity in PL contributes to memory encoding and if so, which specific circuits/cell-types are involved. In addition to excitatory projection neurons (PNs), PL harbors a network of local inhibitory neurons comprised primarily of parvalbumin- and somatostatin-expressing (SST-INs) interneurons. Using fiber photometry, in vivo optogenetics, c-Fos immunohistochemistry, and in vitro optogenetics-assisted electrophysiology, we found that PL SST-INs display cue-related activity and plasticity following fear conditioning and mediate circuit disinhibition to recruit a fear-related brain network. Since we observed plasticity only in certain SST-INs, a specialized subset is likely responsible for directing fear memory encoding. In unpublished work, we identified a PL ensemble recruited following cued fear learning using an activity-dependent neural tagging approach. We found that in addition to PNs, we also captured a population of fear-activated SST-INs. To specifically tag this SST-IN ensemble and examine its contributions to fear memory expression, we combined activity-dependent tagging with intersectional genetics. Using this approach, we tagged a largely pure population of fear-activated SST-INs and found that their optogenetic activation was sufficient to drive fear memory expression. We are also utilizing calcium-based Miniscope imaging to further test the idea that a subset of SST-INs mediates both fear memory acquisition and expression. Overall, our data suggest that a potentially specialized ensemble of PL SST-INs may orchestrate fear memory encoding.

21

Identification and Prioritization of Schizophrenia Master Regulators from Two Independent Causal Networks Integrating Genetic, Transcriptomic and Chromosome Conformation Capture Data

Noam D. Beckmann, Alexander W. Charney, Panos Roussos, Eric E. Schadt

To interpret GWAS results in the broader context of the network of gene expression and 3D structure of the genome, we used Bayesian regulatory networks (BN) to integrate genetic and gene expression datasets from two large cohorts of post-mortem samples with or without schizophrenia (Common Mind Consortium data, N = 594 and Human Brain Collection Core data, N = 386). This enabled us to model causal interactions between genes, as well as the genetic control of their expression by incorporating eQTLs and GWAS loci. To gain power to identify disease signatures, we used schizophrenia diagnosis as well as schizophrenia polygenic risk score as a continuous trait in our differential expression analyses. To focus our networks on disease-relevant signals, we used co-expression network analyses and identified modules enriched for differential expression and GWAS signatures to generate a list of input genes into our BN models. We took advantage of our flexible framework to integrate information from prior studies, including chromosome confirmation capture derived topologically associated domains, to define genes and locus interactions as structure priors boosting power to infer causal relationships and increase network model accuracy. This enabled us to identify master regulators of disease signatures and of genetic loci associated to disease, and prioritize potential mechanisms of action and therapeutic targets for schizophrenia.

22

Cell-type and brain region-specific differential chromatin accessibility analysis in Alzheimer's Disease

Bendl J, Hauberg ME, Girdhar K, Hoffman GE, Fullard JF, Roussos P

Background: Regions of open chromatin house regulatory elements required to mediate cell-type and tissue-specific gene expression. Studies of human brain have shown that dysregulation of these regulatory mechanisms is associated with Alzheimer's Disease (AD). Here, we present the largest cell type and brain region-specific study of differential chromatin accessibility in AD.

Methods: Using frozen postmortem tissue from 209 cases with AD and controls, we performed ATAC-seq to profile chromatin accessibility in 2 distinct populations of cells (neuronal and non-neuronal), isolated by FACS from two different brain regions (BA22/36). We characterized epigenetics changes associated with multiple AD phenotype ratings, i.e., clinical dementia rating, density of neurofibrillary tangles, and the average count of senile plaques. The availability of RNA-seq and whole-genome data for this cohort allowed us to measure the overlap between differentially regulated transcriptome and epigenome signatures and related pathways.

Results: We observed widespread differences in chromatin accessibility associated with AD phenotype, mostly in neuronal samples. While substantial changes between AD-cases and controls can be seen in both brain regions of interest, parahippocampal gyrus is, in general, more affected than superior temporal cortex. The differentially regulated regions of open chromatin were enriched in neurobiological and disease-related pathways.

Conclusions: This dataset provides a unique insight into molecular mechanisms underlying brain region and cell type-specific vulnerability to AD at different stages of the disease progression.

Funding: R01AG050986 and R01AG057440

23

Effects of early life sleep disruption on motor and spatial learning in a mouse model of tauopathy

NV Berryman, WD Pettibone, K Kam, AW Varga

ISMMS

Neurodegenerative diseases characterized by tauopathy often manifest deficits in motor and spatial learning; chronic sleep disruption can accelerate these pathologies. Our study aims to characterize the effects of chronic early life sleep disruption (SD) on motor and spatial learning across the lifespan of a transgenic mouse model of tauopathy.

Eight-week-old PS19 mice and wildtype (WT) littermates were subjected to automated chronic SD for 10 hours or allowed to sleep ad libitum for eight weeks. Testing occurred longitudinally at ages 6, 8, and 10 months. To assess motor learning, mice completed 10 rotarod trials each day across two consecutive days. To assess spatial learning, mice completed three Barnes maze trials each day across four consecutive days.

The results of rotarod testing indicate a deterioration in motor performance with aging in normally sleeping PS19 mice. Early life SD most impacted motor performance at 6 months, suggesting that it may have effects on both tauopathy progression and other plastic processes supporting motor learning. Barnes maze results show an expected decline in spatial memory performance across aging in PS19 mice, with no deterioration in WT controls. Surprisingly, early life SD appeared to mitigate this decline in the PS19 mice.

We report a main effect of genotype on rotarod with sleep condition at 6 months, and a main effect of genotype on Barnes maze across aging.

Funding: Alzheimer's Association

24

Replacement of degenerating motor neurons in a non-human primate model of conus medullaris/cauda equina spinal cord injury

NP Biscola1,2, et al., LA Havton1,2,3,4

1Dept. Neurology, Mount Sinai; 2Dept. Neurology, UCLA; 3Dept. Neurosci. Mount Sinai; 4VA Med Center, Bronx

Neurodegenerative reactions, including neuronal death after conus medullaris (CM)/cauda equina (CE) form of spinal cord injury contribute to functional impairments as paralysis, sensory damage, and loss of bladder, bowel, and sexual functions. No treatments are available to reverse these deficits. We investigated the efficacy of using human stem cell-derived motor neurons, supported by a new immunosuppression protocol, to replace degenerating motor neurons in a rhesus macaque chronic model of CM/CE spinal cord injury (n=8). The animals underwent an L6-S3 ventral root avulsion injury and replantation of the L6 and L7 ventral roots into the spinal cord. Approximately 250,000 cells were injected into the L5 spinal cord segment. Anatomical studies at 2 and 7 months post-op showed survival of human cells in the spinal cord of all animals. The human cells included motor neuron and oligodendrocyte progenitors, but no markers for astrocytes or microglial cells were identified. No tumor formation was detected. A human neuronal phenotype, integration of human cells, cholinergic cells, and synaptic contacts in the primate spinal were confirmed. Cystometrogram and pelvic floor EMG recordings showed preserved micturation reflexes and absence of adverse effects. We conclude that grafted human cells show long-term survival and form neural circuits in the primate spinal cord after a CM/CE injury.

Funding: CIRM, AMRF

25

Large-scale proteomic changes induced by loss of NSUN2-mediated tRNA methylation are associated with impaired synaptic transmission in the cortex and decreased depressive - and anxiety-related behavior

Blaze, J, Heissel, S, Javidfar, B, Phillips, H, Bagot, RC, Nestler, EJ, Yao, WD, Molina, H, Haghighi, F, Akbarian, S

MSSM, The Rockefeller University, SUNY Upstate Medical University

RNA cytosine methylation (m5C) is a post-transcriptional modification most abundant in tRNAs that regulates aspects of protein synthesis. NSUN2, a mammalian tRNA methyltransferase, is expressed at high levels in the CNS and has been linked to neurodevelopmental defects in humans and mice. Previous work has shown that loss of m5C produces protein synthesis deficits in non-neuronal cells, but the role of tRNA methylation in adult neuronal function has not been explored. Here, we used viral overexpression or Cre-driven conditional knockout of NSUN2 in the mouse cortex to alter tRNA methylation levels. We used targeted RNA bisulfite sequencing to assess tRNA methylation, LS-MS/MS for protein expression, electrophysiological recordings to assess synaptic transmission, and behavioral testing for anxiety/depressive-like behaviors.

Results indicate that modifying NSUN2 expression during adulthood directly affects tRNA methylation levels at highly-expressed tRNAs and causes significant changes in expression of 1488 of 6000 proteins measured, enriched for proteins involved in synaptic function and tRNA charging. Further, these changes were associated with potent effects on synaptic transmission and anxiety- and depressive-like behavior. Regulatory functions of tRNA methylation in the adult brain may offer mechanistic insights into aberrant brain function during adulthood potential for novel therapeutic interventions.

NIH, JJPVAMC

26

Deciphering a novel neurodevelopmental disorder: DDX3X syndrome.

Andrea Boitnott1,2,3,4, Dévina Ung1,2,3,4, Danielle Mendonca1,2,3,4, Kristi Niblo1,2,3,4, Marta Garcia-Forn1,2,3,4, Roko-Mladen Rasin5, Joseph D. Buxbaum1,2,3,4, Elodie Drapeau1,2, Silvia De Rubeis1,2,3,4

(1) Department of Psychiatry, Icahn School of Medicine at Mount Sinai, NY, (2) The Seaver Autism Center for Research and Treatment, NY, (3) The Mindich Child Health and Development Institute, NY, (4) The Freidman Brain Institute, NY (5) Department of Neuroscience and Cell Biology, RWJ Medical School, NJ

BACKGROUND: DDX3X syndrome accounts for up to 2% of unexplained intellectual disability in females and is caused by de novo mutations in DDX3X, an X-linked gene that regulates mRNA translation.

METHODS: We have generated a novel mouse model with construct validity for DDX3X syndrome. To determine face validity, a battery of developmental milestone tasks is assessed, along with adult behavior. To understand cortical development, cortical lamination is assessed with layer-specific markers and retrograde tracing.

RESULTS: DDX3X is expressed in a sex-specific manner in the cortex and at synapses. Development and adult behavior assessments show that haploinsufficient female mice (Ddx3x+/-) have delayed physical, sensory, and motor milestones, in addition to anxiety and hyperactivity. Ddx3x is expressed in deeper cortical layers and Ddx3x+/- mice have a misspecification of deep-layer neurons.

CONCLUSIONS: Our results are consistent with clinical features of DDX3X syndrome, supporting face validity of the mouse model. This model will be useful to understand underlying biological mechanisms.

FUNDING: NIH/NICHD; Beatrice and Samuel A. Seaver Foundation; Friedman Brain Institute; Fondation pour la Recherche Médicale

27

Marija Borozan

High School / Undergraduate Student

Stanley Lab, Endocrinology

Diabetes is an issue faced by a large population in the world. Patients receiving antidiabetic treatment can experience life-threatening hypoglycemia. The purpose of our experiment is to see if Enhanced Synaptic Response Element (ESARE) can be used to mark hypoglycemia responsive neurons in the Ventromedial Hypothalamus (VMH) and subsequently study their function. ESARE virus was expressed in the VMH of RosaCre mice, and glucose inhibited neurons are tagged with tamoxifen following 2-deoxyglucose (2DG) injection. After 72 hours animals received another injection of 2DG and were sacrificed. Brains were stained for mcherry and fos (an activity dependent marker). Overlap demonstrated our ability to tag glucose inhibited neurons. ESARE virus and a designer drug receptor were then expressed in the VMH of C57BL/6J mice and tagged with tamoxifen following 2-deoxyglucose (2DG) injection. Designer drug clozapine N-oxide (CNO) was used to activate glucose inhibited neurons and determine their function. We performed a glucose, 2-deoxyglucose, and a pyruvate tolerance test. Our preliminary data demonstrate the feasibility of this novel method and show glucose inhibited neurons increase glucose secretion via gluconeogenesis.

28

Combinatory Effects of Plexin-B2 Knockdown and Anti-Angiogenic Therapy on Glioblastoma

Concetta Brusco, Anirudh Sattiraju, Rut Tejero-villalba, Roland Friedel, Hongyan Zou

Nash Family Department of Neuroscience

Despite the development of therapies, glioblastoma (GBM) has the worst prognosis of all brain tumors. One reason for this is its diffuse invasion into healthy brain tissue. We previously showed that the axon guidance molecule Plexin-B2 plays a crucial role in GBM cell migration (Le et al 2015) and that Plexin-B2 knockdown in patient-derived glioblastoma showed a phenotypic shift toward invasion along vasculature as compared to control tumors (Huang et al 2019; in review). Here, we plan to combine Plexin-B2 knockdown with the anti-angiogenic therapy Axitinib (a VEGFR inhibitor), which has been shown to reduce tumor vascularization. The effects of Axitinib was examined using an orthotopic xenograft model. Human U87MG cells were transplanted into immunocompromised mice and Axitinib was started one week after. Consistent with previous findings, one week of Axitinib treatment greatly reduced tumor vasculature, as measured by reduction in PECAM-1 expression within GBM. In future studies, we aim to investigate the combinatory effects of Plexin-B2 knockdown and Axitinib therapy to see the effect on GBM cell migration.

NIH Funding

29

Basolateral Amygdala Network Dynamics during Unpredictable and Predictable Threat Learning and Memory

Burgess, J.A.1,2, Lim S.H1,2, Lee E.1, Goosens K.A.2

1Anatomy & Neurobiology Department, Boston University, 2 Department of Psychiatry Icahn School of Medicine, Mount Sinai

Background: Small differences in the features of cues can result in radically different forms of aversive memory. For example, unpredictable aversive stimuli evoke anxiety-like states, while clear, direct threats induce transient fear states. Despite this, both states recruit the basolateral amygdala (BLA) during fear learning. How the BLA produces divergent fear states is not known.

Methods: Time-lapse microendoscopy in the BLA to compare calcium dynamics in mice during the encoding and expression of unpredictable (UNPRED) and predictable (PRED) fear memory.

Results: UNPRED-trained mice expressed greater fear memory relative to PRED trained-mice. Calcium dynamics profiles produced similar proportions of neuronal “Winners” of competitive aversive memory encoding (neurons encoded fear memory and later participated in long-term memory recall) in the PRED-and UNPRED-trained mice. Winner neurons from UNPRED mice displayed more spontaneous calcium events and greater tone-evoked and shock-evoked calcium responses compared to PRED Winners and UNPRED “Losers” (neurons that encoded fear memory but did not participate in long-term memory recall). During fear recall, Winner neurons from the UNPRED group expressed greater tone-evoked calcium activity compared to PRED Winner neurons.

Conclusion: Our data suggest that sustained fear relies on stronger associative encoding and generally disinhibited neurons in the BLA, relative to phasic fear.

Funding: DARPA, ARO to KAG

30

BITTER BODYGUARDS: BITTER TASTE RECEPTORS IN THE BRAIN MODULATE NICOTINE AVERSION AND REINFORCEMENT

Stephanie Caligiuri, Purva Bali, Jianxi Liu, Maria Vittoria Micioni Di Bonaventura, Maya Williams, Paul J. Kenny

Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai

BACKGROUND: Through evolution it was thought that bitter taste receptors in the mouth existed to identify the presence of potentially poisonous compounds, which would lead to the induction of satiety and aversion to prevent further consumption. In 2017, it was realized that bitter taste receptors are expressed systemically, including in the brain, of which their function here has yet to be explored. As satiety and aversion are important determinants of drug addiction, we hypothesized that drugs of abuse which happen to largely be plant alkaloids, can act upon the bitter taste receptors in the brain to modulate satiety, aversion, and ultimately drug reinforcement.

METHODS AND RESULTS: Through calcium imaging in vitro, for the first time, we provide evidence that drugs of abuse such as cocaine, oxycodone, and nicotine are agonists to the bitter taste receptors. Modulation of the bitter taste receptors either by pharmacological antagonism, global or choroid plexus CRISPR-mediated KO, attenuated nicotine conditioned place aversion, enhanced nicotine preference, reduced nucleus of the solitary tract recruitment, and increased nicotine taking behavior in oral preference and intravenous self-administration paradigms.

CONCLUSION: The observed impact on nicotine reinforcement with bitter taste receptor modulation underscores the incredible novelty and importance of this distinct chemosensory network in drug abuse.

FUNDING:NIH and CIHR

31

Neuroimaging the effects of drug-related cue-reactivity on inhibitory control in cocaine use disorder

Ahmet O. Ceceli*, Muhammad A. Parvaz*, Matthew Schafer, Pias Malaker, Nelly Alia-Klein, Rita Z. Goldstein

ISMMS

Drug addiction is characterized by impaired Response Inhibition and Salience Attribution (iRISA), particularly affecting drug vs. other cues/reinforcers. Though these functions are associated with frontocingular/corticostriatal regions, their interaction in cocaine use disorder (CUD) remains unclear.

We developed a novel stop-signal fMRI task to investigate the iRISA interaction in CUD. Participants were shown a word (salient—drug/food/threat-related, or neutral) in white text and performed Go responses as soon as text color turned blue/green. Occasionally, text color turned red following a stop-signal delay (SSD), signaling to withhold the prepotent response (Stop trials). Using SSD and Go latency distributions, we derived the stop-signal reaction time (SSRT; a classical inhibitory control measure). We compared drug/food trials, hypothesizing drug words to uniquely elicit higher inhibitory control demands (longer SSRT in CUD vs. controls), and aberrant corticostriatal activations.

Despite task performance similarities across groups (CUD n=26; controls n=36), preliminary fMRI analyses (CUD, n=10) revealed increased putamen/inferior frontal gyrus/medial-prefrontal cortical activity during successful inhibition to drug vs. food words in CUD (cluster-corrected, $p<.05$). Additionally, greater severity of dependence among CUD correlated with longer SSRT (across cues; $r(24)=0.42$; $p=.03$). Bolstering the iRISA model, preliminary results highlight that our novel task parses the neurobehavioral bases of inhibitory control and salience attribution, elucidating how drug-related cue-reactivity (vs. other reinforcers) impacts the neural signature of inhibitory control in CUD.

Funding: NIH

32

Hypoactive medial prefrontal cortex during trauma experience at developmental stages leads to anxiety-like phenotype

Darpan Chakraborty and Roger Clem.

Icahn School of Medicine at Mount Sinai

The experience of traumatic stress (TS) is a significant risk factor in the development of depression and anxiety. Several psychiatric conditions have a higher occurrence of onset during childhood. However, the extent to which stressful experiences are processed differently by developing brains remains poorly understood.

In this study we compared long-term effects of a single episode of TS (unpredictable footshocks) in early adolescent versus adult mice. We have combined behavioral batteries, c-fos activity, electrophysiology and fiber photometry in freely moving animal to determine the cellular mechanism for the effects of TS on medial prefrontal cortex (mPFC) neurons.

Analysis of cFos activity and electrophysiology results revealed that TS induced in early adolescent mice a decrease in prefrontal activity with resultant long-lasting anxiety-like phenotype. Whereas in adult animals the same experience instead induced increased activity in the mPFC and a deficit in social interaction. Both phenotypes were prevented by alpha- and beta-adrenergic receptor blockade at the time of trauma. Moreover, the fiber photometry data indicates one of the key physiological parameters impacted by TS is the hypo-excitability of mPFC neurons and long-lasting hypoactivity during exposure to anxiogenic environment.

We here uncover a role for the hypoactive mPFC in processing aversive stimuli and modulate distinct brain networks in developing mice, which may play a role in their expression of anxiety-like behavioral phenotypes in adulthood.

NIH

33

Region-specific microglial responses to peripheral influenza infection

Andrew Chan, Carles Martínez-Romero, Pinar Ayata, Ana Badimon, Eddie Loh, Molly Estill, Li Shen, Adolfo García-Sastre, Anne Schaefer

Departments of Immunology, Microbiology, and Neuroscience, Icahn School of Medicine at Mount Sinai.

BACKGROUND: Sickness behaviors are a unique paradigm during which the central nervous system (CNS) responds to a peripheral infection with conserved and predictable behavioral changes. However, it is unclear how local responses to peripheral infection lead to changes in neuronal circuitry controlling sickness behaviors. We propose that microglia, the tissue-resident macrophages of the CNS, serve a key role in mediating sickness behaviors by sensing peripheral inflammation and conveying this information to neuronal circuits underlying sickness behavior.

METHODS: We infected mice with a sublethal challenge of mouse-adapted influenza A virus as a physiological model of a peripheral infection. We subsequently assessed the temporal dynamics of the peripheral immune response, sickness behaviors, and region-specific microglial activation.

RESULTS: We observed that microglial are early responders to peripheral infection and display significant transcriptional changes occurring prior to the onset of sickness behaviors. Notably, these changes also occur in a region-specific manner.

CONCLUSION: We comprehensively profiled the temporal and spatial responses of microglia following peripheral influenza challenge. Because transcriptional changes in striatal microglia appear temporally correlated with the onset of sickness behaviors, we speculate that striatal microglia may modulate sickness behaviors. We will test this specific hypothesis using region-specific microglial depletion models.

FUNDING: NIAID, NIH

34

Chronic social defeat stress increases intestinal permeability and endotoxemia in mice

KL Chan1, KB LeClair1, Y Shimo1, F Cathomas1, MP Kaster1, G Price1, Y Schmitt1, SJ Russo1

1ISMMS

Major depressive disorder (MDD) represents the leading cause of disability, affecting >300 million people worldwide. Largely characterized behaviorally, it is critical to identify biological changes associated with MDD. Emerging literature recognize a correlation between MDD and inflammation; however, it is not fully known how this inflammation initiates. Recently, several chronic inflammatory conditions have been associated with increased intestinal permeability. We hypothesize that chronic stress compromises the gut barrier, allowing translocation of gut microbial byproducts into circulation, triggering inflammation associated with depression-like behavior.

To model depression-like behavior in mice, a 10-day chronic social defeat stress (CSDS) model was used. Following CSDS, mice were separated into ‘susceptible’ or ‘resilient’ groups based on social avoidance, and compared with control mice, which never encountered aggressor mice.

To test intestinal permeability following CSDS, mice were orally-gavaged with FITC-labelled dextran, with its concentration measured in circulation 1-4 hours later. At all time points, blood FITC levels were elevated in susceptible mice. Moreover, circulating bacterial endotoxins, possibly arising from gut bacteria, were greater in susceptible mice. Additionally, several tight junctions, including claudins-4, 8, and 12 were downregulated in the intestines from defeated mice. Evaluating gut inflammation, IFNγ+ T cells were upregulated, and IL4+ T cells were downregulated in susceptible mouse colons. Collectively, these results reveal that CSDS induces intestinal barrier breakdown, which may promote systemic inflammation.

Funding: NIH, CIHR

39

TYROBP deficiency improves motor function in a mouse model of Huntington's disease

Jordi Creus Muncunill, Michelle E. Ehrlich

Department of Neurology, ISMMS, 1468 Madison Avenue, New York, NY, 10029, USA.

Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin (htt) gene. This leads to motor and cognitive deficits associated with cortical, striatal and hippocampal alterations. Microglia appear to contribute to HD pathology following activation of the innate immune system. We previously demonstrated that deficiency of TYROBP/DAP12, a microglial transmembrane signaling polypeptide, ameliorates the phenotype of mouse models of amyloidosis and tauopathy. Mechanistically, absence of TYROBP reduces complement cascade initiator C1q levels, which contributes to dysfunctional synaptic pruning in Alzheimer's disease. Here we aim to evaluate the effects of TYROBP deletion in a mouse model of HD. The Q175 knockin mouse model of HD, either heterozygote or homozygote, was placed on a TYROBP null background. Using a panel of behavioral, morphologic and biochemical/molecular assays, we characterized the effects of TYROBP deletion on motor performance, htt aggregation, and transcriptional dysregulation in the Q175 mouse. Genetic deletion of TYROBP ameliorated motor dysfunction in Q175 mice at 6 months of age. However, it did not normalize either the number of microglial cells or transcriptional dysregulation, as determined by levels of DARPP-32. Notably, improved motor performance was accompanied by a decrease of C1q levels and a normalization of CD68+ particles. TYROBP deletion ameliorates the motor phenotype in Q175 knockin mice, perhaps via a decrease in C1q levels.

NIH

40

A Map for Goals in the Human Brain

Denise Croote1, Alison Montagrin1, Liron Lerman2, Daniela Schiller1

1Department of Neuroscience 2KreatAR

Episodic memories allow us to travel back in time, for example, to relive a past birthday party, but also to project ourselves into the future. The ability to plan for future events is a key component of survival, and episodic memory and future simulation have been shown to engage the same core network of brain regions, including the hippocampus, parahippocampus, and posterior parietal cortices. Here we examine how the hippocampus maintains an updated representation of future goals. We test whether the hippocampus creates a cognitive map of goals, where goals are mapped based on their relevance and the time left to achieve them. We hypothesize that the anterior hippocampus will be preferentially activated while processing distant future goals, while the posterior hippocampus will be activated while processing proximal goals. We designed an innovative paradigm where participants went on a 4-year 'Mission to Mars' during 7.0T fMRI. While on Mars, participants kept track of goals that they needed to accomplish in the current Mars' year, in the near future, in the distant future, and goals that they had already accomplished. We scanned 34 participants and behavioral analyses revealed that participants took significantly longer to process future goals when compared to past goals. This suggests that past and future goals are construed differently, and ongoing analyses are examining how the brain maintains an updated representation of an individual's goal space.

41

Epigenetic mediated paternal transmission of stress phenotypes to offspring

Ashley M. Cunningham, Deena M. Walker, Aarthi Ramakrishnan, Eric J. Nestler et al.

The Friedman Brain Institute

Background: Depression risk is highly influenced by both genetic and environmental factors. Recently, it has been proposed that epigenetic mechanisms may also be a contributing factor. We tested the hypothesis that epigenetic alterations in sperm during chronic social defeat stress (CSDS) transmit increased susceptibility to stress phenotypes to F1 offspring.

Method: Adult male mice exposed to CSDS, or control non-defeated mice, were bred with non-stressed female mice and their offspring were assessed behaviorally to examine depressive- and anxiety-like measures at baseline and following offspring exposure to a submaximal stressor. Artificial insemination (AI) was used to assess the direct role of male gametes in the transmission of stress phenotype to offspring. We used RNA sequencing of mature sperm cells to show transcriptomic changes occurring in susceptible and resilient males following CSDS.

Results: We show that both male and female offspring from resilient and susceptible fathers show altered depressive- and anxiety-like phenotypes at baseline and following exposure to a submaximal stressor when produced via natural mating. However, with AI only susceptible fathers transmit stress phenotypes to their offspring which may in part be explained by epigenetic mechanisms such as lncRNAs.

Conclusion: These results suggest that while both resilient and susceptible fathers transmit stress phenotypes to the F1 generation only susceptible fathers do this via epigenetic mechanisms.

Funding: Hope for Depression Research Foundation and NIMH

42

Elucidating the role of formin proteins in dendritic spine morphology and plasticity.

Aaron Das

Benson Lab

Mentor: Abhishek Sahasrabudhe, PhD

The actin cytoskeleton is an integral structure in the formation and maturation of synapses. Actin filaments are formed from the assembly of G-actin monomers in a process called actin nucleation. Formin's role as an actin nucleating protein involves elongating actin filaments. The specific functions and effects of the formin proteins in the formation of dendritic spines aren't completely clear. This research tests which proteins specifically affects synaptic development and maturation by individually knocking-out different formin genes in cortical mice neurons using CRISPR/Cas9. The phenotypes that we will be quantifying from imaging the neurons are spine density, size, head length, neck length, and the intensity of synaptic signals. By studying the formin family's effects on dendritic spine morphology, we can further understand the genetics that influence synapse development, which in turn allows us to target mutations in those genes and understand their relationship to cognitive disabilities.

43

Rare Copy Number Variation and Common Polygenic Risk in Bipolar Disorder Subtypes

A de Pins, PGC CNV Working Group

Icahn School of Medicine at Mount Sinai, Department of Psychiatry

Background: Studies of bipolar disorder (BD) show that common single nucleotide polymorphisms (SNPs) confer risk, while rare copy number variants (CNVs)'s implication is debatable. We integrated CNV, SNP, and clinical data from 26,055 cases and 27,814 controls to assess if different genetic variations confer risk to different psychiatric symptoms.

Methods: We will test CNV burden in BD cases compared to controls at various thresholds and follow-up previously-reported associations of CNV burden in BD. Next, we will test common SNPs' and rare CNVs' contribution to different psychiatric symptoms using CNV burden and polygenic score metrics for each case subject.

Results: We analyzed a subset of 6,353 cases and 8,656 controls and found no significant CNV burden difference between cases and controls. Schizoaffective disorder (SAB) cases had increased rare CNVs compared to other subjects. SAB is characterized by psychosis so we investigated CNVs' role on psychosis. CNV burden and SCZ polygenic risk scores (PRS) were significantly higher in SAB compared to other cases yet did not differ between BD I groups stratified by psychosis. SCZ PRS was higher in BD I group with psychosis.

Conclusion: We will present the largest study of CNVs in BD to date. Integrating CNV, SNP and clinical data will help dissect the contribution of genetic variations to different symptoms in BD.

Funding: NIMH

44

Synergistic impact of simultaneous, bi-directional manipulation of multiple schizophrenia eQTL genes in a human neuronal model.

P.J. Michael Deans et al.

Background: Schizophrenia is a neuropsychiatric illness impacted by hundreds of common genetic variants of small effect, accounting for a substantial proportion of disease risk. Combinatorial analyses of genome wide association studies (GWAS) and post-mortem studies of RNA-sequencing expression in human brains permit predictions of the impact of these variants on gene expression in the brain (expression quantitative trait loci (eQTL)). However, it is not known whether multiple eQTLs impacting a single functional pathway have a greater impact on neuronal function than eQTLs across multiple functional pathways. Comparing the synergistic impact of these eQTLs requires a scalable, bi-directional method to simultaneously perturb multiple genes in neural cells.

Methods: hiPSC-derived neuronal cultures were transcriptionally manipulated using both CRISPR activation and RNA interference targeting each of the genes in each of three schizophrenia eQTL gene functional sets, as well as multiple genes in each set simultaneously. The impact of each of these combinations of schizophrenia gene perturbations on neuronal function was assessed using a combination of RNAseq, multi-electrode array recording and high-throughput imaging.

Results: gRNAs and shRNAs targeting the selected genes have been successfully validated in hiPSC-derived excitatory neurons using qPCR.

Conclusions: CRISPR activation and RNA interference can be used together to perturb multiple schizophrenia eQTL genes simultaneously in human neurons. This model thus provides a means for studying the synergistic impact of schizophrenia eQTLs on neuronal function.

Funding: NIH

45

Investigating medial amygdala circuits in glucose homeostasis

Kavya Devarakonda, Kaetlyn Conner, Darline Garibay, Mitchell Bayne, Paul Kenny, Sarah Stanley

ABSTRACT: One out of every 10 Americans has diabetes, increasing their risk of death by 50% and more than doubling their health care costs. Delineating how the brain regulates metabolism, including feeding behavior and glucose homeostasis, may shed light on how those processes are altered in disease. The medial amygdalar nucleus (MeA) regulates the intersection of stress, social behavior, and metabolism. Fos expression in the MeA of mice is altered by changes in energy availability – fasting/re-feeding and hyper-/hypoglycemia – suggesting this nucleus may regulate feeding behavior and blood glucose levels in response to internal cues. The primary downstream targets of the MeA are the principle nucleus of the bed nucleus of the stria terminalis (prBNST) and ventromedial hypothalamus (VMH), regions previously shown to regulate metabolism. Cfos immunohistochemistry and retrograde labeling show that MeA neurons that project to the VMH (MeA->VMH) are preferentially activated by a 36h fast, compared to ad libitum feeding and a 1h refeed. Selectively activating MeA->VMH neurons using chemogenetics induces hyperglycemia via increased liver gluconeogenesis. Ongoing fos, axonal tracing, and behavioralstudies aim to delineate the contributions of different MeA cell types to glucose homeostasis in the context of other competing behaviors including social interaction and stress.

FUNDING: American Diabetes Association, American Heart Association

46

Minian: an open-source miniscope analysis pipeline with interactive visualization tools

Zhe (Phil) Dong; Yu (Susie) Feng; William Mau; Lingxuan Chen, PhD; Zachary T. Pennington, PhD; Yosif Zaki; Kanaka Rajan, PhD; Tristan Shuman, PhD; Daniel Aharoni, PhD; Denise J. Cai, PhD

Miniature microscopes have gained a lot of traction for in vivo calcium imaging in freely behaving animals. However, extracting calcium signals from raw videos is a computationally complex problem and remains a bottleneck for many researchers utilizing single photon in vivo calcium imaging. Recently, a few analysis pipelines have been developed and work well on extracting calcium events. However, most analysis packages that are available either have key parameters that are hard-coded or lack detailed documentation on how to set parameters properly. Furthermore, there is a need for a user-friendly tool that offers informative visualization of how altering parameters affect the output of the data. Our open-source analysis pipeline, Minian, facilitates transparency and accessibility of the underlying algorithm of the pipeline. Minian contains interactive visualization tools for every analysis step, as well as detailed documentation and tips on parameter tuning. The visualization tool guides users to explore and select the appropriate parameters which is especially helpful in analyzing different cell-types and brain regions. Minian has been validated to reliably and robustly extract calcium events across different cell types and brain regions. In practice, Minian provides an open-source calcium imaging analysis pipeline with user-friendly interactive visualization to explore parameters and validate results.

Funding: Friedman Scholar Award, NIMH-1DP2MH122399-01, NIH-R01-MH120162

47

Exploring de novo Identified Enhancer RNA in Schizophrenia and Controls

Pengfei Dong, Pasha Apontes, Samir Rahman, Wen Zhang, Gabriel Hoffman, Panagiotis Roussos

Genetics and Genomic Sciences, Ichan school of medicine at Mount Sinai

Background: The majority of identified psychiatric disease-associated genetic variants lie in non-coding regions, where it is expected to affect gene expression by cis-regulatory elements such as enhancers. A growing body of evidence has revealed widespread transcription at active enhancers, resulting in short, bidirectional non-coding enhancer RNAs (eRNAs). However, the relationship between eRNAs and the target gene expression as well as its role in disease status remains to be further determined.

Method: We developed a new computational method, which combines epigenomic signals including H3K27ac ChIP-Seq and ATAC-Seq with RNA-Seq data, to de novo identify transcribed enhancers.

Result: With this approach, we found thousands of non-coding eRNAs in neuronal and non-neuronal cells derived from human brain tissue. Comparing to other enhancers, transcribed enhancers are enriched for cell type-specific super-enhancers and long-range chromatin loops. Neuronal eRNAs significantly overlapped with schizophrenia and autism-associated variants. We further explore the mRNA and eRNA expression profiles in 1534 schizophrenia and control RNA-seq samples from the CommonMind Consortium.

Conclusion: Our eRNA identification can be used to investigate the transcribed enhancer expression with large scale non-polyA RNA-seq samples. Our study shows how gene expression is regulated by distal expressed enhancers and genetic variants

48

Fine-mapping validation of the MS4A AD risk locus in a human microglia model

Efthymiou AG1, Novikova G1, Marcora E1, and Goate AM1

1Ronald M. Loeb Center for Alzheimer's Disease, Nash Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029

BACKGROUND Understanding the role of common genetic variants in Alzheimer's disease (AD) risk and progression is an important component of future drug discovery. We have previously integrated human genomic and epigenomic data to fine-map AD risk loci to identify putative causal genes and variants that mediate disease risk. Intergenic variants within the MS4A locus on chromosome 11 are associated with reduced AD risk, delayed age-at-onset of AD, and higher levels of soluble TREM2 (sTREM2) in human cerebrospinal fluid. We have identified a putative causal variant present in an active myeloid cell enhancer that correlates with decreased MS4A4A and MS4A6A gene expression.

METHODS Using CRISPR/Cas-9 gene editing, we have created three pairs of isogenic human induced pluripotent stem cell (iPSC) lines for this variant and differentiated them to microglial-like cells (iMGLs).

RESULTS Preliminary data suggests that the addition of the protective variant in these isogenic lines decreases MS4A gene expression, consistent with our hypothesis. We will continue to use these lines to compare the impact of low MS4A and high MS4A expression in iMGLs with respect to phagocytosis, sTREM2 release, and response to different stimuli.

FUNDINGThis work is supported by the JPB Foundation, the National Institutes of Health, and the Neurodegeneration Consortium.

49

Systemic administration of dezchloroclozapine does not alter resting state functional connectivity in macaques

Elorette, C1; Fujimoto, A1; Russ, BE1,2; Rudebeck, PH1

1Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA 2Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962

The combination of functional neuroimaging (fMRI) and pathway specific manipulation of neural activity using chemogenetics in non-human primates has the potential to reveal the underlying basis of functional connectivity measures that are widespread in human neuroimaging. DREADDs, designer receptors exclusively activated by designer drugs, are a chemogenetic system allowing for selective, reversible manipulation of neural activity via systemic administration of a synthetic ligand. Deschloroclozapine (DCZ) is a newly developed ligand that efficiently activates DREADD constructs (Nagai et al. 2019). DCZ's impact on functional resting-state networks in the absence of DREADD receptors is unknown. We evaluated the effects of systemic DCZ administration (0.1 mg/kg IV, 1 ml) in rhesus macaques during resting state fMRI. Whole brain functional images were acquired on a Siemens MAGNETOM Skyra 3T scanner (TR/TE 2100/16 ms, voxel size 0.5x0.5x0.5 mm). DCZ's effect on functional connectivity maps was negligible. DCZ did not alter the pattern of amygdala-PFC functional connectivity observed after saline injection (1 ml IV; $p<0.05$). These findings provide the essential first step in the development of fMRI-chemogenetics research by showing that DCZ alone, at doses used to activate DREADD receptors, does not alter resting-state functional connectivity patterns.

Funding: NIH

50

Dynamic of value representation in the prefontal cortex

Pierre Enel (1), Joni Wallis (2), Erin Rich (1)

1-Neuroscience Department, Mount Sinai School of Medicine, New York, NY 2-Department of Psychologie, University of California at Berkeley, Berkeley, CA

Optimal decisions require us to keep track of the value of different choice options. When the outcome is delayed, updating the value of an option requires us to temporarily hold the value of that option in memory to compare it with the actual outcome. The orbitofrontal (OFC) and anterior cingulate (ACC) cortices have been shown to represent the value of expected and received outcomes, however little is known about the dynamics of value representation in these areas over an extended delay. In other areas of prefrontal cortex that specialize in holding information online across delays, there has been debate about whether this information is maintained by stable or dynamic neural representations. Here we extend these ideas to investigate the dynamics of neural representations of value in a value-based decision making performed by monkeys and compare the key dynamical properties found in these regions to an artificial neural network model of the prefrontal cortex and its interaction with the basal ganglia. Preliminary results indicate that a network trained only to predict upcoming events and rewards exhibits strong representation of value across cue-outcome delays.

Funded by NIH R01 DA19028, R01 MH097990, and K08 DA039051 and the Hilda and Preston Davis Foundation

51

Investigation of the Clinicopathological and Genetic Signatures of Primary Age-Related Tauopathy

Kurt Farrell1, Megan Iida1, Natalia Han1, Alan Renton1, Jamie Walker2, Tim Richardson3, Tushar Bhangale4, Charles White5, John F. Crary1

1) Departments of Pathology and Neuroscience, Friedman Brain Institute, Ronald Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai 2) Department of Pathology, UT San Antonio Health 3) Department of Pathology, SUNY Upstate 4) Department of Human Genetics, Genentech 5) Department of Pathology, UT Southwestern

Background: Here we investigate the clinical neuropathological and genetic drivers of a category of Alzheimer disease (AD) neuropathologic change termed primary age-related tauopathy (PART). Subjects with PART have no or sparse amyloid-beta peptide containing-plaques but do have AD-type neurofibrillary tangles (NFTs) confined within the medial temporal lobe (MTL).

Methods: PART tissues were curated from twenty brain banks (n > 1000). Fixed tissue of targeted brain regions was stained immunohistochemically for abnormal hyperphosphorylated tau (p-tau) and assessed using quantitative and semi-quantitatively approaches. DNA was genotyped using a SNP array and a genome-wide association analysis was performed with Braak NFT stage as a quantitative trait.

Results and conclusions: One SNP on chromosome 4 (rs56405341, MAF=0.27) achieved genome-wide significance (p=4.82x10-8) in a locus containing the SCLT1 and JADE1 genes. Additionally, we observed signals in loci previously implicated in AD, but not APOE, the strongest common risk allele for sporadic AD. Lastly, we observed significantly more pathological tau in the MTL in subjects with cognitive impairments verses those without.

Funding NIH

52

Altered synapse size in hippocampus and dorsolateral prefrontal cortex in adolescent rhesus monkeys exposed to sevoflurane in infancy

Tristan Fehr, William G. M. Janssen, Mark G. Baxter

Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai

Background: Human studies indicate increased risks for learning disability and other behavioral changes following multiple, early-life (<4yrs) general anesthesia exposures. Animal models of early-life anesthesia indicate widespread neural and glial death, synapse loss, and mitochondrial damage. Adolescent rhesus monkeys exposed repeatedly to anesthesia in infancy exhibited enduring altered anxiety and cognition. However, long-term impacts of infant anesthesia exposures on synaptic ultrastructure have not been thoroughly studied.

Methods: Female and male rhesus monkeys received four-hour exposures to sevoflurane, or brief maternal separation as a control, on ~P7, P21, and P35. At 48 months, we performed blinded electron microscopy in CA1 of the hippocampus and dorsolateral prefrontal cortex (dlPFC) to assess synaptic ultrastructure. Data were analyzed by ANOVA and linear mixed models.

Results: In CA1, anesthesia monkeys showed an 8.9% reduction in mean synapse area, with an anesthesia and sex interaction in the largest 5% of synapses. In dlPFC, anesthesia monkeys had reduced mean synapse area in the largest 5% of synapses. Other synaptic and mitochondrial measurements were unchanged. Conclusions: Repeated exposure to general anesthesia in infancy can cause region- and sex-specific changes in synaptic ultrastructure in hippocampus and prefrontal cortex that persist into adolescence, and may relate to long-term behavioral changes.

Funding: NIH, NSF Predoctoral Fellowship, ISMMS

53

Differential effects of adolescent THC experience on decision making in adulthood: dose effects

JMN Ferland, YL Hurd, et al.

Adolescent cannabis experience is associated with increased risk of psychiatric disease in adulthood. Furthermore, THC, the primary psychoactive component of cannabis, has risen to unprecedented levels, which may enhance risk for psycho-pathologies. Cost/benefit decision-making deficits are common in psychiatric disease, as well as after chronic cannabis experience, and may serve as a unique trait to study how cannabis affects cognitive biases relevant to psychiatric disease. To investigate the impact of adolescent THC exposure, and dose, on decision making in adulthood, adolescent rats were exposed to a "recreational" dosing schedule of vehicle, 1.5 mg/kg, or 5 mg/kg dose of THC, followed by a rat gambling task to assess decision making and impulsivity. After reaching stability, animals underwent an acute THC challenge to assess whether adolescent dose would mediate the response to drug-induced cognitive effects. At baseline, 1.5 mg/kg rats showed increased advantageous choice. In contrast, 5 mg/kg rats showed significantly increased impulsivity and some-what impaired decision making after acute THC, an effect opposite to vehicle and 1.5 mg/kg rats. Surprisingly, after the acute THC challenge, vehicle and 1.5 mg/kg rats showed impairments in choice and impulse control, whereas 5 mg/kg behavior was unchanged. These results show adolescent THC experience differentially affected decision making at baseline, on drug, and after adult drug experience. Ongoing molecular assays are underway to determine whether CB1 functionality and cell-type specific expression underlie these effects.

54

Cell type specific functional impact of aberrant NRXN1α splice isoforms from patient derived hiPSC-neurons

Michael B. Fernando1, Aleta Murphy1, Erin K. Flaherty1, Shijia Zhu1, Gang Fang1,3, Paul A. Slesinger1, Kristen J. Brennand1,2,3

1Departments of Neuroscience, 2Psychiatry and 3Genetics and Genomics

Neurexins are pre-synaptic proteins involved in the construction of neural circuits. The diversity of neurexins arise from isoform variants due to extensive alternative splicing. Heterozygous deletions in NRXN1 are strongly associated with psychiatric and neurodevelopmental disorders. Patient-specific NRXN1+/- hiPSC- forebrain neurons show greater than two-fold reduction of half of the wildtype NRXN1α isoforms and express dozens of novel isoforms from the mutant allele. The overexpression of a single mutant isoform (MT) in control neurons decreased network activity, while the overexpression of a wildtype isoform (WT) rescued two cases. However, because forebrain neurons yield a population of mixed cell types, we seek to resolve the cell type specific impact of MT splice variants.

We will employ a combination of electrophysiological, proteomic, and transcriptomic strategies in NGN2-glutamatergic and ASCL1/DLX2-GABAergic induced neurons. First, we will attempt to rescue reduced neuronal activity in patient-specific NRXN1+/- neurons via CRISPR/CasRx mediated selective knockdown of MT isoforms and assess the impact on synaptic transmission. Second, we will apply mass spectrometry to contrast synaptic binding partners of WT/MT isoforms. Third, we will compare bulk and single cell RNAseq to explore the impact of WT/MT isoforms on cell type composition and downstream gene expression. Overall we will evaluate excitability, neurotransmission, gene pathways, and protein binding partners of NRXN1a.

NIH

55

TIMP2 regulates hippocampus-dependent cognitive function

Catarina Ferreira1, Annie Phan1, Yihang Wang1, Jeffrey Zhu1, Danielle Schwartz1, Amanda Fakira2, Robert Blitzer2, Joseph Castellano1

1Nash Family Department of Neuroscience, Friedman Brain Institute, Loeb Center for Alzheimer's Disease, 2Departments of Psychiatry and Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Aging is the major risk factor for neurological disorders such as Alzheimer's disease (AD), and exposure to youthful-blood factors counteracts age-related decline. The blood-borne, youth-associated factor tissue inhibitor of metalloproteinases-2 (TIMP2) was shown to revitalize aged mice hippocampus, while its depletion impairs LTP, arguing for unknown TIMP2' roles mediating hippocampal function. To assess this role, and how it relates to AD revitalization, we characterized hippocampus-dependent memory upon TIMP2 manipulation, as well as its putative cellular and molecular targets. Similarly, we analyzed markers of AD pathology in AD mice models lacking TIMP2. We show that hippocampal TIMP2 is restricted to hilar mossy cells, and its deletion affects DG granule cells intrinsic membrane properties, decreased adult hippocampal neurogenesis and increased microgliosis. Concomitantly, TIMP2KO mice presented impaired hippocampus-dependent cognition. Moreover, TIMP2KO hippocampi present increased levels of TIMP2's target MMP2, suggesting that it may exert its role through MMPs to regulate extracellular matrix. Finally, peripheral and hippocampal TIMP2 levels were reduced in AD mouse models, phenocopying deficits observed in aging and suggesting interactions with pathology. Together, our findings reveal TIMP2 as important for hippocampal function, thus representing an important target for aging and AD-associated therapies.

NIH, BrightFocusFoundation, Katz-Martin Friedman Brain Institute Scholar Award

56

The effect of delay to reward on probabilistic learning in non-human primates

J. Megan Fredericks, Jared E. Boyce, Peter H. Rudebeck

Maladaptive reinforcement learning is a defining symptom of depression and anxiety disorders. Clinical studies have localized this maladaptive learning to the prefrontal-cortex (PFC) and amygdala. In non-human primates both the amygdala and ventrolateral-PFC are required for probabilistic reward learning. Despite this knowledge, the specific contribution of these areas to reward learning has not been deciphered. We hypothesize that within this circuit the ventrolateral PFC, but not amygdala, is specifically required to hold information about chosen options online until a reward is delivered. To test our hypothesis, we developed a touch screen based dynamic two-choice probabilistic behavioral paradigm where the delay between the choice and the reward delivery was manipulated. The delay between choice and reward (0, 1, or 2 seconds) was fixed for the duration of a daily session. Monkeys readily learned the task when there was no delay between choice and reward delivery, but in sessions where there was a delay, there was a progressive effect on performance. As the delay increased, performance on the task was negatively impacted as measured by the number of choices of the option associated with the highest probability of reward. While there was a change in learning, the rate at which monkeys initiated trials was unchanged. Overall we interpret these data as showing that the delay manipulation reduced the associative strength of the reward, not the value of the reward.

Funding: R01MH110822

57

Assessing effects of inhibiting BIN-1 or PICALM on lifespan in wild-type and paralysis in a C. elegans model of Alzheimer's Disease.

Ann-Nicole Frimpong

Nicholas Grimaldi

Charles Mobbs, PhD

Alzheimer's disease (AD) is characterized by the accumulation of Beta-amyloid plaques and neurofibrillary tangles, which can not be destroyed by the body. This project utilizes the model organism Caenorhabditis elegans as an in vivo approach to aid in understanding the effect that the brain's genetic expression levels can have on the onset and progression of the disease.

The project used RNA-interference to knockdown genes believed to be implicated in the aging process and late-onset Alzheimer's disease. An RNAi-feeding method was used for knockdown. Motility was measured in the wild type strain (N2) measuring lifespan, while paralysis was measured in a transgenic strain (CL2006) where the paralysis phenotype is characteristic of Abeta accumulation. Through further research, we can use the data generated from the motility and paralysis assays to identify genes implicated in the process of aging and the onset and or progression of Alzheimer's Disease.

58

A critical role of the amygdala on the influence of interoception during decision-making.

Atsushi Fujimoto1, Elisabeth A. Murray2, and Peter H. Rudebeck1*1.

Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai2. Section on the Neurobiology of Learning and Memory, Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health

Abstract: Both prefrontal cortex and amygdala are heavily implicated in interoceptive processes, but the neural mechanisms engaged are largely unknown. Here we sought to determine the contribution of the amygdala to representations of bodily states in the prefrontal cortex during decision-making. We conducted neuronal recordings from the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) while we simultaneously recorded electrocardiograms from male macaque monkeys (N = 3) that were performing a reward-based decision-making task. Recordings were made both before and after all three subjects received excitotoxic lesions of the bilateral amygdala. Before lesions, baseline HR was positively correlated with subsequent choice latencies and a substantial proportion of neurons reflected baseline HR (HR coding) in OFC and ACC. After lesions, the relationship between the baseline HR and choice latency was degraded and HR coding decreased in OFC, while it increased in ACC. These data indicate that amygdala-prefrontal circuits are essential not only for value coding (Rudebeck et al., 2013), but also for shaping the influence of bodily states on decision-making.

Fundings: NIMH-R01MH110822 and NIMH-R01MH117040 (to PHR), and by the Takeda Science Foundation Overseas Research Fellowship (to AF).

59

Sasha Fulton

Nash Family Department of Neuroscience

Although MDD has been predominantly studied in the context of neuronal function, emerging evidence indicates that dysregulation of glia may be equally important – particularly during chronic neuroinflammation in response to stress, which is known to contribute to the pathophysiology of MDD. However, the cell-type specific transcriptional dynamics driving these processes remain unclear. Our laboratory has recently implemented the newly developed technique FANS (Fluorescence-Activated Nuclear Sorting)-coupled ATACseq (Assay for Transposase-Accessible Chromatin-Sequencing) to profile the cell type-specific regulatory landscape in human MDD in orbitofrontal cortex (OFC), a brain region that processes reward-based decisionmaking and may mediate anhedonic symptoms in MDD. Interestingly, we only detected MDD-specific open chromatin regions (OCRs) in the glial, but not the neuronal OFC cell population. Gene set analyses of MDD-specific OCRs showed significant enrichment of astrocyte-specific genes regulating NF-KB inflammation response. Using motif discovery, I identified ZBTB7A, a chromatin remodeling protein with recognition sequences significantly overrepre-sented in MDD-specific OCRs. ZBTB7A has been shown to orchestrate chromatin accessibility for a distinct subset of delayed induction NF-Kb target genes, suggesting that ZBTB7A may regulate the transduction of chronic NF-Kb stress signals from adaptive to pathological. Our pilot data shows that ZBTB7A is upregulated in the OFC of both human MDD and in OFC astrocytes of a preclinical chronic social defeat stress (CSDS) mouse model. I hypothesize that upregulation of ZBTB7A in OFC astrocytes acts as a pathogenic driver of proinflammatory NF-Kb activation in MDD through modulation of chromatin accessibility at key downstream target genes, leading to MDD-related behavioral deficits.

60

Effects of In-utero Cannabis Use and Exposure to Superstorm Sandy Stress on Infant Temperament

Christine Ginalis1, Lexi Pritchett1, Yonglin Huang1, Westar Zong1, Greg Rompos2,3, Yasmin Hurd2,3, Yoko Nomura1,

Queens College, CUNY1, Addiction Institute2, Icahn School of Medicine at Mount Sinai3

Background: Previous research indicates that newborns exposed to cannabis exhibit heightened sensitivity, prolonged startle response, and fearfulness. However, it is unknown whether those behavioral phenotypes are amplified by maternal prenatal stress.

Method: A prospective study of pregnant mothers and their offspring ascertained maternal cannabis use among mothers exposed or unexposed to stressful natural disaster, Superstorm Sandy. At 6-months postpartum, infant temperament was assessed. A multivariable GLM assessed differences in infant temperament among exposure groups.

Results: Infants prenatally exposed to cannabis evince greater distress to limitations (p=0.03) and slower recovery from distress (p=0.05). Infants exposed to cannabis both prenatally and postnatally displayed elevated fearfulness (p=0.05), perceptual sensitivity (p=0.02), and excitatory behaviors (p=0.03). Exposure to Superstorm Sandy in-utero further exacer-bated the impact of cannabis, such that reported soothability was significantly lower (p=0.04). Placental gene expression analysis revealed networks related to infant temperament related to cannabis/stress.

Conclusions: This study confirms that prenatal cannabis exposure is associated with negative affect in infant neurodevelop-ment. In-utero Superstorm Sandy exposure further disrupted regulatory processes among cannabis exposed infants. As infants with poor self-regulation are at an increased risk for developmental psychopathology and that intense natural disasters are more common, increased preventive measures targeting cannabis users for education and interventions are recommended.

Funding: NIMH

61

Kiran Girdhar

Genetics and Gneomics Sciences, Icahn School of Medicine at Mount Sinai

Genome wide association studies (GWAS) of schizophrenia (SCZ) have revealed that disease-associated variants are mapped to gene regulatory sequences. Moreover, pathway analyses of GWAS-SCZ risk loci showed strongest association with histone modifications. Yet, we understand very little about the role of regulatory elements underneath these disease specific signals. For example, how are regulatory elements (RE) coordinated to modulate gene expression in brain of schizophrenia patients vs. healthy brains?

To answer this, we profiled histone modifications (H3K4me3, H3K27ac) in fluorescence-activated cell sorted (FACS) nuclei from prefrontal cortex (PFC) brain regions of 149 schizophrenia postmortem brain samples and 145 matched controls. We estimated the correlation of chromatin peaks across all individuals to probe the coordination of regulatory elements as a function of distance. We find that neuronal genomes is partitioned into 9,000 cis-regulatory domains (nCRDs) with median length of 32 kb, which encompasses distinct patterns of histone marks. A total of 75 nCRDs were identified at significance of 5% FDR that show neuronal dysregulation across SCZ cases and controls. Pathway analyzes of dysregulated nCRDs showed association with calcium mediated signaling. Next, we characterized the association of genes with nCRDs , wherein, ~50% of the genes were associated with nCRDs within the window of ±1 Mb. We show that nCRDs are clusters of active REs that control expression of genes.

Our psychencode sponsored work provide 1) a reference resource to better interpret disease and quantitative trait-associated variants, 2) a framework to integrate functional genomics of the 3D nucleus and population variability

62

40Hz Auditory Steady-State Response in ASD and PMS

Grosman, H., Guillory, S., Foss-Feig, J.H.

Background: Sensory abnormalities exist in approximately 90% of individuals with autism spectrum disorders (ASD). Neural oscillations are a key mechanism by which communication and synchronization occur in the brain. Specifically, gamma band oscillations reflect GABAergic synaptic dysfunction, a known alteration in ASD. Therefore, measurement of gamma oscillations may offer a biological tool to reveal mechanisms underlying cognitive dysfunction. Auditory steady-state response (ASSR) is a neurological response that, in the gamma frequency range (30-50Hz), is a robust measure of abnormal GABAergic function. This study used electroencephalography to explore gamma oscillations with ASSR to probe funda-mental disruptions in ASD and Phelan McDermid Syndrome (PMS), a related rare disorder with autism-like features and known excitatory dysfunction.

Methods: Twenty-two individuals participated in the study: 8 ASD,5 PMS, 9 controls. The auditory stimulus was a 500ms click train with a 40Hz stimulation rate). 128-channel EEG was and inter-trial phase coherence (ITC) was calculated.

Results: Results revealed significant differences in 40Hz gamma-band ASSR among groups, F(2,19)=8.60, p=¬.002. Both ASD (0.25±0.09; t(15)=-3.99, p=0.001) and PMS (0.27±0.11; t(12)=-2.85, p=0.015) had significantly weaker ITC than controls (0.43±0.10). ASD and PMS groups did not differ (p=0.68).

Conclusions: Results reinforce prior findings of diminished ASSR in ASD and extend them to PMS. Collected through a passive, non-invasive task, ASSR is a promising biomarker for ASD screening and stratification. ASSR also may be useful as a biomarker of change in clinical trials, particularly for GABAergic drugs.

Funding: Seaver

63

Altered Synaptic and Intrinsic Properties Associated with the LRRK2-G2019S Perturbs Responses to Acute Social Stress

Christopher Guevara, Swati Gupta, Mofida Abdelmageed, Roxana Mesias, Pamela Del Valle, Katherine LeClair, Scott Russo, Deanna Benson, and George Huntley

Nash Family Dept of Neuroscience; Friedman Brain Institute; Graduate School of Biomedical Sciences

The G2019S mutation in LRRK2 is the most common genetic cause of late-onset Parkinson's Disease (PD) and is prevalent in idiopathic PD patients. Although PD is diagnosed by the onset of motor symptoms, comorbid non-motor cognitive symptoms (depression, attentional deficits, psychosis) appear early and can be hallmarks of PD. PD risk is also increased by stress. In order to probe relationships between PD mutation, stress, and neural circuits, we examined synaptic function in WT and G2019S knockin mice following 1d of social defeat stress in the nucleus accumbens (NAc), which is enriched in LRRK2 expression and known to regulate stress responses. Stressed G2019S mice displayed greater social avoidance in comparison with WT, and post hoc whole-cell recordings of striatal projection neurons (SPNs) in the NAc showed increased sEPSC amplitudes and a blunted change in excitability in G2019S compared to WT mice. These data suggest that mice expressing G2019S mount entirely distinct behavioral and cellular responses to acute social stress. On-going experiments are probing additional metrics of synapse responses such as spine and dendrite alterations and mechanisms regulating glutamate receptor trafficking. Ultimately the data may reveal novel targets for ameliorating mood-related and cognitive symptoms associated with PD.

Funding: 1R01NS107512-01A1, 5T32MH087004-10

64

electrophysiological evidence of atypical predictive processes in autism spectrum disorder

Sylvia Guillory, Christopher McLaughlin, Emily Isenstein, Hannah Grosman, Katharine Thakkar, Daniel Mathalon, and Jennifer Foss-Feig

Seaver Autism Center for Research and Treatment, Psychiatry Department, Icahn School of Medicine at Mount Sinai, UCSF, MSU

Background: Sensory, motor, and social impairments represent key features of autism spectrum disorder (ASD). A growing body of work suggests that alterations in predictive processes may contribute to these symptoms, where the ability to anticipate upcoming events is disrupted. In neurotypical individuals sensory events triggered by self-initiated motor actions evoke a smaller neural response than externally-generated events. Previous work suggests this response suppression is related to differentiating the sensory consequences of one own's action. Here, we hypothesized that the suppression to self-generated events would be present in controls but reduced in ASD.

Method: Electroencephalography (EEG) was used to compare neural responses in ASD (n=34) and typically-developing (TD) children (n=29). Suppression of the N1 event-related potential (ERP) was computed when participants pressed a button to initiate a tone (self-generated condition) versus passively listening to a sequence of tones without pressing a key (externally-generated condition).

Results: ASD individuals showed weaker N1 suppression (0.90±0.64 uV) compared to TD controls (-0.84±0.27 uV), t(61)=-2.35, p=0.022.

Conclusions: Our findings reveal differences in neural response to self-generated versus externally-generated auditory stimuli in ASD versus controls. Specifically, in ASD the lack of N1 attenuation to self-generated tones supports the notion of prediction-related signaling deficits in this disorder.

Funding: NIMH, Seaver Foundation, NCATS

65

Emerging role of bHLH-PAS transcription factors as repressors of axon growth and neuroregeneration

Dalia Halawani1*, Yiqun Wang1,4*, Aarthi Ramachandran1,2, Roland Friedel1,2 and Hongyan Zou1,2

1Nash Family Department of Neuroscience, 2Friedman Brain Institute, and 3Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, US. 4Department of Orthopedics, Second Affiliated Hospital of Xi'an Jiaotong University, China.

*equal contribution

The limited capacity of the injured mammalian CNS to regenerate after injury remains a critical challenge. Successful axon regeneration of injured neurons requires coordinated activation of intrinsic axon growth transcriptional programs, while overcoming extrinsic inhibitors at the injury milieu. However, there is a gap in knowledge of how extrinsic factors from the injury-associated microenvironment interact with intrinsic transcriptional programs to affect axon growth and neuronal repair. Previous studies from our group and others uncovered an essential role for TET3-DNA hydroxymethylase in DRG sensory neuron regeneration. Genomic wide analysis of DhMRs revealed strong association with regeneration associated genes. Unbiased analysis of transcription factor binding sites revealed enrichment of bHLH-PAS motifs within DhMRs. Preliminary analysis of bHLH-PAS protein expression in regenerating DRG sensory neurons after sciatic nerve lesion demonstrated downregulation. Knockdown of specific bHLH-PAS family members enhanced axon growth and promoted neurodifferentiation. Pharmacological targeting of bHLH-PAS family members, Bmal1, promoted axon growth of stem cell-derived neurons after replating injury. Together our results suggest bHLH-PAS transcription factors as negative regulators of axon growth and pose the hypothesis that disengagement of bHLH-PAS sensory activity is necessary for axon growth and neuroregeneration.

Funding: NIH, XJTU, NY state DOH.

66

miR155 modulates Aß-amyloidosis, neuropathology, and cerebrocortical transcriptome in a mouse model of Alzheimer's pathology

Jean-Vianney Haure-Mirande*,1, Ben Readhead*,2, Diego Mastroeni2, Mickael Audrain1, Tomas Fanutza1, Soong Kim1, Robert Blitzer1, Sam Gandy1, Joel Dudley1* and Michelle Ehrlich1*

1Icahn School of Medicine at Mount Sinai, New York, NY2 ASU-Banner Neurodegenerative Disease Research Center, Tempe, AZ

Background. MicroRNAs (miRNAs) are small (20-24 nucleotides), single-stranded, non-coding RNAs that bind to 3′ untranslated region of target mRNAs to induce mRNA degradation and translational repression. miR155 is a mediator of the TREM2-APOE pathway, and we reported that multiple miR155 mRNA targets are differentially expressed in brains of patients with Alzheimer's disease (AD). Moreover, expression of miR155 is modulated by Human Herpes Virus-6A, positioning miR155 at a molecular crossroad involving innate immunity, viral response, and AD. Here, we sought to investigate the role of miR155 on AD pathogenesis.

Methods: We crossed WT and the APP/PS1 amyloid mouse onto a miR155-null background. Using a panel of biochemical, physiological, behavioral, and transcriptomic assays, we characterized the effects of miR155 deletion on memory, neuropathology, and cortical transcriptome.

Results: While deletion of miR155 in APP/PS1 mice was associated with partial restoration of synaptic plasticity and learning memory, deletion of miR155 in WT mice produced deleterious effects on these parameters and induced a transcriptomic signature similar to that of the APP/PS1 mice and human AD and suggests a loss of an excitatory neuronal subpopulation.

Conclusion: miR155 deletion induces complex, amyloid-dependent effects on learning, Aß deposition, and gene expression.

Funding: NIH

67

The BNST invokes resiliency vs susceptibility via dynamic modulation of CRF Neurons

Sherod Haynes, Hyun Seong Seo, Aurelie Menigoz, Larry Young, Ming-Hu Han

Icahn School of Medicine at Mount Sinai, New York, NY; Yerkes National Primate Research Center, Atlanta, GA

Chronic psychological stress plays a precipitating role in the development of Major Depressive Disorder (MDD), yet its cause remains elusive. We show that the Bed Nucleus of the Stria Terminalis (BNST), a region of the extended amygdala, is crucially important. Using patch-clamp electrophysiology, chemogenetics, optogenetics, and fiber-photometry in a cell-type selective manner, we uncovered a stress-sensitive window of plasticity that determines the development of susceptibility versus resiliency. The oval nucleus of the BNST containing dense Corticotrophin Releasing Factor (CRF) neurons encodes the nature and chronicity of psychological stress and produce behavioral responses that mimic the clinical picture of depression. This study may provide novel mechanistic insight into the somewhat complicated findings involving the role of CRF in depression.

Funding: NIH

68

Social Control Deficits in World Trade Center First Responders

Matthew Heflin et al.

Psychiatry, ISMMS

Post Traumatic Stress Disorder (PTSD) is characterized by the persistent re-experience of a traumatic event and disturbances in mood, cognition and arousal. While some estimates show that nearly 90% of the population has experienced a traumatic event, as measured by DSM-5 criteria, only approximately 10% develop PTSD, the rest showing resilience to trauma. For those that do develop the disorder, marked social deficits are observed.

We examined a group of 22 individuals who were first responders during the September 11th attacks on the World Trade Center. 7 of these developed PTSD, while the other 15 were resilient to the effects of the trauma. Participants completed a neuroeconomic task in which they could (“In Control”) or could not (“No Control”) influence monetary offers proposed by simulated partners .

Computational modeling revealed that in contrast to healthy controls, both PTSD and resilient groups failed to gain control over their partners due to a lack of model-based forward thinking; they also reported a reduced sense of control in controllable interactions. Compared to resilient individuals, PTSD patients had higher rejection rates in uncontrollable situations, possibly reflecting their heightened feelings of anger and frustration. Taken together, our pilot study provides a computational paradigm and model that might help delineate the common and distinct social deficits in both PTSD and trauma exposed but resilient individuals.

Funding: NIH

69

Validation of DB2313 as an inhibitor of PU.1

Manon Herbinet, Anna Pimenova, Edoardo Marcora, Alison Goate

ISMMS

Background: Based on genome-wide association studies of Alzheimer’s disease (AD) altered myeloid cell function are strongly implicated in the etiology of AD. In particular, we have identified SPI1/PU.1, a transcription factor and master regulator of myeloid cell development and function, as an AD risk gene that modulates the expression of several other AD risk genes in myeloid cells like microglia. SPI1/PU.1 risk-increasing allele is associated with higher expression and earlier AD age-at-onset. Thus molecules reducing SPI1/PU.1 expression or activity, such as DB2313 that disrupts the interaction of SPI1/PU.1 with its cognate DNA, may have therapeutic potential for delaying AD onset.

Methods: To validate the effect of DB2313 on myeloid cell function we performed dose-response experiments using BV2 mouse microglial cells (stably transfected with PU.1 overexpression or knock-down constructs and their respective controls) and assayed viability, proliferation, phagocytosis, immune response and other cellular phenotypes.

Results: DB2313 potently reduced myelind phagocytosis and NO secretion in response to LPS in control and PU.1 overexpressing cells, but showed no effect in PU.1 knock-down cells.

Conclusion: DB2313 inhibition of myelin phagocytosis and NO secretion in response to LPS by BV2 mouse microglial cells seems to be specific to inhibition of PU.1.

Funding: NIH, JPB, BrightFocus.

70

Knockdown of the gut microbiome alters opioid reward and striatal gene expression

Rebecca S. Hofford, Katherine R. Meckel, & Drew D. Kiraly

Mount Sinai Psychiatry

Background: There is growing evidence that the resident bacteria of the gastrointestinal tract, referred to as the gut microbiome, contribute to brain health. Previous literature suggests that shifts in microbiome composition can affect behavioral response to opioids. Yet it is unknown if perturbation of the microbiome might influence opioid reward and reinforcement.

Method: To achieve microbiome knockdown, animals were given a cocktail of broad-spectrum antibiotics (Abx) in their drinking water 2 weeks before the start of any experiments. Morphine reward was tested in control and Abx-treated mice using morphine conditioned place preference. Control and Abx-treated rats were trained to self-administer fentanyl before assessment of motivation using a progressive ratio task. RNA-sequencing was performed on the nucleus accumbens of control and Abx-treated mice given seven daily injections of morphine or saline.

Results: Knockdown of the microbiome reduced morphine place preference in mice and high dose fentanyl intake in rats but increased breakpoints for low-dose fentanyl. RNA-sequencing of the nucleus accumbens determined that microbiome knockdown led to a 10-fold increase in the number of genes regulated by morphine; many of the genes identified were involved in chromatin modification and gene transcription.

Conclusion: Our results indicate that reduction of the microbiome influences both opioid reward and brain responses to opioids. This represents a new and exciting area for translational research.

Funding: NIDA and NARSAD

71

Altered striatal-dependent learning in mice expressing a single point mutation associated with Parkinson's Disease

Ayan Hussein, Mark G Baxter, Deanna L Benson, George W Huntley

Nash Family Dept of Neuroscience, Friedman Brain Institute

The LRRK2-G2019S mutation is a major genetic cause of late-onset Parkinson's disease (PD). PD is diagnosed clinically by motor symptoms reflecting neurodegeneration of dopamine neurons, but non-motor cognitive symptoms are prevalent and can manifest earlier in the course of the disease. LRRK2 is enriched in striatum and cortex, with an onset of expression that parallels early postnatal corticostriatal development. We and others have established previously that G2019S alters baseline properties of excitatory synaptic neurotransmission within striatum by 3 postnatal weeks. Moreover, striatal projection neurons (SPNs) are unable to express corticostriatal LTP, an early and persistent loss, rendering normal bidirectional synapse plasticity abnormally unidirectional. Bidirectional synaptic plasticity is important for the full range of striatal-dependent reward-based behaviors that rely on synaptic plasticity in dorsomedial striatum, leading to the prediction that striatal-dependent cognitive tasks would be impacted later in life. To test this, we used both operant chambers and a touchscreen system to compare goal-directed learning in adult WT and G2019S knockin mice. We observed significant deficits in goal-directed learning in mutants that could not be attributed to differences in motivation. These data suggest that early and persistent alterations in corticostriatal synaptic plasticity may significantly impair goal-directed action-outcome associations in dorsomedial striatum by young adulthood, which may contribute to non-motor cognitive symptoms in PD.

Supported by NIH, NSF.

72

Microglial maintenance of neuronal function and circuitry in epilepsy

Philip H. Hwang1, Ana Badimon1 ,Mary K. Duff1, Diogo Ribeiro1, and Anne Schaefer1

1Graduate School of Biomedical Sciences and Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029

Tight regulation of neuronal activity is critical for maintenance of normal brain function. Neuronal activation can be modulated intrinsically, by activation of suppressive signaling and transcriptional networks, or extrinsically by specialized inhibitory neurons that balance the circuit output. Malfunction of extrinsic modulators leave neurons prone to aberrant activity, a primary characteristic of seizures and epilepsy disorders. We recently identified a novel mechanism of extrinsic negative feedback control of neuronal activity reliant on microglia. Microglia can sense increased neuronal activity and suppress it by a metabolite-based feedback mechanism, suppressing hyperactivity and seizure behavior in instances of acute pharmacological neuronal activation. In epilepsy syndromes however, seizures increase in severity with age and microglia become chronically active, potentially exacerbating seizure phenotypes. This may introduce adverse plasticity or loss of extrinsic microglial regulation resulting in maladaptive circuits and activity. Using a combination of genetic and pharmacological epilepsy models, behavioral assessments, and molecular techniques, we will determine how the microglial response is affected by conditions of chronic neuronal hyperactivity, and how the microglial activation seen in epilepsy patients may exacerbate their disease phenotype. These findings will elucidate key mechanisms underlying the maintenance of proper neuronal function.

73

Tau phosphorylation regulates subcellular location of tau under Glucose deprivation

R. Ibán-Arias1, S. Efthimiopoulos2, N. Robakis1

1Department of Psychiatry, Icahn School of Medicine, Mount Sinai2Department of Biology, University of Athens, Greece

Background: Tau protein is a microtubule-associated protein that binds to and stabilizes microtubules. Moreover, tau has been involved in synaptic functions and its phosphorylation might regulate tau distribution in different neuronal compartments. The purpose of this study was to investigate the role of Glucose deprivation(GD) in the phosphorylation of Tau and its distribution.

Methods: C57BL/6J wild type mice(8-12 months) were utilized. Brain coronal slices were incubated in two different Glucose solutions: 2mM: GD group, and 10mM: control group. Total tau(TG5), and phosphorylation of Serine epitopes 396, 356 and 404 were investigated in total extracts, postsynaptic Density(PSD) and non-PSD fractions obtained through differential subcellular fractionation, by Western blot.

Results: Total tau levels increased in PSD fractions under conditions of GD although no changes were observed in total extracts. GD resulted in a decrease of phospho-tau at Ser396, Ser356 and Ser404, in both PSD and non-PSD fractions, compared to total extracts. Interestingly, a decrease on tau phosphorylation was observed in PSD fractions under normal conditions compared to total extracts.

Conclusions: GD might trigger the exit of total tau levels to the postsynaptic compartment and shift the phosphorylation profile of tau in different subcellular compartments. These results suggest that the phosphorylation state of tau might affect its synaptic distribution and thus its synaptic function.

Funding: Supported by NIH grants 2RF1AG008200 and P50AG05138

74

Voluntary ethanol consumption leads to adaptative changes in GABAergic transmission in a subset of VTA dopaminergic neurons

Ilari A.1,Iezzi D.2,Gerace E. 2,Mannaioni G.2,Han M.H. 3,Ciccocioppo R.1,Masi A 1,2.

1School of Pharmacy,University of Camerino, Italy; 2Department NEUROFARBA, Section of Pharmacology and Toxicology, University of Florence, Italy 3Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, NY

Background: Dopaminergic (DA) projections from ventral tegmental area (VTA) are implicated in the rewarding properties of most abuse substances. Permanent changes in these pathways lead to compulsive drug-seeking behavior. Here, we studied the effect of voluntary ethanol (EtOH) drinking on VTA DA neurons properties.

Methods: We recorded from VTA DA neurons in acute slices obtained from TH-GFP mice previously exposed to a voluntary alcohol drinking paradigm and from EtOH-naive mice. Passive membrane properties, firing rate and spontaneous excitatory/inhibitory synaptic activity in baseline conditions and following 40 mM EtOH perfusion were measured to study the remodeling of intrinsic and network properties induced by voluntary EtOH intake.

Results: We found that chronic EtOH causes a significant reduction in basal firing rate, while increasing the firing-enhancing effect of bath-applied EtOH. Moreover, chronic EtOH increases the basal frequency of GABAergic inputs onto VTA DA neurons, while reducing the normal response to acute EtOH. Finally, voluntary EtOH consumption blunts the normal increase in amplitude caused by acute EtOH.

Conclusion: Our data suggest that VTA network adapts to voluntary EtOH consumption by changing both basal synaptic drive and response to single EtOH administration.These changes may correlate to a hypodopaminergic state and mark the inception of an addictive state.

Funding: University

Abstracts

75

Iliyan Ivanov

Department of Psychiatry, Icahn School of Medicine at Mount Sinai

Background: The objective of this functional magnetic resonance (fMRI) study was to determine the relationship between clinical improvement in attention deficit/hyperactivity disorder (ADHD) symptoms after treatment with lisdexamfetamine [LDX] vs. placebo and changes in brain reward related signaling using a probabilistic learning task and computational variables (e.g. estimated value and prediction error).

Methods: In a single-blind placebo-controlled study 20 adults with ADHD were scanned twice after receiving 3-5 weeks of treatment with both placebo and LDX. Blood oxygenated level dependent (BOLD) signal was modeled using regressors for the images at the time of decision (chosen vs. refused), weighted by subject expectation (reward cue or not), and at the time of feedback (reward or punishment outcome), weighted by prediction error (expected vs actual outcome). Scores on the ADHD-Rating Scale (ADHD-RS) were entered in whole-brain regression analyses. Group-level mass-univariate analyses between treatment-related symptom improvement (measured in each subject by the percent change of the ADHD-RS total scores at baseline vs drug condition), and the 4 contrast images under the Choice- and Feedback-conditions were performed.

Results: Symptom improvement was accompanied by significant increase of brain activation during object refusing and reward/punishment conditions (all $p < 0.05$ FWE corrected; cluster threshold of 50 contiguous voxels) in regions including left caudate and putamen (reflecting increased reward signaling) and left middle frontal and right inferior parietal gyri (reflecting increased attentional control).

Conclusions: Critically, the current study results support the hypothesis that stimulant treatment for ADHD can restore balance to dysfunction (e.g. hypoactivation) within motivation-reward related brain circuitry.

76

Exploring the phenome-wide consequences of Anorexia Nervosa associated genes

Jessica Johnson, MPH, et.al; Laura M. Huckins, PhD

ISMMS, James J. Peters VA

BACKGROUND: Anorexia nervosa (AN) is a complex psychiatric disorder with unknown etiology. We applied transcriptomic imputation methods to translate PGC-ED GWAS findings into higher-order biology (genetically regulated gene expression, GReX), and performed PheWAS using Mount Sinai BioMe data to test the clinical consequences of aberrant expression of these genes.

METHOD: We applied S-PrediXcan to PGC-ED GWAS summary statistics across 50 tissues (GTEx; CMC; DGN predictor models), and tested for association with AN (ptissue<1.88e-06). For ptissue significant genes, we imputed GReX in BioMe (N=31,633), and ran a PheWAS testing for association with 1,700 clinical outcomes. Analyses were run separately across six ancestry-defined cohorts and meta-analysed using an inverse-variance approach in METAL. We required at least 10 instances of a diagnosis per cohort for inclusion.

RESULTS: S-PrediXcan identified 47 unique genes over 12 loci for PheWAS follow-up. These were associated with phecodes for gastrointestinal and autoimmune disorders (p<1.06x10-06); alcohol abuse and tobacco use (p<1.35e-24); endophenotypes of AN (p<1.35e-05), and anthropometric phenotypes including adult lifetime lowest weight (2.74-04).

CONCLUSION: PheWAS allows us to study the clinical consequences of ANGReX. AN-genes are independently associated with commonly comorbid traits and AN-endophenotypes, even among individuals who do not have the disease. Future work will probe the tissue- and sex-specificity of our PheWAS associations, and the clinical impact of these genes conditioned on healthy and unhealthy psychiatric and BMI phenotypes.

FUNDING: Klarman Family Foundation

77

Plexin-B2 is a mechanoregulator during multicellular organization: from small GTPases to force-mediated regulation of nuclear physical properties

Chrystian Junqueira Alves et al.

During the multicellular organization, individual cells evolved to respond to environmental signals and adjust internal and external forces to accommodate tissue expansion while maintaining cellular cohesion. Semaphorins and Plexins are ligand-receptor pairs that appeared >600 million years ago in ancestor of Metazoa, suggesting a fundamental function in cellular dynamics. We discovered that proper signaling strength of Plexin-B2 is required for maintaining epithelial geometry and spheroid cytoarchitecture during the self-aggregation of human embryonic stem cells. Plexin-B2 enhances contractile forces of the actomyosin network while matching adhesive strength of E-cadherin-based intercellular junctions and integrin β1-based cell-matrix attachment. Atomic force microscopy demonstrates that Plexin-B2 enhances cell stiffness, which in turn impacts YAP and β-catenin signaling. On a molecular level, Plexin-B2 engages both ectodomain and intracellular Ras-GAP domain to regulate cell biomechanics. Consistent with this mechanoregulatory role, Plexin-B2 regulates Rap1/2 and Rnd3 leading to stress fiber formation, in part by activating actomyosin contraction. In neuroprogenitor cells, Plexin-B2 enhances focal adhesion contractile forces as confirmed by vinculin-based elastic FRET sensor. Strikingly, Plexin-B2 also impacts the nuclear size, shape, and lamin A/C levels, which is an inducer of pluripotent stem cell differentiation. Proper Plexin-B2 signaling strength is also critical to maintaining cell-cell alignment and neuroepithelium during cerebral organoid development. Our findings establish an evolutionary mechanoregulatory function of Plexin-B2 during the multicellular organization, which have implications for understanding neurodevelopmental disorders and advancing stem cell-based regenerative strategies.

78

WaveSleepNet for autoscoring of rodent sleep and wake

Korey Kam PhD and Andrew Varga MD, PhD

Division of Pulmonary, Critical Care and Sleep Medicine

Here, we present the development of WaveSleepNet (WSN), a supervised deep convolutional neural network for the classification of rodent NREM sleep, REM sleep and wakefulness in a continuous manner (1 second epochs). Model evaluation was assessed in three separate datasets on an epoch by epoch basis referenced to a single human scorer: 1. A leave-one subject out cross-validation of WSN to a random forest power spectrum classifier (RF-ps, n=20), 2. WSN classification of an off-site recordings compared to a separate human scorer (n=10), 3. WSN classification of mechanically-induced sleep disruption for 18 of the 24 hr long recording (n=5). In the leave-one subject out cross-validation, the WSN achieved a mean F1 score of 0.82±0.02 and mean Cohen's Kappa of 0.69±0.03 to the human reference. In contrast, the RF-ps achieved a mean F1 score of 0.64±0.01 and mean Cohen's Kappa of 0.55±0.04 to the human reference. Both the F1 score ($p<0.001$) and Cohen's Kappa ($p=0.005$) were significantly greater by the WSN compared to the RF-ps classifier. Secondly, WSN classification of the off-site, separate scorer test achieved a F1 score of 0.79 and Cohen's Kappa of 0.73. Finally, the WSN classification of mechanically disrupted sleep recordings achieved a F1 score of 0.75 and Cohen's Kappa of 0.74.

Funding: NIH, Alzheimer's Association

79

Chronic intermittent hypoxia enhances tau seeding and propagation and exacerbates Alzheimer's-like memory and synaptic plasticity deficits and molecular signatures

Syed Faraz Kazim, Abhijeet Sharma, Chloe S. Larson, Aarthi Ramakrishnan, Robert D. Blitzer, Li Shen, Catherine J. Peña, John F. Crary, Larissa A. Shimoda, Eric J. Nestler, Ana C. Pereira

Departments of Neurology & Neuroscience, ISMMS, New York, NY, USA.

Obstructive sleep apnea (OSA), characterized by sleep fragmentation and chronic intermittent hypoxia (CIH), is a risk factor for Alzheimer's disease (AD) development and progression. Recent epidemiological studies point to CIH as the best predictor of developing cognitive decline and AD in elderly with OSA. However, the precise underlying mechanism(s) remain unknown. Tau pathology, a major neuropathological hallmark of the disease, is known to correlate with cognitive impairment in AD. Further, increase in tau pathology was linked to CIH suggesting that CIH may mediate AD risk through tau pathology. Here we tested the effect of CIH on tau seeding and spread, critical processes in the progression of AD pathology. Experimentally induced CIH significantly enhanced human tau seeding and spread in the brains of a P301S mutant human tau model of AD. CIH also exacerbated memory deficit and synaptic plasticity impairment and increased disinhibition-like behavior in P301S mice, however, CIH had no effect on network hyperexcitability. Finally, CIH exacerbated AD-related pathogenic molecular signaling in P301S mice. These data provide a mechanistic basis of a role for CIH and OSA in the pathogenesis of AD.

Funding: NIH, Alzheimer's Assoc., ADDF, BrightFocus & DANA foundations.

80

EEG correlates of excitatory/inhibitory balance in ASD and Schizophrenia

Keller, K. and Foss-Feig, J.

Seaver Autism Center, Department of Psychiatry, ISMMS

Background: Excitatory/Inhibitory (E/I) imbalance theory purports to explain dysfunction in autism spectrum disorder (ASD) and schizophrenia (SZ). E/I balance is essential for surround suppression effects in the visual cortex. This study uses EEG to assesses integrity of surround suppression effects across ASD, SZ, and typically developing (TD) participants by comparing neural responses to central vertical gratings in parallel and perpendicular surround conditions.

Methods: 70 participants (17 ASD, 14 SZ, 39 TD) observed vertical sinusoidal gratings filling a central annulus during high-density EEG. N1 and P2 components over occipital scalp were targeted for analyses. Current ASD and psychosis symptoms also were assessed.

Results: A main effect of condition was observed for N1 ($F(1,67)=46.58$, $p<.001$) with suppressed amplitude during the parallel condition across groups. Conversely, P2 amplitude was greater in parallel vs. perpendicular conditions ($F(1,67)=11.54$, $p=.001$). A main effect of group was observed ($F(2,67)=3.61$, $p=.032$) where P2 amplitude was larger in ASD vs SZ($p=.028$) and TD($p=.016$)

across conditions. Greater N1 suppression correlated with fewer positive psychosis symptoms transdiagnostically($r=.36$, $p=.05$). Weaker P2 suppression correlated with greater ASD symptoms($r=.39$, $p=.032$).

Conclusions: EEG markers of surround suppression effects were detected across groups. The association between strength of N1 suppression and degree of positive psychosis symptoms across groups suggests E/I imbalance may represent a state-specific property of neural function corresponding to periods of increased delusions and hallucinations transdiagnostically.

Funding: R01-MH119172-01, R01-MH107426, BBRF, ASF

81

Impact of APOE genotype on the phagocytic uptake of brain tissue debris by microglia

Riana M. Khan, Saima I. Machlovi, Alison Goate and Edoardo Marcora

Ronald M. Loeb Center for Alzheimer's disease, Dept. of Neuroscience, Icahn School of Medicine at Mount Sinai

Background: Genetic linkage and association studies strongly implicate Apolipoprotein E (APOE) as a major gene for late-onset Alzheimer's disease (LOAD). APOE is the main cholesterol transport protein in the brain and is produced primarily by astrocytes but also by microglia. In light of AD risk variants including genes associated with the innate immune system, phagocytosis, and cholesterol transport, we aim to explore the impact of APOE genotype on the phagocytic uptake and clearance of cholesterol-rich brain tissue debris by microglia.

Methods: Primary microglia cultures from P1-P3 pups of Apoe+/+, Apoe-/-, ApoE33, and ApoE44 knock-in mice was prepared. Primary microglia were exposed to pHrodo-labeled myelin fragments and uptake was measured over time by live imaging. Endpoint cellular phenotype was measured to determine lysosomal burden and lipid accumulation.

Results: ApoE44 microglia showed increased uptake of myelin fragments and longer fluorescence half-life (38h) when compared to ApoE33 (30h). Endpoint cellular phenotype show significant increase in lysosomal area and lipid accumulation in ApoE44 upon myelin treatment.

Conclusions: ApoE44 microglia present increased uptake of lipid debris compared to ApoE33 which leads to increase lysosomal content due to lipid accumulation. This suggests increasing phagocytic uptake of cholesterol-rich brain tissue debris by microglia that may be implicated in AD pathogenesis.

Funding: BrightFocus Foundation

82

Transcription and chromatin accessibility analyses in primary human microglia.

Roman K1, Bendl J1,2, Dong P1,2, Zhang W1, Voloudakis G2, Charney, A1, Kellner, C3, Haroutunian V2, Fullard JF1,2, Roussos P1,2.

1Genetics and Genomics, ISMMS; 2Psychiatry, ISMMS; 3Neurosurgery, MSH.

Background: Microglia comprise an immune component of brain glial cells implicated in Alzheimer's Disease (AD) etiology. Most AD GWAS loci map outside gene-coding regions, likely altering cell type-specific enhancer-mediated transcription. Prior investigations of microglia contribution to AD focused on cells other than primary human microglia. Here we present a comprehensive transcriptome and regulome of freshly isolated microglia from AD and non-AD patients.

Methods: Starting from FACS-sorted microglia from freshly processed cortical brain tissue (autopsies/biopsies) from local brain banks (VA/MSH) we obtained high-quality transcriptional data (RNA-seq) from 127 patients, and chromatin accessibility (ATAC-seq) from 108 patients. Pairing with genome-wide genotypes generated maps of genetic regulation of expression (eQTLs) and chromatin accessibility (caQTLs). Available AD phenotype ratings allowed the identification of AD-associated changes.

Results: We identified a large number of open-chromatin regions (>200K) describing human microglia regulome, and integration with GWAS results (LDscore partitioning) supported involvement of microglia in AD etiology. Combining the regulome and transcriptome data we identified the contribution of chromatin state on relevant genes' expression. Generated eQTL and caQTL datasets predicted genetically-driven regulation of AD associated genes (EpiXcan).

Conclusions: This dataset provides a unique resource of regulatory mechanisms underlying microglia-specific contribution to different stages of AD progression, critical to understanding the microglial pathophysiology of AD.

Funding: NIA

83

(De-)multiplexing and droplet-based single-nucleus RNA-sequencing of human microglia nuclei from schizophrenia postmortem tissue.

Raphael Kübler1,3, Gijsje Snijders1,2,4, Amanda Allen2, Towfique Raj2, Lot D. de Witte1,4.

1Department of Psychiatry, 2Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, USA; 3Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; 4Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands.

BACKGROUND. Schizophrenia is a debilitating neurodevelopmental disorder of which the molecular complexity prevails unexplained. Large-scale RNA-sequencing studies implicate microglia to mediate a certain proportion of the schizophrenia-specific transcriptome. The precise functional architecture of microglia populations within the context of schizophrenia, however, remains to be understood. The advent of high-throughput droplet-based single-nucleus RNA-sequencing technologies presents the opportunity to exclusively sequence microglia, providing an unprecedented resolution to investigate microglia subtypes. Disadvantageous technology costs, however, have hindered such scientific efforts.

METHOD. A four-sample pilot with follow-up (16 control, 16 schizophrenia) aims to process microglia nuclei from frozen human postmortem tissue (medial frontal gyrus) on the 10x Genomics Single-Cell platform. This platform enables to multiplex samples while preserving sample identity through integrating genotype information with sequencing data in the demuxlet algorithm, thereby improving cost-efficiency of library preparation (objective 1). The generated library will be sequenced on the Illumina NovaSeq NGS system. Data will be preprocessed, quality control checked, and validated with single-cell microglia data (objective 2). Subsequently, sequencing data will be analyzed on differential gene expression and microglia subclusters with Seurat (objective 3).

FUNDING. Maastricht University.

84

Revealing Recurrent Latent Brain State Dynamics That Support Cue-Elicited Craving of Marijuana

Kaustubh Kulkarni et al

Nash Family Department of Neuroscience, ISMMS, New York, NY, Department of Psychiatry, ISMMS, New York, NY, Behavioral and Brain Sciences, UT Dallas, Dallas, TX

Cue-reactivity paradigms are a ‘gold standard’ for studying craving, an important component of drug addiction. Here, we propose a novel hypothesis that craving is influenced not only by external drug cues, but also underlying latent brain states. We utilize a novel Bayesian switching dynamical system (BSDS) model [1], which uses unsupervised learning to identify dominant multivariate latent neural states, and the transition probabilities that govern latent state space dynamics.

In this study, we examine 98 marijuana users who completed an fMRI cue-elicited craving task, consisting of recurring presentations of marijuana and control cues, as well as a rating period. Previous work with this group suggests that VTA, ACC, insula activation is increased during subjective craving [2], so these regions are used for BSDS analysis.

We discover a weak correspondence between latent states and cue-reactivity task structure. In addition, BSDS identifies a novel preparatory state proceeding cue onset. We further analyze subject-specific parameters of dynamics to discover associations with behavioral measures. Our study extends the original BSDS model to demonstrate its use in uncovering ecologically meaningful states in a subjective craving task, and provides a deeper understanding of the state dynamics governing drug craving.

1-Taghia et al. (2018). Nature Communications.

2-Filbey et al. (2009). PNAS.

Funding: NIH, Ream Foundation

85

A c-Fos map of extinction memory retrieval

Anthony Lacagnina, Saqib Khan, Roger Clem

Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai

Background: Fear extinction is a process where defensive responses to a conditioned stimulus diminish when the stimulus no longer predicts a threat. While plasticity in prefrontal-hippocampal-amygdala circuits has been implicated in extinction learning, much less is known about the mechanisms of extinction retrieval. Here we sought to identify brain regions associated with extinction retrieval by mapping expression of the activity-related gene c-Fos in mice retrieving a contextual fear extinction memory. Additionally, based on recent evidence that prefrontal somatostatin-expressing interneurons (SST-INs) participate in fear memory expression, we assessed if SST-INs were differentially recruited during extinction retrieval.

Method: Brain-wide c-Fos mapping was performed in mice retrieving either a contextual neutral, fearful, or extinguished memory. The activity of SST-INs was also analyzed in these regions.

Results: We found that both fear and extinction retrieval similarly engaged a number of cortical, hippocampal, and thalamic regions. However, extinction retrieval was associated with elevated c-Fos expression in the stratum oriens layer of hippocampal area CA1, which predominantly co-express somatostatin.

Conclusion: Our results suggest extinction retrieval may be mediated in part by activity in CA1 SST-INs, which could function to regulate the output of particular ensembles within the hippocampus.

Funding: NIH

86

R-loops as Mechanisms Governing Neural Differentiation and Cell-type Specific Transcription

Elizabeth A. LaMarca, Atsushi Saito, Allyse Hellmich, Bibi Kassim, Esther Cheng, Will Liao, Nadejda Tsankova, Atsushi Kamiya, Kristen J. Brennand*, Schahram Akbarian*

The neuropsychiatric disorders schizophrenia and autism together affect over 15% of children in the US. Development of effective therapeutics and diagnostic tools for these disorders has been hindered by our incomplete understanding of their complex neurodevelopmental etiologies. Gene expression variation is a common attribute of these disorders, thought to arise from developmental stage- and tissue-specific RNA regulation during neurodevelopment. New genome- wide mapping strategies have identified a connection between R-loops (DNA/RNA hybrids) and transcriptional regulation, suggesting a link between R-loops and gene expression variation. However, R-loops have never before been characterized on a genome-wide scale in the human brain. Here, we have mapped R-loops genome-wide for the first time in the developing human brain, and our research indicates that R-loops may poise developmental genes for transcription during neural differentiation. Functional manipulation of R-loop levels in human iPSC-derived neurons and mouse neurons in utero lead to long-lasting deficits in neuronal morphology, synaptic formation, electrophysiological activity, and neurodevelopmental gene transcription. We are currently testing the hypothesis R-loops stall RNA polymerase II (RNAPII), as stalled RNAPII is thought to keep developmental genes transcriptionally inactive but ready for expression upon developmental cues. These first steps toward understanding R-loop function in neural cells will facilitate our long-term objective to uncover the epigenetic mechanisms of aberrant RNA regulation in neuropsychiatric illness.

NIMH F31 MH121062

87

Maintenance of Social Dominance In Male Mice is Associated with Resilience and Increased Active Coping Behaviors

Katherine LeClair, Kenny Chan, Lyonna Parise, Long Li, Manuella Kaster, Flurin Cathomas, Scott Russo

MSSM

Background: The establishment of social hierarchy is an evolutionarily conserved phenomenon that determines access to resources. Across species, rank within social hierarchy can affect health and behavior. In humans, one measure of relative social rank is Socioeconomic Status (SES). SES is one of the single strongest predictors of mortality and morbidity, with low SES being associated with higher risk of disease. In particular, major depressive disorder (MDD) has been associated with low SES even after accounting for lifestyle factors such as smoking, alcohol use, physical activity, and diet. However, little is known about the biological underpinnings between low rank and high disease risk. We seek to investigate this relationship by using an animal model of social rank.

Methods: Male and Female C57BL/6J mice in established social hierarchies were exposed to chronic social defeat stress (CSDS) followed by a social interaction test to assess vulnerability to social stress. Behavioral analysis of coping behaviors during defeat were also assessed.

Results: Dominant male mice but not female mice show significantly less susceptibility to chronic social defeat stress compared to all other ranks of animals. Dominant males show increased active coping behaviors during defeat compared to the most subordinate animals.

Conclusions: Higher rank in males is associated with active coping behaviors during defeat, and confers resilience to depressive-like behavior.

88

Striatal circRIMS2 overexpression promotes a resilient-like phenotype following chronic social defeat stress.

Vanessa Lehmann1, Mary Heyer1, Aarthi Ramakrishnan1, Orna Issler1, Paul Kenny1

Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, 1470 Madison ave, New York, NY, 10029.

Circular RNAs (circRNAs) are an emerging class of noncoding RNAs that are formed by backsplicing non-adjacent intronic or exonic sequences. Though circRNAs are expressed throughout the body, they are particularly enriched in the brain. circRNA expression is further localized to synapses, where their mechanism of action is currently unknown. We obtained an RNAseq dataset from isolated DRD1-positive nuclei from the nucleus accumbens, through which we were able to identify raw counts of circRNA transcripts in each individual subject. RIMS2, a synaptic calcium tethering protein, was identified as a host gene for several circRNAs. We developed a strategy to overexpress circRIMS2 in vitro and in vivo to uncover both its potential mechanism of action and its relation to behaviors associated with depression. circRIMS2 appears to interfere with CREB signaling in a cell culture model leading to decreased levels of phosphorylated CREB and decreased transcription of CREB-responsive genes. Previous literature suggests a relationship between CREB activity in nucleus accumbens (NAc) D1 medium spiny neurons (MSNs) and resilience following chronic social defeat stress (CSDS), leading us to test the effects of circRIMS2 overexpression on depressive-like behaviors induced by CSDS. We found that circRIMS2 overexpression in the NAc reverses the depression-like behaviors associated with subthreshold CSDS, suggesting a connection between NAc circRIMS2 expression and resilience.

89

Environmental and Psychosocial Mediators of Emotion Regulation and Neurodevelopment in ABCD

WAGNER, LEPOW, RAMAKRISHNAN, IVANOV, PARVAZ

Psychiatry, Icahn School of Medicine

The development of emotion regulation may inform predisposition or resilience to affective psychopathologies. The Adolescent Brain Cognitive Development (ABCD) Study provides an opportunity to identify factors that contribute to divergence in neurodevelopment and functioning. We predict that prenatal exposure to drugs of abuse (PDE) and childhood trauma (CT) disrupt processes involved in emotion regulation, which will be reflected in less accurate and efficient behavioral performance and maladaptive engagement of limbic circuitry.

Sample: ABCD release 2.0 n=8,761 ages=9-10. The dependent variables were mean reaction time (MRT) and accuracy rate (RATE) on the Emotion N-back by contrasting performance during emotional and neutral trials [EMO-NEU] and task-based fMRI ROIs. Predictor variables were CT, defined by “yes” on the PTSD module of the KSADS, and PDE was determined by mothers’ self-report. Linear modeling accounted for race, family income, school grade, and parent marital status.

Neither PDE nor CT significantly predicted behavior, as seen in MRT and RATE models. Income and PDE together accounted for 0.22% of the variance of the dlPFC activation. PDE explained 0.062% of variance of bilateral mOFC (0=0.051), PDE, 0.11% of variance of bilateral lOFC (p=0.0095)

Preliminary results demonstrate that the activation of frontal regions involved in emotion regulation are affected by PDE and CT although task performance remains intact. Our poster will reflect further psychological and environmental variables and their effect on brain and behavior.

FUNDING: NIH

90

Notch1 promotes mouse spinal neural stem and progenitor cells proliferation via p-p38-pax6 induced cyclin D1 activation

Rui Wang, Chenguang Zhaob, Jianjun Li, **Yuhuan Li** et al.

Neural stem and progenitor cells (NSPCs) are important for nerve regeneration after spinal cord injury (SCI).Their proliferation, however, is limited. In this study, we investigated the role of Notch1 signaling in NSPC proliferation using adult mouse spinal cord derived NSPCs. We observed that Notch1 promoted proliferation of NSPCs and that Notch1 overexpression led to an expansion of cells in the S-phase and increased cyclin D1 expression. When investigating the functional relationship between Notch1, p-p38 and Pax6, we found that Notch1 suppressed p-p38 while promoting Pax6 expression. Functional inhibition of p38 with SB202190 led to increased Pax6 expression and to proliferation, as determined by BrdU. Furthermore, we confrmed that Pax6 induced proliferation in adult mouse spinal cord derived NSPCs. In conclusion, we demonstrate that Notch1 promotes the proliferation of mouse spinal NSPCs via a p-p38-pax6-cyclin D1 signaling pathway. This pathway constitutes a promising new therapeutic target for SCI treatment.

This work was supported by the Fundamental Research Funds for the Central Universities of China, and grant from the National Natural Science Foundation of China.

Abstracts

91

Mechanism for Clearance of Protein Aggregates Through p62/SQSTM1 Selective Autophagy in Neurons

Xingjian Li, Kerry Purtell, and Zhenyu Yue

Department of Neurology, The Friedman Brain Institute

Background: Recovering impaired autophagy can clear toxic protein accumulation and protect neurons in multiple neurodegenerative diseases, but the exact mechanism is poorly understood. We aimed to determine the selective autophagy degrades protein aggregates in neurons and leverage our findings to develop assays to this process.

Methods: We generated conditional knockout (KO) mice in which autophagy gene Atg7 is deleted specifically in CNS neurons. We then performed stereotaxic injection of AAV-Atg7 gene in substantia nigra of KO mice and examined TH+ neurons for aggregate formation. Furthermore, we expressed a reporter, which contains autophagy substrate p62 protein fused to mEOS 3.2, a photoconvertible fluorescent protein (PFp62), in neurons to assay p62 aggregate degradation as a readout for autophagy. Autophagy inhibitor Bafilomycin A1 and inducer Torin 1 were applied to the neurons, and the changes of PFp62 levels were detected by time lapse imaging.

Results: Atg7 KO brains showed significant accumulation of p62-ubiquitinated inclusions, while delivery of Atg7-GFP via AAV in the substantia nigra of the mutant mice recovered autophagy and cleared p62-ubiquitinated aggregates in dopaminergic neurons through a piecemeal fashion. Furthermore, PFp62 was degraded through selective autophagy. The PFp62 degradation was blocked by Bafilomycin A1 and facilitated by Torin 1.

Conclusions and findings: P62-ubiquitinated protein aggregates are cleared through p62/SQSTM1 selective autophagy in neurons. PFp62 is a robust real-time reporter of autophagy function in live neurons.

92

Mechanism for Clearance of Protein Aggregates Through p62/SQSTM1 Selective Autophagy in Neurons

Xingjian Li, Kerry Purtell, and Zhenyu Yue

Department of Neurology, The Friedman Brain Institute

Background: Recovering impaired autophagy can clear toxic protein accumulation and protect neurons in multiple neurodegenerative diseases, but the exact mechanism is poorly understood. We aimed to determine the selective autophagy degrades protein aggregates in neurons and leverage our findings to develop assays to this process.

Methods: We generated conditional knockout (KO) mice in which autophagy gene Atg7 is deleted specifically in CNS neurons. We then performed stereotaxic injection of AAV-Atg7 gene in substantia nigra of KO mice and examined TH+ neurons for aggregate formation. Furthermore, we expressed a reporter, which contains autophagy substrate p62 protein fused to mEOS 3.2, a photoconvertible fluorescent protein (PFp62), in neurons to assay p62 aggregate degradation as a readout for autophagy. Autophagy inhibitor Bafilomycin A1 and inducer Torin 1 were applied to the neurons, and the changes of PFp62 levels were detected by time lapse imaging.

Results: Atg7 KO brains showed significant accumulation of p62-ubiquitinated inclusions, while delivery of Atg7-GFP via AAV in the substantia nigra of the mutant mice recovered autophagy and cleared p62-ubiquitinated aggregates in dopaminergic neurons through a piecemeal fashion. Furthermore, PFp62 was degraded through selective autophagy. The PFp62 degradation was blocked by Bafilomycin A1 and facilitated by Torin 1.

Conclusions and findings: P62-ubiquitinated protein aggregates are cleared through p62/SQSTM1 selective autophagy in neurons. PFp62 is a robust real-time reporter of autophagy function in live neurons.

93

Differences in Gene Expression Between Living and Postmortem Brain States Confound Psychiatric Genetics Studies

Lora Liharska, Noam Beckmann, You-Jeong Park, Brian Kopell, Alexander Charney

Icahn School of Medicine

Background: The Living Brain Project (LBP) recently identified widespread differences in gene expression between living and postmortem human brain specimens (the “LBP signature”). We investigate whether these differences have confounded previous gene expression studies of psychiatric traits.

Method: The previously identified LBP signature was used to define a reference “dead” signature (genes up-regulated postmortem) and a reference “living” signature (genes down-regulated postmortem). The fractions of “living” and “dead” gene expression present in 2247 PsychENCODE Consortium (PEC) transcriptomes were calculated by repurposing cell-type deconvolution methods using these reference signatures. DE was then performed for each PEC psychiatric trait (schizophrenia, bipolar disorder, autism) with and without the resulting estimates as covariates.

Results: Analysis was performed on a subset of PEC schizophrenia cases and controls. Results of DE analysis in the schizophrenia datasets performed with and without adjustment for the estimated dead proportion were compared. Adjusting for the LBP DE signature resulted in an increased number of differentially expressed genes. Complete results on all PEC phenotypes will be presented.

Conclusion: We present evidence that the widespread molecular differences between living and postmortem human brain specimens confound postmortem studies of psychiatric traits. Our observations are of urgent importance for the field due to the pervasive use of postmortem tissues for investigating the neurobiology of human brain disorders.

Funding: Charney Lab seed fund

94

Necessity of Adhesion Proteins in Synaptic Cleft Width

Angelo Lontok, Deanna Benson

I work in the Benson Laboratory as part of the Science and Technology Entry Program of New York State.

Structure is crucial for the function of a synapse. Changes in the cleft width, for example, may negatively affect the transmission of chemicals. Although the cleft is formed when adhesion molecules attach pre- and postsynaptic membranes together, the cleft being the space in between, it is not yet known which adhesion molecules directly affect its width. I hypothesized that a specific adhesion molecule was necessary to determine the width. I obtained images via electron microscopy of mouse brain slices that underwent immunostaining, and I then analyzed individual synapses on ImageJ, measuring the cleft widths via a line scan. Wild-type synapses measured around 68 nm, and the synapses from mice lacking Neuroligin measured around 62 nm, which was not significant. In contrast, the synapses from mice lacking N-cadherin and β1-integrin were around 74 nm and 52 nm respectively, which were both significant. The data shows that N-cadherin and β1-integrin are both necessary in determining synaptic cleft width.

95

Effect of microglial APOE isoforms on endo-lysosomal pathway in response to lipid rich cellular debris

Saima I. Machlovi, Alison Goate and Edoardo Marcora

Ronald M. Loeb Center for Alzheimer's disease, Dept. of Neuroscience, Icahn School of Medicine at Mount Sinai

Background: Genetic linkage and association studies strongly implicate Apolipoprotein E (APOE) as a major gene for late-onset Alzheimer's disease (LOAD). APOE is the main cholesterol transport protein in the brain and is produced primarily by astrocytes but also by microglia. In light of AD risk variants including genes associated with innate immune system, phagocytosis and cholesterol transport, we aim to explore the impact of APOE genotype on the phagocytic uptake of cholesterol-rich brain tissue debris by microglia.

Methods: Primary microglia cultures from P1-P3 pups of Apoe+/+, Apoe-/-, ApoE33 and ApoE44 knock-in mice was prepared. Primary microglia were exposed to pHrodo-labeled myelin fragments. Uptake was measured overtime by live imaging and flow cytometry. Samples were collected for RNA-seq to identify changes in the transcriptome profile by Apoe genotype and myelin treatment.

Results: ApoE44 microglia showed increase uptake of myelin fragments at 24 hours after treatment. Pathway analysis showed increased expression of genes involved in cholesterol metabolism and decreased expression of genes involved in endo-lysosomal function compared to ApoE33. However, endo-lysosomal genes showed increase expression upon myelin challenge.

Conclusions: ApoE44 primary microglia present increased uptake of lipid rich cellular debris and increase in endo-lysosomal network compare to ApoE33, suggesting defective lysosomal function in microglia that may be implicated in AD pathogenesis.

96

Examining the role of axon guidance gene, PLXNB2, in hypoxic cell invasion in glioblastoma patient derived stem cells

Valerie J. Marallano, Anirudh Sattiraju, Dr. Hongyan Zou, and Dr. Roland Friedel

Hypoxia has been associated with adverse effects in tumor biology by exaggerating the capability of invasion, proliferation, and survival of tumor cells within the tumor microenvironment. Our studies are focused on the implication that axon guidance genes, especially PLEXIN-B2, are being upregulated due to exposure to hypoxia in order to allow glioblastoma patient derived stem cells, UCA and UNB, to become more aggressive and resistant to conventional forms of therapies. These glioma stem cell lines will be transduced with a Lenti-virus-PLXNB2-Knock Out and tested for reduced invasion and overall tumor burden in SCID mice after intracranial injections.

3D invasion assays, RNA sequencing analysis, Western blots, orthotopic intracranial injections in SCID mice, Lenti-virus-PLXNB2-KO, histology, and quantification of invasion, growth

Our hypothesis, based on preliminary data, suggests that our glioma patient derived stem cells, UCA and UNB, relies on PLXNB2 to be able to upregulate their migratory/invasive ability that is triggered when responding to hypoxic stress.

National Institute of Neurological Disorders and Stroke

97

Altered gene expression in World Trade Center first responders with post-traumatic stress disorder

Shelby Marchese1, Gabriel Hoffman1, Robert Pietrzak2,3, Dannielle Lebovitch1, Nikos Daskalakis4, Rachel Yehuda1,5, Panos Roussos1,5, Adriana Feder1, Laura Huckins1

ISMMS1, Yale University2, CT VA3, McLean Hospital4, Bronx VA5

Background: Only a subset of World Trade Center (WTC) responders develop Post-Traumatic Stress Disorder (PTSD). Identification of biomarkers is critical to the development of targeted interventions for treating WTC responders and preventing future PTSD cases.

Methods: We established a well-phenotyped cohort of 355 WTC first-responders by obtaining blood, urine, self-reported survey data, and longitudinal electronic health records. Utilizing bulk RNA-sequencing from whole blood, we analyzed the cohort using a Clinician Administered PTSD Scale (CAPS) for quantitative differential gene expression, accounting for sex, age and genotyped ancestry principal components.

Results Analysis of the CAPS quantitative variable revealed that 468 genes reach $p<0.05$, and 18 genes remain significant after FDR-correction. Quantitative analysis of four lifetime symptom clusters of PTSD also define genes that reach significance. The avoidance and reexperiencing clusters demonstrate 478 and 648 genes at $p<0.05$, and 15 and 21 genes after FDR-correction, respectively. Splitting the arousal cluster into dysphoric and anxious categories reveals 595 genes at $p<0.05$ and 14 FDRcorrected genes for dysphoric arousal, and 818 genes at $p<0.05$ and 36 FDRcorrected genes for anxious arousal.

Conclusions The homogenous traumatic experience of responders analyzed here makes this a small but unique study. Current analysis demonstrates the prospect of disease biomarkers and relevance of trauma exposure.

Funding sources: NIOSH

98

EEG Markers of Attention in Autism Spectrum Disorder

McLaughlin, C., Foss-Feig, J.H.Affiliations: Seaver Foundation

Background: Autism spectrum disorder (ASD) is characterized by sensory abnormalities. It remains unclear if attention to sensory stimuli differs between ASD and typically developing (TD) individuals. We sought to quantify differences in neural markers of attention to visual and auditory stimuli between ASD and TD.

Method: EEG was recorded from ASD and TD participants during visual and auditory oddball tasks (VOD and AOD). Each task included 450 trials in pseudorandom order; 80% presented a "standard" stimulus, 10% a "target" stimulus, and 10% a "novel" stimulus. Participants responded only to target stimuli. Amplitudes of P3a (novel) and P3b (target) event-related potentials were assessed.

Results: During VOD, ASD (9.53μV) and TD (8.96μV) displayed similar P3a amplitude ($p=0.75$), but ASD had significantly enhanced P3b response (ASD: 11.42μV; TD: 8.12μV; $p=0.04$). During AOD, ASD and TD did not differ in either P3a (ASD: 9.25μV; TD: 7.16μV; $p=0.19$) or P3b amplitude (ASD: 9.29μV; TD: 6.91μV; $p=0.13$). In ASD, VOD P3b amplitude correlated with severity of visual sensory symptoms ($r=-.76$, $p=.01$) and sensory sensitivity across modalities ($r=-.64$, $p=.05$).

Conclusion: Group difference restricted to visual P3b suggests individuals with ASD attend more strongly to visual target stimuli than TD, consistent with enhanced visual perception in ASD. The inverse relationship between attention to visual target stimuli and sensory symptoms in ASD suggests those who attend more to behaviorally-relevant visual stimuli may be less likely to experience clinically-impairing sensory symptoms.

Funding: Seaver Foundation

99

Microbiome depletion increases cocaine-seeking after abstinence

K.R.Meckel1, R.S.Hofford1, E.S.Calipari1, J.J.Faith2, P.Roussos1, D.D.Kiraly1

Mount Sinai Psychiatry1, Microbiology2

Background: Psychostimulant addiction represents a public health crisis leading to tremendous morbidity. Growing evidence suggests gut bacteria and their metabolites significantly affect brain and behavior in animal models of psychiatric disease. Our research examines the effects of the microbiome in models of cocaine use disorder.

Methods: Depletion of gut bacteria and their metabolites was induced in Sprague-Dawley rats via addition of antibiotics in their drinking water and compared to untreated controls. Rats were trained to self-administer cocaine and subjected to either within-session threshold testing to evaluate motivation for cocaine at a range of doses or 21 days of abstinence followed by a cue-induced cocaine-seeking task. Nucleus accumbens was then isolated and tissue processed for RNA-sequencing analysis.

Results: Antibiotic-treatment enhances motivation for low doses of cocaine in a behavioral economics task. Microbiome depletion increases cue-induced cocaine-seeking following prolonged abstinence, and supplementation with bacterial metabolites short-chain fatty acids (SCFAs) reverses these effects. Microbiome-deficient animals exhibit significant alterations of gene expression in gene networks known to affect synaptic plasticity.

Conclusion: Animals lacking a complex gut microbiome show significantly increased cocaine-seeking behaviors as well as altered gene expression. In the absence of a normal microbiome, repletion of bacterial metabolites SCFAs restores baseline behavior. These findings suggest that gut bacteria via their metabolites may serve as homeostatic regulators of gene expression in the brain, and suggest that the microbiome has potential as a translational research target.

Funding: NIDA, NARSAD

100

Conditional Cadherin-8 ablation disrupts mPFC->Striatal circuit development

Roxana Mesías; Yosif Zaki; Christopher Guevara; Karen Therrien; Mofida Abdelmageed; Deanna L. Benson and George W. Huntley

Nash Family Department of Neuroscience; Friedman Brain Institute; Graduate School of Biomedical Sciences

Motor and executive tasks are supported by proper development of functional corticostriatal networks. However, systematic characterization and mapping of the mPFC->Striatal connections at early postnatal stages, and the molecules directing such development, are lacking. We used a viral-targeted approach to label mPFC projection neurons in WT mice at different postnatal ages. Axonal innervation and striatal topographic patterning were quantified using two approaches:1) spaceballs stereological probe and 2) hotspot analysis, a clustering algorithm adapted from the geosciences. Our data suggest adult-like targeting to dorsomedial striatum already evident by P21, with subsequent directed growth of terminal fibers through later ages. This groundwork of normal development will be used to study anatomical effects arising from presynaptic (cortical-L5) Cadherin-8 (Cdh8) conditional knockout (cKO) in mice. We previously demonstrated that Cdh8, an autism-linked gene and a type II classical Cadherin, is enriched in corticostriatal neurons and in striatal spiny projection neurons (SPNs). Functionally, presynaptic Cdh8-cKO reduced sEPSC frequency recorded from dorsomedial SPNs at P21. Additionally, postsynaptic ablation of Cdh8 from SPNs show lower frequency and amplitude of sEPSCs compared to controls. We hypothesize that ablation of Cdh8 from the mPFC alters axon targeting to, and functional connectivity with, the striatum. These data may contribute to behavioral deficits observed in Cdh8 haploinsufficient patients with autism.

Funding: NIH-NIMH; Autism Speaks

101

Mesolimbic circuit dynamics underlying individual alcohol drinking

S.E. Montgomery, C. Morel, B. Juarez, S. Ryan, R. Durand-de Cuttoli, M. Flanigan, E.S. Calipari, S. Russo, E.J. Nestler, M.H. Han.

Icahn School of Medicine at Mount Sinai, New York, NY.

Harmful alcohol use remains a serious public health issue, resulting in 3 million deaths globally per year. An interesting phenomenon is the variability of alcohol consumption in the population; some individuals drink casually while others drink in an uncontrolled manner.Using in vivo fiber photometry and in vivo electrophysiology, we are able to determine the neural response of the VTA-NAc DA circuit before and after the establishment of alcohol drinking profile. This will allow us to uncover the neural circuit dynamics underlying the individual transition to low or high alcohol drinking phenotypes in male, isogenic mice. Our preliminary data show that the magnitude and temporal dynamics of the VTA-NAc DA circuit to novel and reward-related stimuli at baseline correlates significantly with future alcohol preference. Further, alcohol-induced neuroadaptations affect LAD and HAD mice differently; these groups exhibit distinct changes in natural behavior and either a sensitized or blunted response to direct alcohol exposure. By assessing VTA-NAc DA circuit activity before and after alcohol drinking in freely behaving mice, this study will provide novel insight into the behavioral and neurophysiological predictors of future, alcohol drinking phenotypes and how alcohol reciprocally attenuates or exacerbates innate VTA-NAc DA circuit function and natural, evolutionarily conserved behaviors. Future experiments will uncover molecular targets for pharmacology.

NIAAA: F31, R01.

102

Sex-specific gene regulation after intervertebral disc injury in two peripheral pain pathways

Grace E. Mosley, Minghui Wang, Bin Zhang, James C. Iatridis

Icahn School of Medicine at Mount Sinai, New York, NY, USA

Lumbar intervertebral discs (IVDs) are dual innervated by the segmental sinuvertebral nerve and non-segmental gray ramus communicans fibers that travel via the paravertebral sympathetic chain. This study used a rat IVD puncture model of low back pain and used RNAseq to measure gene expression changes in these two peripheral pathways after injury, in both females and males. L1 and L2 dorsal root ganglia (DRGs) were used for the non-segmental gray ramus pathway, and L4 and L5 DRGs adjacent to the injured IVDs were used for the sinuvertebral nerve pathway. Distinct DRG gene enrichment patterns were seen between pathways and sexes following IVD injury, with immune-related gene sets showing the largest differences. This work suggests that immune differences may specifically influence sex differences in the development of IVD-related low back pain. Future therapies may need to specifically target each peripheral pathway to alleviate chronic non-specific low back pain.

Funding: NIH

103

Uncovering RNA editing using deep-transcriptomics in complex mental illnesses

Enrico Mossotto1, Michael S Breen11. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, NY

BACKGROUND Transcriptomics analyses demonstrated pronounced differences between schizophrenia, bipolar disorder and major depression. Alternative splicing driven by inherited genetic risk factors only partially explains such transcriptional heterogeneity. Recent studies implicated a crucial role of RNA editing in controlling gene expression by modulating RNA stability, alternative splicing and regulatory cis-motifs. This study aims to characterize RNA editing levels in a cohort of patients affected by complex mental illnesses using deep-transcriptome sequencing.

METHOD RNA sequencing data were obtained from 200 post-mortem brain samples of patients affected by schizophrenia (n=46), bipolar disorder (n=39), major depression (n=54) and unaffected controls (n=61). Aligned sequencing data were quality controlled and subsequently analysed using REDItools to detect known and novel RNA editing events.

RESULTS The deep-transcriptomics approach resulted in a higher resolution where each gene in each sample is represented on average by 10 reads. Such superior performance allowed precise estimates of editing effects across all mental illnesses. Moreover, by combining RNA editing events in at the gene level, it was possible to rank genes according to their editing burden.

CONCLUSION This study will serve as blueprint for further investigations on the relationship between RNA editing levels and clinical phenotypes which might inform disease pathophysiology.

FUNDING This project is supported by the Icahn School of Medicine at Mount Sinai and the Beatrice and Samuel Seaver Autism Center for Research and Treatment.

104

A method for exosomal RNA extraction from paired human brain and blood specimens

Emily Moya, Lillian Wilkins, Esther Cheng, Lisa Linares, Brian Kopell, Navneet Dogra, Bojan Losic, Alexander Charney

Background: Exosomes are nanovesicles that mediate intercellular communication. It's been shown that brain derived exosomes can be found in peripheral blood (PB), but determining whether peripheral exosomes reflect ongoing brain processes hasn't been possible due to the absence of paired living brain and blood specimens. Here, we present a method for paired sampling of the dorsolateral prefrontal cortex (DLPFC) and PB from living human subjects for exosomal RNA profiling.

Methods: Paired brain and blood specimens were collected from 8 patients at two deep brain stimulation electrode implantation procedures. We developed protocols to profile RNA from exosomes of brain tissue extracellular matrix and PB. Exosomes were isolated via our in-house protocol using ultracentrifugation. RNA was extracted from the exosomes using the Qiagen miRNeasy Mini Kit protocol. Quality control (QC) was performed to determine whether RNA obtained was sufficient for next-generation sequencing (NGS).

Results: Bioanalyzer traces and QC data show a mean total RNA of 14.83ng (range 1.72–137.17ng) and no samples fell below the threshold required for library preparation and sequencing (10pg).

Conclusion: We performed the first study to sample pairs of DLPFC and blood from living human subjects for exosomal RNA for subsequent NGS. This non-invasive approach to probing neurobiology in the living human brain may facilitate the development of exosome-based diagnostics for neuropsychiatric disorders.

Funding: FBI Pilot Grant and GGS

105

Insights into the genetics of suicide attempt from the International Suicide Genetics Consortium

Niamh Mullins

International Suicide Genetics Consortium

Suicide accounts for >800,000 deaths annually and suicide attempts (SA) occur ~30 times more frequently. SA is moderately heritable and only partially overlaps with the genetic etiology of psychiatric disorders. The International Suicide Genetics Consortium conducted the largest genome-wide association study (GWAS) of SA, including >27,000 cases, from 20 studies worldwide.

Cases of SA or death were ascertained using psychiatric interviews, questionnaires, hospital or coroners' records. Aside from 3 population studies, cases were drawn from cohorts of psychiatric patients. To account for different cohort types, three GWAS models were used: attempters (n=15,581) vs. non-attempters with the same psychiatric disorder (n=71,067;model1); attempters (n=21,552) vs. nonattempters with psychiatric disorders and controls without disorders (n=465,017;model2); and attempters (n=17,614) vs. controls without disorders (n=66,465;model 3). The polygenicity of SA was investigated via SNPheritability, polygenic risk scores (PRS), and genetic correlations (rg). Models1,2 and 3 identified 0,2 and 4 SA-associated loci respectively (P<5e-8). Two loci were previously implicated in psychiatric disorders, and four were specific to SA. Significant SNP-heritability was observed in models 2 (5.9%,P=7.62e-24) and 3 (12.5%,P=3.17e-44) only. PRS from model3 were associated with SA in independent samples (maxR2=0.9%,P=3.03e-15).

Models2 and 3 showed rg with >150 traits (P<6.5e-5), including psychiatric disorders, poorer general health, smoking, pain and lower educational attainment. Ongoing work will dissect the biological mechanisms underlying genetic associations and explore the genetic architecture unique to SA and pleiotropic with associated psychiatric disorders.

Funding: NIMH

106

Neural Mechanisms of Affective States in Non-human Primates

Jairo A. Munoz(1), Megan E. Young(1), Eliza Bliss-Moreau(2), and Peter H. Rudebeck(1)

1. Friedman Brain Institute and Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY; 2. Department of Psychology and California National Primate Center, University of California Davis, Sacramento, California

This work is supported by the seed funds to the Rudebeck lab from the Icahn School of Medicine at Mount Sinai, an NIMH BRAINS Award and a NARSAD Young Investigator Award.

Studies implicate a network of areas centering on ventral anterior cingulate cortex(ACC) and amygdala in the control of long-term changes in affect. To better understandthe neural mechanisms engaged, we set out to determine how neurons in macaquesubcallosal ACC (scACC) and amygdala are affected under positive and negativeaffective states. Affective states were induced in rhesus macaques by showing themvideo clips, ranging in affective valence from extremely negative to extremely positive,and characterized by assessing heart rate. We found heart rate increased as valencewent from negative to positive, showing the induction of affective states. Linear arrayswere also placed in scACC and amygdala and neural activity was recordedsimultaneously with heart rate. Activity in both areas was modulated by video content,providing a translational model in which the mechanisms that control affective states innon-human primates can be elaborated to gain insights into human mood disorders."

107

Multidimensional computational analyses of human prenatal single cell data reveal high resolution cellular lineages within cortical development

Zarmeen Mussa, Elisa Nabel, Kimaada Allette, Maggie Cai, Robert Sebra, Kristin Beaumont, Alexander Tsankov, Nadejda M. Tsankova

The human brain is composed of billions of diverse neurons and glia which arise from common progenitors during fetal development. Prior histologic and bulk analyses of this process have revealed important features of cortical development, but knowledge about particular differentiation patterns has been limited due to lack of high resolution and integrative analyses at the level of single cells across multiple gestational stages. Specifically, the lineages of ultimately highly differentiated cell types lack high spatiotemporal resolution. Here, we apply novel techniques in single nuclei RNA sequencing (snRNAseq) combined with recently developed computational approaches to reveal cell-type specific differentiation patterns. Specifically, we performed snRNAseq on the germinal matrix and cortical plate of 16 human fetal samples, ranging in age from 17 to 36 gestational weeks, as well as on 3 adult patient samples. Using unbiased clustering and diffusion mapping, we defined distinct neuronal and glial populations and related those clusters across time to infer patterns of cellular differentiation. Initial findings include novel relationships among cell types within glial lineages, as well as the identification of transient cellular populations. Ongoing analyses are redefining lineage hierarchies within late prenatal human neurodevelopment and uncovering novel cell-type and cell-state markers through unbiased analysis, including several related to migratory fate specification in neural and glial progenitors.

Funding: NIH

108

Impaired Forward Thinking Disrupts Control of Social Interactions in High-Functioning Adults with Autism Spectrum Disorder

Soojung Na et al.

MSSM.

Autism spectrum disorder (ASD)1 is a neurodevelopmental disorder hallmarked by profound deficits in social functions. Social control, the ability to influence others2, is a key computational element involved in complex interpersonal interactions but never been examined in ASD.8 high-functioning ASD adults and 48 neurotypicals (NT) played an fMRI social control game 2 in which one may (“In Control”) or may not (“No Control”) influence the monetary proposals made by the partners. We developed a neurocomputational model to understand how individuals update their expectations about social norms and how they exert control over partners.In sharp contrast to NTs, ASD participants failed to exert influence over partners (i.e. raise their offers) and did not feel a sense of control in controllable interactions. Computational modeling revealed that (1) ASD participants’ choices were better explained by the stand-alone norm-learning model while NTs choices were better fit by a forward-thinking model; and (2) ASD participants were also less adaptive to norms and had inappropriately higher initial expectations for the offers than controls2. Finally, we found reduced neural encoding of value and norm prediction error signals in the anterior cingulate cortex (ACC) and the anterior insula in ASD than NT individuals.These findings show that the impaired model-based forward thinking and norm adaptation in interpersonal settings underlie dysfunctional social control in ASD.

Funding: MSSM Internal Fund1 CDC, 20182 Na et al., 2020

109

Induction of neurons from human fibroblasts for Alzheimer’s disease research

Narcis JO(1), Radu A(1), Farrel K(2), Lida MA(2), Crary JF(2), Robakis N(1).

Department of Psychiatry(1) and Pathology(2), Mount Sinai, New York.

Background: Conversion of human fibroblasts into functional induced neurons (iNs) by direct reprogramming was recently achieved. This new technology offers unique access to human neurons from patients for the study of neurological disorders in vitro, like Alzheimer’s disease (AD). Unlike other technologies such as induced pluripotent stem cells (iPSCs), this approach maintains age-related signatures, such as epigenetic markers, present in the original fibroblasts into the reprogrammed neurons.

Methods: iNs were generated by directly reprogramming fibroblasts obtained from post-mortem sporadic AD-patients or non-demented controls. Fibroblasts were transduced with a single lentiviral vector containing neural lineage-specific transcription factors (Acsl1 and Brn2) and two shRNAs against the RE1-silencing transcription factor (REST) complex. Cells were then stimulated with neural differentiation medium up to 25 days or experiment endpoint.

Results: We observed morphological changes from fibroblast to neuronal phenotypes such as development of processes and the expression of neuron-specific markers including Microtubule-associated protein (MAP2) and neuronal nuclei (NeuN).

Conclusions: After establishing differentiation of fibroblasts to mature iN, we will examine potential differences between iNs from AD patients and those from controls. To this end, we will utilize multiplex technology, a high-content image-based assay for morphological profiling. Furthermore, we will use iNs to test for the presence of AD-related biochemical and genetic hallmarks.

Funding: Supported by NIH grants 2RF1AG008200 and P50AG05138.

110

A Robotic Cell Culture System

Zachary Nelson, David Sachs (MS), Kevin Costa (PhD)

Icahn School of Medicine, HSMSE

Background: Culturing cells, and in particular changing the media, is a time-consuming and effort-demanding process that is highly prone to the variability of different scientists’ techniques, making it less replicable. Changing the media is a complex multi-step process which involves different mechanisms. The process includes removal of the cell culture plate from its cubby and removal of the plate lid. The cells are inspected to determine if they need to be replated. This is followed by either replating or removal of old media and replacing with new media and addition of differentiation factors.

Methods: I have been researching, designing and building a machine to automate this multi-step process that is compact enough to fit inside a standard laboratory cell incubator. This machine requires a combination of custom-built components, novel control systems, and tailored storage methods. I am training a machine learning algorithm to use microscope imaging to automatically determine cell confluency and replating requirements.

Results: I have been testing the functionality of the individual systems that I have built. I will test the machine once fully built. I anticipate that the machine will result in time saving for scientists and more consistent results in their experiments.

Conclusion: I anticipate that the approach will result in time savings for researchers and more consistent results.

Funding: NIH, STEP (Science and Technology Entry Program)

111

Elucidating the role of EED in Alzheimer's disease

Sarah Neuner, Gloriia Novikova, Edoardo Marcora, Manav Kapoor, Alison Goate

Background: Genome-wide association studies (GWAS) have identified several loci associated with Alzheimer's disease (AD). However, the genes and pathways through which these loci act to modify disease risk remain unknown. We previously discovered that AD risk variants are enriched in active enhancers of myeloid cells, implicating gene expression regulation in these cells as critical to disease etiology.

Methods: Functional genomics was used to nominate candidate AD risk genes at each locus. To experimentally test our findings, a combination of targeted siRNA, CRISPR-based approaches were used in human immortalized macrophages and iPSC-derived microglia. Functional assays were used to assess the effect of gene manipulation on myeloid cell physiology.

Results: Computational approaches prioritized EED as a candidate causal AD gene at the traditionally-annotated PICALM locus and identified reduced EED expression as associated with reduced risk for AD. Targeted reduction of EED, but not PICALM, resulted in increased phagocytosis and lipid storage in human myeloid cells.

Conclusion: Our work underlines the importance of integrative functional genomic studies in nominating causal genes within AD-associated loci, as AD risk variants can impact the expression of genes located many base pairs away. Work here suggests EED is a novel AD risk gene which may modify disease susceptibility by regulating the behavior of human myeloid cells. Future work will evaluate the mechanism by which EED mediates myeloid phenotypes in vitro and in vivo.

Funding: NIH and JPB Foundation.

112

Post-error Recruitment of Frontal-sensory Cortical Projection Promotes Attentional Behavior

Kevin Norman, H.Koike, J.Bateh, S.Lopez, K.Caro, D.Kato, K.Yamamuro, M.Flanigan, Y.Garkun, E.Nabel, D.Brady, C.Cho, J.Riceberg, M.Sadahiro, M.Demars, M.Shapiro, S.Russo, M.Baxter, P.Rudebeck, H.Morishita

FBI

Background: Flexible goal-directed behavior, such as attention, requires a cognitive control system which not only monitors contextually relevant internal states and external events, but also implements strategic adjustment in informational processing and behavior. Across species, attention is regulated by direct projections from the prefrontal cortex to sensory areas. Here, we aim to identify the specific conditions that recruit frontal-sensory projections from the anterior cingulate area to the visual cortex (ACA>VIS) to causally influence attentional behavior in mice.

Methods: We integrate circuit-based techniques to monitor and manipulate neural activity in mice performing freely moving attentional behavior with a translational automated touchscreen system.

Results: Projection-selective fiber photometry imaging of ACA>VIS neurons in behaving mice during the 5-choice serial reaction time task points to a key role of this circuit in error monitoring during attentional behavior. Excitatory optogenetic modulation of the projection further reveals frequency-dependent improvement of attention specifically following a recent history of errors. Direct optogenetic inactivation of ACA>VIS circuits during period of sustained attention selectively disrupts attentional performance only following errors.

Conclusion: Our data identify prior error history as a key internal condition to recruit top-down frontal-sensory cortical projections and drive post-error attentional enhancement. Our findings may provide circuit-based insight into the pathophysiology and intervention strategy for impaired visual attention in neuropsychiatric disorders.

Funding: NIH

113

Integration of Alzheimer's genetics and myeloid genomics reveals novel disease risk mechanisms

Gloriia Novikova1, Mavav Kapoor1,2, Julia TCW1, Edsel M. Abud3, Anastasia G. Efthymiou1, Haoxiang Cheng2, John Fullard2,4, Jaroslav Bendl2,3, Panos Roussos2,4, Wayne W. Poon3, Ke Hao2, Edoardo Marcora1,2,*, Alison Goate1,2,*

1Neuroscience 2Genetics and Genomics 3Institute for Memory Impairments, UC Irvine 4Psychiatry

Background: Several lines of evidence implicate myeloid cells in the etiology of AD. Genome-wide association studies (GWAS) have identified more than thirty loci associated with Alzheimer's disease (AD), but the causal variants, regulatory elements and genes remain largely unknown thus impeding a mechanistic understanding of AD pathogenesis.

Methods: We developed an integrative genomics approach that incorporated partitioned LD Score regression, Mendelian randomization and Bayesian fine-mapping approaches. We integrated GWAS, expression-trait quantitative loci (eQTL), histoneQTL, epigenetic and chromatin interaction datasets from myeloid cells.

Results: Using this approach we link myeloid enhancer activity to target gene expression regulation and AD risk modification. We nominate AD risk enhancers and target genes in sixteen loci, including AP4E1, AP4M1, APBB3, BIN1, CD2AP, MS4A4A, MS4A6A, PILRA, RABEP1, SPI1, SPPL2A, TP53INP1, and ZYX. We fine-map seven loci and identify candidate functional variants that likely modify AD risk by regulating myeloid gene expression. In the MS4A locus we identified a single candidate functional variant and validated it experimentally in human induced pluripotent stem cell (iPSC)-derived microglia.

Conclusions: Our results strongly implicate dysfunction of the myeloid endolysosomal system in the etiology of AD.

Funding: NIH and JPB Foundation.

114

Differential Impact of Borderline Personality Disorder and Avoidant Personality Disorder on Social Control

Madeline O'Brien et al.

Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY

Borderline personality disorder (BPD) and avoidant personality disorder (AvPD) are both characterized by social dysfunction. While AvPD patients experience diminished self-esteem and fear of rejection, BPD patients tend to fluctuate between high and low self-esteem, causing paradoxical increases in both disagreement and eventual submissiveness. Here, we examined BPD patients, AvPD patients, and matched healthy controls during a neuroeconomic game where they could ("In Control" condition) or could not ("No Control" condition) influence the proposed monetary offer from partners. Our previous work suggests that healthy volunteers use a 'model-based' approach to strategically plan future interactions and gain social control. BPD ($p<0.0001$) and AvPD patients ($p<0.0001$) both received lower monetary offers than controls in the "In Control" condition. Furthermore, computational modeling demonstrated that while controls simulated future offers to decide whether to accept the current offer, neither patient group used this strategy. In line with their respective clinical phenotypes, BPD patients perceived themselves to have lower control than their healthy counterparts in the "In Control" condition ($p=0.0469$), while AvPD patients rejected fewer offers than controls ($p=0.0196$). These results mark two socio-behavioral differences between the disorders: while both groups struggled to utilize social control, AvPD patients were particularly hesitant to send a negative social signal to their partner while BPD patients had trouble gauging their control over social situations.
Funding: NIH

115

Threat memory updating and reconsolidation in post-traumatic stress disorder

Temidayo Orederu (1,2), Charles Gordon (3), Ifat Levy (3), Ilan Harpaz-Rotem (3), and Daniela Schiller (1,2)

Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States (1); Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, United States (2), Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States (3)

Recent work has revealed the ability for a consolidated memory to return to its originally unstable state. Once destabilized, the memory can be altered—a process often called "reconsolidation." This finding can potentially modify maladaptive memories in disorders such as PTSD. Memory reconsolidation may be impaired in PTSD due to heightened threat reactivity overall. Alternatively, it may bypass areas impaired in PTSD and have treatment potential in altering traumatic memories. To examine this, 42 combat veterans (PTSD=21, Control=21) underwent a reconsolidation protocol while in an fMRI scanner. They first learned an association between two images and a wrist shock. This was followed by a retrieval-extinction protocol, which activated memory updating and reconsolidation for one of the reinforced stimuli. Our behavioral results suggest diminished memory updating in PTSD, however additional neural analyses are needed before firm conclusions can be made.

Funding was provided by NIMH R01 105535 grant and a Klingenstein-Simons Fellowship Award in the Neurosciences to D.S.; and NIMH 105535-04S1 to D.S. and T.O.

116

Gut-Brain Interactions in a Mouse Model of Autisim Spectrum Disorder

A.Osman, D.D.Kiraly

(Psychiatry)

Background: Mounting evidence demonstrates a role for the gut microbiome in Autism Spectrum Disorder (ASD), with signaling via the microbially produced Short Chain Fatty Acid (SCFA) acetate being one of the proposed modes of communication. In order to investigate this we combined antibiotic depletion of the microbiome with acetate replenishment in a genetic model of ASD – deletion of the Shank3 gene (Shank3KO). This model allows for investigating shifts in microbiome composition and metabolic signaling on brain and behavior in a model of ASD.

Methods: Shank3KO mice, and wild-type (Wt) littermates were divided into control, antibiotic-depletion (Abx), acetate replenishment or Abx + Acetate groups at weaning. On postnatal day 60, animals were subjected to behavioral testing using three-chambered social interaction. Cecal contents were collected for gut microbial and metabolic profiling.

Results: Shank3KO results in a dysregulated gut microbiome and decreased levels of acetate. Shank3KO mice have baseline social deficits which are further exacerbated following Abx treatment. Treatment with Acetate or Abx + Acetate reversed the social deficits.

Conclusions: Shank3 knockout results in significant changes to the gut flora and metabolome which may be linked to autism-like phenotypes. Additionally, the autistic-like behaviors in Shank3KO mice are exacerbated following depletion of the endogenous flora, while replenishing the metabolome with acetate reversed the behavioral deficits. Taken together, these data suggest suggests a gene x microbiome interaction driven by microbially derived metabolites in the development of ASD.

Funding: Seaver Foundation

117

Circuit interrogation of fear sensitization following an acute traumatic stressor

Zachary T. Pennington, Taylor R. Francisco and Denise J. Cai

Department of Neuroscience. Icahn School of Medicine at Mount Sinai

Post-traumatic stress disorder (PTSD) is characterized by the persistent sensitization of fear and stress responses. Moreover, one of the greatest risk factors for PTSD development is a prior history of traumatic experience. As such, understanding how stressful experiences produce persistent sensitization of fear circuits is of utmost importance. We have adapted a model for studying this phenomenon – stress-enhanced fear learning – for use in mice, showing that a single acute stressor is able to produce a long-lasting potentiation of fear learning. This potentiation of fear learning is present in both male and female mice, is modulated by the intensity of the first stressor, and effects subsequent learning about multiple aversive stimuli. Moreover, we have found that systemic administration of the protein synthesis inhibitor anisomycin at the time of the first stressor is able to mitigate the subsequent sensitization of fear learning observed, while leaving initial fear during the first stressor intact. Using a combination of activity-dependent cell tagging and whole brain staining of immediate early genes we are now probing the circuit and molecular cascade responsible for this sensitization.

Funding: Friedman Scholar Award, NIMH-1DP2MH122399-01, NIH-R01-MH120162

118

Decision-making in the context of multi-attribute decisions

A.Q. Perkins, Z. S. Gillis, E. L. Rich

Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai

In order to decide optimally between two or more options, a decision-maker may need to evaluate options on the basis of more than one attribute. While it is known that orbitofrontal cortex (OFC) plays a role in encoding stimulus values, it is currently unknown how attributes are represented by neural activity and incorporated into a unified value for each option. Additionally, it is yet unclear how these neural processes change when multiple options are present. To address these goals, we employed a behavioral task in which rhesus macaques were presented with choices of two or three options. For each option, the sweetness and probability of receiving the reward were represented by differently colored bars. We determined that monkeys tend to prefer options with high sweetness and high probability, but this preference changes over the course of the session, and with the specific arrangements of value-irrelevant option features. We will use eye-tracking to explore how overt visual attention might influence or belie the decision-making process, and record neural data from OFC using a multi-contact array and acute electrodes to determine how the value of complex stimuli is instantiated in neural activity.

K08 DA039351, Pew Biomedical Scholars Program, NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

119

Brain-specific patterns of HIV integration

Amara Plaza-Jennings 1, Tianxiong Yu 2, Zhiping Weng 2, Lotje de Witte 1, Susan Morgello 3, Schahram Akbarian 1

1 Department of Psychiatry at The Icahn School of Medicine at Mount Sinai; 2 University of Massachusetts Medical School, 3 Department of Neurology at The Icahn School of Medicine at Mount Sinai

Characterization of organ-specific reservoirs is critical as we look toward a functional cure for HIV. Due to the lack of reliable brain biomarkers of persistence and the difficulty of studying the human brain in vivo, there have not been in depth molecular studies of the viral reservoir in the brain. Studies in T-cells have shown that HIV preferentially integrates into highly expressed and highly spliced genes due to the association of the pre-integration complex with LEDGF and CPSF6. These proteins do not appear to be expressed in microglia, the dominant cell-type infected in the brain, raising the possibility that there may be different mechanisms of integration in the brain. Here we sequenced viral integration sites in the brain for the first time from human postmortem tissue of HIV+ patients. We find that, similarly to T-cells, integration sites are found preferentially in protein coding genes, more highly spliced genes, and regions of open chromatin, as marked by H3K27ac. However, we see brain-specific patterns of integration site distribution across the chromosomes that do not correspond to gene density. Furthermore, brain integration sites are enriched in genes with neuronal functions.

Funding: NIDA

120

Modeling disease-associated microglia (DAM) in vitro

Anna Podlesny-Drabiniok, Edoardo Marcora, Alison Goate

BACKGROUND: Microglia are involved in phagocytosis of cellular debris. In lipid-rich environment e.g. degenerated myelin, amyloid beta plaques or apoptotic corps, microglia transition from homeostatic to disease-associated microglia (DAM) and activate a clearance program upregulating APOE, TREM2, CD11c, LPL and other markers. Whereas DAM are well characterized in vivo in mouse models of Alzheimer's disease (AD), obesity and demyelination, development of simplified cellular DAM model may be of interest in understanding the switch between homeostatic and DAM microglia in neurodegeneration.

METHODS: Using THP-1-derived macrophages and life-imaging we investigated phagocytosis of different microglial stimulus including early apoptotic Jurkat cells (EAJ), myelin, bacterial particles and latex beads followed by assessment of DAM markers by flow cytometry and immunofluorescence. We also defined a cytokine composition that allow to reprogram THP-1 macrophages and microglia derived from human induced pluripotent stem cells (iMGL) to enhance phagocytosis and DAM response.

RESULTS We found that THP-1 macrophages challenged with EAJ upregulate DAM markers (APOE, TREM2, CD11c, LPL). In addition, we proposed that anti-inflammatory THP-1 macrophages (M2) and iMGL display higher phagocytic index of EAJ and greater proportion of DAM positive cells than proinflammatory (M1) and M0 THP-1 macrophages. Interestingly, DAM signature was not observed upon engulfment of healthy myelin, latex beads and bacterial particles.

CONCLUSION Our data propose a new cellular model of DAM that can be suitable for testing small molecules that modulate the transition and enhance clearance.

FUNDING: Eli Lilly 18-1595-01005-01-PD

121

Genetic Risk for Schizophrenia and the Genome in Three Dimensions

Samuel K. Powell, Callan O'Shea, Rahat Elahi, Kristen Brennand, Schahram Akbarian

Departments of Neuroscience and Psychiatry

Background: Common risk variants for schizophrenia are enriched in gene-regulatory loci and may impact the 3D structural organization of the genome; however, it is currently unknown how risk loci map to the 3D genome among neurotransmitter systems implicated in schizophrenia. Furthermore, little work has been done to investigate the functional implications of risk variant localization to 3D genomic structures.

Method: We generated isogenic dopaminergic, GABAergic, and cortical excitatory neurons from human iPS cells from four donors (half male, half female). Immunocytochemistry, qPCR, and RNA-sequencing analyses were employed to confirm appropriate neuronal specification. In situ Hi-C and risk-variant Capture Hi-C (rvCHiC) libraries were generated to determine global genome structure and risk variant-enriched chromatin interactions, respectively. Additional RNA-sequencing libraries were generated to test hypotheses relating genome structure to its output function of gene expression across all samples and matched iPS cells. All sequencing data were processed with appropriate pipelines. CRISPR-GO and CLOUD9 techniques are being piloted to manipulate chromatin positioning and test functional consequences to neuronal gene expression and activity.

Results: Neuronal subtypes showed robust evidence of appropriate identity specification. Hi-C and rvCHiC analyses documented both shared and subtype-specific genomic structures mapping to schizophrenia risk loci.

Conclusion: Schizophrenia risk variants show shared and subtype-specific localization to 3D chromatin structures. Ongoing work seeks to test mechanistic hypotheses concerning these structures.

Funding: NIMH, R01 MH117790-01

122

Oligodendrocyte-specific ATG14 deletion in mice leads to impaired myelination

Mathilde Pruvost1,2, Yuanxi Zhang2, Haiyan Tan3, Qian Wang2, Benjamin Inbar1, Junmin Peng3, Patrizia Casaccia1,2*, and Zhenyu Yue2*

Autophagy is a fundamental cellular process leading to the degradation of protein aggregates and damaged organelles. Initiation of autophagy requires the autophagy-related gene Atg14, which targets the class III phosphatidylinositol-3-kinase (PI3KC3) complex to the ER and regulates its kinase activity. While autophagy has been intensively studied in neurons, its role in glial cells is less understood, although recent studies have highlighted its importance for myelin formation and maintenance. The goal of this study was to define the consequences of oligodendrocyte lineage-specific ablation of the autophagy-related genes Atg14 on myelination. This was achieved by crossing floxed Atg14 mice with the Olig1Cre line. Myelination was assessed by immunohistochemistry, electron microscopy, and myelin protein composition further evaluated by proteomics and validated by western blot analysis.

We demonstrate that loss of Atg14 early in oligodendrocyte development leads to severe behavioral deficits in mice. Atg14 cKO mice showed defective myelin at 6 weeks of age and proteomics analysis of myelin extracts revealed increased levels of proteins regulating ER stress and decreased levels of cell adhesion proteins and ion transport. These findings explain the ultrastructural findings that fewer myelinated axons, aberrant myelin density and axo-myelinic junction. In summary, we show that Atg14 expression in oligodendrocytes is critical for proper myelin function in the adult CNS.

This work was supported by NIH.

123

Elucidating the role of KCNJ6 in the activity and alcohol response of human excitatory neurons

Iya Prytkova

Slesinger and Goate laboratories

Background: Alcohol Use Disorder (AUD) is highly heritable, affecting adults and adolescents worldwide. GWAS have identified multiple variants within KCNJ6 associated with an electrophysiological endophenotype for AUD risk, which are associated with elevated KCNJ6 mRNA levels in frontal cortex. KCNJ6 encodes GIRK2, a G protein-coupled inwardly-rectifying potassium channel, which regulates neuronal excitability and is directly activated by alcohol. This project aims to elucidate the contribution of KCNJ6 in controlling excitability of human neurons as well as their response to alcohol.

Methods & Results: NGN2 induction is used to generate a pure population of excitatory neurons. Preliminary data from low dose (.08 g/dL) alcohol exposure shows changes in NGN2 neurons' gene expression, assayed by qPCR and RNAseq. CRISPRa is used to upregulate endogenous KCNJ6, followed by whole-cell patch clamp measurements of GIRK current and high throughput assessment of basal activity and excitability by calcium imaging. We hypothesize that elevated KCNJ6 expression will result in less active and less excitable neurons, and that this may modulate responses to alcohol.

Conclusions: This human-based neuronal model provides a platform for probing the role of an AUD gene (e.g., KCNJ6) and testing the functional effects (e.g., activity, transcriptomics) of alcohol exposure on neurons.

Funding: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (1 F31 AA027949-01) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA U10AA008401).

124

Crem Isoform Dysregulation in the Nucleus Accumbens Mediates Impulsivity and Heroin Self-Administration Vulnerability

Tanni Rahman, Yanhua Ren, Joseph Landry, Yasmin L. Hurd

Departments of Psychiatry and Neuroscience, Addiction Institute, Icahn School of Medicine at Mount Sinai.

Heroin addiction is a debilitating neuropsychiatric condition. Impulsivity, a behavioral trait that is thought to be mediated in part by the nucleus accumbens, has repeatedly been demonstrated to be a risk factor for addiction. The complex molecular mechanisms within the nucleus accumbens that contribute to impulsivity are, however, still unknown. Our previous work linked the cAMP Response Element Modulator (Crem) gene to impulsivity and heroin addiction. Nevertheless, limited information exists regarding the potential function of Crem isoforms, Cremτ and Icer, in these maladaptive behaviors. Here, we utilize a rodent ADHD model of impulsivity, consisting of the spontaneously hypertensive rats (SHRs) and Wistar Kyoto rats (WKYs). Gene expression results revealed that Cremτ is down-regulated in the nucleus accumbens core and shell of SHRs. Furthermore, Cremτ expression in the nucleus accumbens shell negatively correlates with impulsivity and heroin self-administration. Icer, instead, is upregulated in the nucleus accumbens core of SHRs after acute heroin exposure. The results suggest that dysregulation of Crem isoforms in subregions of the nucleus accumbens may mediate impulsivity and vulnerability to heroin self-administration in SHRs. Current studies are underway to determine the causal role of Crem isoforms in regulating impulsive behavior and heroin self-administration that could help guide the development of novel therapeutic interventions.

This study was funded by NIDA.

125

Deciphering donor- and cell-type-specific interactions between schizophrenia risk variants

Kristina Rehbach1,2,3,4, Nadine Schrode1,2,3,4, Kristen J. Brennand1,2,3,4 et al.

1 Department of Neuroscience, 2 Department of Genetics and Genomics, 3 Friedman Brain Institute, 4 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York

Schizophrenia (SZ) is a common (1%), highly heritable (80%) polygenic disorder that imposes an immense burden on patients and society. A substantial proportion of risk arises through interactions between over 145 SZ common risk loci of small effect in several distinct brain cell types. The extent to which the additive impact of each additional common risk variant is dependent upon the risk factors already present in an individual is unknown. Here, we explore how the functional impact of one common variant, FURIN rs4702, varies between donors and neural cell types. We applied CRISPR-editing to engineer the risk variant, rs4702, in human pluripotent stem cells (hiPSCs) with high and low SZ polygenic risk score (PRS) donor backgrounds, to study the effect in isogenic neuronal cell types implicated in SZ, including astrocytes, glutamatergic neurons and GABAergic neurons. Whereas in neurons derived from donors with average PRS, allelic conversion at rs4702 results in reduced FURIN expression, neurite length, average burst duration and action potential height in donors, our preliminary data suggests that the impact of rs4702 on neuronal activity is greater in high PRS neurons. Our long-term objective is to uncover the cell-type-specific convergence and synergy between the many risk variants linked to SZ.

Funding: NIH

126

Discrete and interactive roles for maternal cannabis use and stress during pregnancy in shaping the placental transcriptome

Gregory Rompala1,4, Yoko Nomura1,5, Yasmin L. Hurd1,2,3,4

Departments of Psychiatry1, Neuroscience2, and Pharmacological Sciences3, Icahn School of Medicine at Mount Sinai. Addiction Institute at Mount Sinai4. Department of Psychology, Queens College, CUNY5.

Background: Although cannabis use is prevalent during pregnancy (10-27%), the effects of prenatal exposure are not clearly understood. Leveraging a unique cohort of 380 women in the NY metropolitan area that were pregnant before, during, or after Superstorm Sandy (SS) in 2012, we examined the impact of in utero exposures to maternal cannabis use and SS-stress. Preliminary results suggest that both cannabis use and SS-stress associate with elevated fear and anxiety in childhood. To interrogate in utero mechanisms involved, we processed placentas from mother-child dyads for transcriptomic analysis.

Methods: 131 placental samples were derived from an ongoing study at two prenatal obstetrics clinics. Bulk samples were processed for RNA sequencing and bioinformatic analyses.

Results: Maternal cannabis use was associated with reduced expression of immune gene sets involved in interferon- and cytokine-signaling. Exposure to SS-stress associated with robust effects among gene sets involved in estrogen/glucocorticoid metabolism and growth-hormone signaling which were amplified when co-occurring with maternal cannabis use. Gene co-expression networks and supervised regression modelling revealed an intriguing relationship between the placenta transcriptome and infant/child temperament.

Conclusions: Maternal cannabis use associates with placental immune gene dysregulation and exacerbates the link between prenatal stress and glucocorticoid-related genes.

Funding: NIMH

127

YAP-TEAD ACTIVITY REGULATES ACTIN CYTOSKELETON REMODELING AND MIGRATION IN HUMAN GLIOBLASTOMA

Halle Ronk, Anne Marie Barrette PhD, Nadejda Tsankova MD PhD

ISMMS, The Friedman Brain Institute

Glioblastoma (GBM) is a highly lethal primary brain tumor characterized by a great capacity for migration. The aggressive infiltration of GBM cells into the brain parenchyma challenges surgical resection, yet the mechanisms underlying GBM migration are poorly understood. Recent studies have identified the downstream Hippo pathway effectors TEAD and YAP/TAZ as essential regulators of GBM migration in vitro and in vivo. Hippo dysregulation is thought to promote epithelial-mesenchymal transition (EMT), a process wherein expression of epithelial E-cadherin is switched to mesenchymal-associated cadherins such as cadherin-11. The resulting mesenchymal phenotype displays enhanced migration and altered cell-cell adhesion. We investigated how dysregulation of the Hippo pathway impacts the migratory abilities of patient-derived GBM by using the small molecule YAP-TEAD inhibitor Verteporfin (VP), which is FDA-approved for the treatment of macular degeneration. VP treatment demonstrated decreased GBM cell migration in vitro, in spheroid migration assays. We used immunocytochemistry to examine the cellular effects in VP-treated GBM cells associated with migration. Preliminary studies reveal that migratory-deficient VP-GBM cells become rounder in shape, inhibit TEAD1, and downregulate levels of actin and cadherin-11. These results suggest that YAP/TEAD activity may promote GBM migration by maintaining cellular shape, actin cytoskeletal organization, and expression of mesenchymal cadherin adhesion molecules and support the hypothesis that dysregulated activation through the Hippo pathway promotes EMT and drives GBM migration.

Funded by ISMMS SCHOLaR Program

128

Individualized IAP Protocol Modification In Under-Studied Languages: A Case Study

Adam E. Saad, James Young, Jessica Spat-Lemus, Sydney Jacobs, Michelle Cohen, I. Paul Singh, Heidi A. Bender

The intracarotid amobarbital procedure (IAP) is often considered key to minimizing neuropsychological morbidity post-resection/ablation. While IAP procedures have been validated and extensively studied in English-speakers, further research is needed in patients speaking under-studied languages. This case study describes a right-handed surgical candidate whose primary language is Mixtec, an indigenous tonal language. Given increased possibility for atypical language dominance in languages where pitch changes are used to signal differences in word meaning, IAP findings were critical prior to LITT of seizure focus in dominant hemisphere structures. The patient was diagnosed with epilepsy age of 18. MRI was significant for left MTS. An empirically-validated English IAP protocol was modified, with selection of Mixtec targets completed with the aid of a Mixtec speaking individual. Confrontation naming items which shared cognates in Spanish and Mixtec were eliminated to guard against utilization of both tonal and non-tonal languages during the procedure, thus, reducing additional risk of bilateral hemispheric activation due to procedural confounds. Results of the IAP indicated left hemisphere language dominance (0% right; 69% left). Bilateral impairment of memory with right representation greater than left (50% right; 29% left). Given the unexpected finding of typical language dominance in a tonal language speaker, these findings underscore the importance of modifying existing IAP procedures to meet the unique linguistic and cultural needs of patients speaking under-studied languages.

129

Mentalizing deficits in cocaine addiction: associations with social competence, cognition, and gray matter integrity

Sahani V, Kamilar-Britt P, Moeller SJ, Perez-Rodriguez M, Gabbay V, Hurd YL, Bachi K

(Department of Psychiatry)

Mentalizing (inference during social interaction) is crucial for healthy reciprocal relationships. Individuals with cocaine use disorder (iCUD) show multiple social cognition deficits and thereby may exhibit alterations in mentalizing behavior and underlying structural integrity of mentalizing circuitry (prefrontal cortex, superior temporal sulcus, temporoparietal junction, temporal poles; regions similarly implicated in the pathophysiology of drug addiction). We therefore examined the behavioral and gray matter volume correlates of mentalizing in 15 iCUD and 15 demographically similar healthy controls. Participants completed the Movie for the Assessment of Social Cognition (a validated video-based mentalizing task), and social and cognitive assessments (i.e. memory). On the task, iCUD showed lower mentalizing accuracy ($p<0.05$) and more nonmentalizing errors ($p<0.05$). Analysis of structural integrity, using voxel-based morphometry applied to T1-weighted MRI scans is ongoing. In correlation analyses, mentalizing accuracy was positively correlated with reporting of greater cocaine craving ($p<0.01$) and overall cognitive performance ($p<0.001$). One explanation for this correlation (that can be tested in future studies) may be interoceptive functioning, which itself would be expected to correlate with higher craving and better mentalizing. Furthermore, nonmentalizing errors were negatively correlated with social network size ($p<0.05$), extending previous findings that mentalizing deficits predict real-life social impairments in iCUD. If the current findings are maintained, then treatment to enhance mentalizing in iCUD could improve clinical and functional outcomes.

Funding: NIDA

130

Regional and temporal segregation of actin nucleators at the synapse

Abhishek Sahasrabudhe, Fatema Begum and Deanna Benson

Dept of Neuroscience, Friedman Brain Institute

The maturation and remodeling of dendritic spines and synapses depend on an intricately structured underlying actin cytoskeleton. The Arp2/3 complex is the dominant actin nucleator at mature postsynaptic sites, but its removal fails to eliminate spines. We hypothesize that the actions of Formins complement those of Arp2/3. There are 15 members of the Formin family, most are expressed in neurons, and mutations in Formin genes have been identified in humans with intellectual disabilities. To identify relative contributions of Arp2/3 and Formins to mechanisms regulating synapse morphology and plasticity, filled neurons were exposed acutely to selective inhibitors and morphology at identified synapses was measured in response to a chem-LTP protocol. Inhibiting either Arp2/3 (CK666) or Formins (SMIFH2) alters relative proportions of filopodial and mushroom spines and abolishes spine enlargement. Volumes occupied by pre- and postsynaptic markers like vGlut1 and Homer1 also increase significantly with either inhibitor following cLTP, suggesting a role for actin in constraining the PSD and vesicle clusters following cLTP. Additionally, our data show that the activity of Arp2/3 and formins is segregated spatially and temporally, consistent with evidence that particular Formins show precise targeting to particular subcellular and synaptic domains. Current efforts in the lab are focused on establishing a CRISPR/Cas9 based screen to identify novel formins regulating spine morphology and synaptic scaffolding.

(Funding source: R01 MH104491)

131

Investigating cell type vulnerability in Parkinson's disease using an in vitro genetic model

Lily Sarrafha, Gustavo Parfitt and Tim Ahfeldt

CDRB, BFSCI, Department of Neuroscience, Loeb Center of Alzheimer's Disease, ISMMS

Familial Parkinson's Disease (PD) is caused by several genes with diverse functions. Human pluripotent stem cells (hPSCs) can be differentiated into different cell types with midbrain or hypothalamic identities, including vulnerable nigral dopaminergic neurons (DNs), giving us an opportunity to understand the mechanisms of cell-type vulnerability in PD. Parkin is an E3 ubiquitin ligase that mediates mitophagy. Loss of Parkin causes early onset autosomal recessive PD and has been shown to cause mitochondrial dysfunction in DNs. Understanding the dysregulation pathways in the absence of Parkin can help elucidate regulatory networks that are relevant for all forms of PD. Moreover, it will allow us to determine whether vulnerability in PD follows a stochastic model or affects a specific cell population (elite model). Using CRISPR technology we have modeled PD by knocking out Parkin in independent isogenic hPSC lines. We utilized knock-in fluorescent reporters to track and isolate midbrain DNs and demonstrated phenotypes such as increased oxidative stress and cell death in Parkin-/- DNs. Preliminary tests in hypothalamic DNs confirmed the expression of specific genes. Side-by-side comparison of midbrain and hypothalamic DNs will be performed to identify vulnerable populations of cells in the Parkin-/- lines. Results from this work will help in understanding the underlying mechanisms of vulnerability in PD and open new avenues for therapeutic approaches.

Funding: ISMMS, Illumina

132

Role of Plexin-B2 in GBM-Associated Microglia/Macrophage Corralling

Anirudh Sattiraju, Shalaka Wahane, Roland Friedel, Hongyan Zou

Department of Neuroscience and Neurosurgery

Glioblastoma (GBM) remains deadly and it achieves fast expansion through several mechanisms. Tumor microenvironment (TME) can profoundly influence GBM progression, but the complex interactions between invading GBM cells, microglia, astrocytes, and endothelial cells at tumor-stromal interface remains poorly understood. Tumor invasion border is a particularly active zone of cellular contacts, both physical and biochemical. Impact of glial cells and extracellular matrix (ECM) alignment at tumor border on immune response, tumor angiogenesis, and GBM invasion is unknown. In our recent study, our lab discovered a novel role of injury-activated microglia and macrophages (IAM) in promoting corralling and wound healing after spinal cord injury via axon guidance receptor Plexin-B2. Plexin-B2 is upregulated in IAM and its conditional knockout (cKO) in IAM impairs corralling, leading to diffuse tissue damage and inflammatory spillover. Mechanistically, Plexin-B2 enhances microglia motility, steers IAM away from colliding cells, and promotes matrix compaction through focal adhesion. Analogously, here we tested the hypothesis that Plexin-B2 in tumor-associated microglia/macrophages (TAM) promotes corralling and formation of a glial barrier at the GBM border. We found that Plexin-B2 is robustly upregulated in TAM, and Plexin-B2 cKO in myeloid cells resulted in impaired corralling and intermingling of GBM cells and microglia at the tumor border in a murine GBM model. Importantly, the disruptive glial border at the GBM border resulted in enhanced infiltration of cytotoxic T cells, vascular disarray, and reduced GBM expansion.

133

Automated statistical and functional fine-mapping of Parkinson's disease loci

Brian M. Schilder [1], Towfique Raj [1]

1. Department of Neuroscience, Department of Genetic & Genomic Sciences, Icahn School of Medicine at Mount Sinai

Background: A recent large-scale GWAS of Parkinson's Disease (PD) identified 78 loci containing PD-associated SNPs. However, for any given locus the SNP with the smallest p-value may merely be a proxy for the true causal SNP (or set of causal SNPs) due to linkage disequilibrium (LD). Fine-mapping aims to identify the causal SNP(s), which can greatly reduce the number of false-positive genetic associations. We fine-mapped all 78 loci by developing echolocatoR, an open-access R package that enables automated end-to-end fine-mapping.

Method: We used multiple statistical (ABF, SUSIE, FINEMAP) and functional fine-mapping (PolyFun). High-confidence Consensus SNPs were defined as SNPs that multiple tools proposed in their credible sets. Brain cell type-specific epigenomic assay data were then used to identify the target cell types affected by the fine-mapped variants.

Results: Our pipeline reduced the number of SNPs per locus from an average of 165.1 significant GWAS SNPs, to 16.5 95% probability Credible Set SNPs, to 2.3 Consensus SNPs. For example, in the LRRK2 locus we identified a Consensus SNP that fell within an active promoter in microglia and neurons, whereas the lead GWAS SNP fell outside these functionally relevant regions.

Conclusions: We identified SNPs that are likely to be causal in PD, which we are now experimentally validating in vitro.

Funding: Michael J Fox Foundation

134

"Chronic Social Defeat Stress Increases Markers of Permeability in Large Intestine"

Yasemin Schmitt and Kenny Chan, PhD

From the Scott J. Russo Lab in the Department of Neuroscience.

Major Depressive Disorder (MDD) is an extremely prevalent disease and despite decades of research, many patients are unresponsive to traditional antidepressant medication. Emerging research indicates the importance of the gut membrane in regulating the passage of chemicals and the stimulation of the immune system. My project examines markers of intestinal permeability and their association with the development of depression. Using Chronic Social Defeat Stress (CSDS), an animal model for depression, and Social Interaction Test (SI), mice can be classified as either susceptible or resilient to developing depression-like phenotypes. The rationale for my project is to look at the Claudin (Cldn) protein family, prevalent in the tight junctions between gut epithelial cells, and their possible role in the permeability of the gut membrane after stress. I hypothesized that susceptible mice would have downregulated Cldn proteins by causing "leaky gut." To test my hypothesis, I extracted RNA from intestinal tissue and measured the transcript level of Cldn proteins in samples provided by a qualified scientist, using a quantitative polymerase chain reaction (qPCR). My data indicates that the upregulation of Cldn1 and Cldn3 and downregulation of Cldn4 is associated with susceptible behavior. Cldn3 appears to be most significantly different between both resilient and susceptible groups, indicating this protein may more closely modulate the differences in gut permeability and phenotype behavior.

135

PATTERNS OF MISMATCH NEGATIVITY DEFICITS IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS AND ASSOCIATION WITH SYMPTOMS

Shaik RB1,Parvaz MA1,Bilgrami ZR 1,Sarac C1,Herrera S1,Haas S1,Garg S1 ,Lopez-Calderon J2, Corcoran CM1.

1. Psychiatry, ISMMS; 2. Universidad Autónoma de Chile, Talca;

BACKGROUND: Auditory processing deficits are core to schizophrenia, reflected in impaired generation of EEG-derived event-related potentials such as the auditory mismatch negativity (MMN), elicited in response to deviant stimuli. Among individuals at clinical high risk (CHR) for psychosis, auditory MMN impairments exist and predict outcome. We hypothesized that auditory MMN deficits in CHR patients would be associated with symptom severity.

METHODS: Participants included 43 CHR patients and 19 healthy controls (HC), who completed an auditory MMN paradigm that included deviants in duration, frequency, intensity, and frequency modulation. Symptoms assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS). Group differences assessed and association with clinical symptoms determined.

RESULTS: CHR patients had reduced duration MMN (p=.022). Among CHR patients, negative symptom severity was correlated with reduced duration (p=.014), intensity (p=.048), and pitch (p=.001) MMN. General symptom severity was associated with reduce intensity (p=.002) and pitch (p=.006) MMN.

CONCLUSIONS: Our findings of reduced duration MMN in CHR patients replicate prior studies, supporting its candidacy as a psychosis risk marker. Negative and general symptom severity in CHR patients appears to be broadly associated with auditory processing deficits, including duration, intensity and pitch deviants. Data collection is ongoing, including assessment of auditory MMN based on location and frequency modulation deviants.

FUNDING: R01MH107558(CMC), R01MH49334(DCJ)

136

Intergenerational effects of adolescent THC exposure on circadian regulation

J Sherman1, A Ly1, J Landry1, J Callens1, M McCarthy2, E Loh1, L Shen1, N Patel1, T Uzamere1, YL Hurd1 and H Szutorisz1

1Departments of Neuroscience and Psychiatry, Icahn School of Medicine at Mount Sinai; 2Department of Psychiatry, University of California San Diego

Cannabis is now consumed by young people of childbearing age to a greater extent than cigarettes and our research has demonstrated that effects can even be transmitted to the subsequent generation. In this study, we utilized an animal model to examine the intergenerational consequences of exposure to the main psychoactive component of cannabis, delta 9-tetrahydrocannabinol (THC). Behavioral studies in adult offspring revealed sex-specific changes in reward-related, anxiety, and depression-like behaviors especially pronounced in females. To gain insight into the underlying mechanisms, RNA sequencing was conducted in the female nucleus accumbens (NAc) and revealed a robust and highly reproducible dysregulation of Cryptochrome Circadian Regulator 2 (Cry2) and several genes functionally related to epigenetic mechanisms. To address potential dysregulation in the circadian rhythm, we employed a fibroblast cell culture approach established from rat tissue. Using this model, we explored the relationships between circadian gene expression and several behavioral measures obtained from the same animals. The analyses revealed that Cry2 expression significantly correlated with affective behaviors and parental THC exposure altered these relationships. Altogether, the results suggest circadian regulation as a potential link between intergenerational epigenetic changes and behavioral phenotypes as the result of parental THC exposure. Funding: NIH/NIDA.

137

To be honest: modelling the impact of social norms and antisocial traits on dishonesty

Anastasia Shuster1, Madeline O'Brien2, Soojung Na1, Vincenzo Fiore1, Xiaosi Gu1,2,3

1Psychiatry, ISMMS2Neuroscience, ISMMS3James J. Peter Veterans Affairs Medical Center

Others' actions teach us about the appropriateness of behaviors, and this normative information should serve as a powerful signal guiding decision-making. Because several psychiatric disorders are marked by abnormal compliance with social norms, we aimed to computationally characterize the influence of social norms on moral decision-making and its interaction with antisocial traits. We used a task in which the participant sends either a deceitful (yet profitable) or truthful (and less profitable) message to their partner. Payoffs varied for both players, conflicting one's own benefit with another's loss. After completing a series of choices, participants were presented with social information regarding the choices of past participants on each trial and chose again. We used the first stage as a baseline measure of dishonesty, and choices in the second stage to operationalize conformity. Participants also completed self-report questionnaires. Firstly, psychopathy positively correlated with dishonest choices. Secondly, participants indeed conformed to norms when presented with social information. Importantly, participants' conformity was related to their antisocial traits - highly antisocial individuals were less sensitive to normative social information.Our results show variation in the influence of norms on dishonesty, which is related to antisocial traits. These findings may help elucidate the normative components of pro- and anti-social behaviors and have broader implications on mental health.

* Funding: NIH

138

Screening peripheral biopsies for α-synuclein pathology using deep machine learning

Max Signaevsky, MD-PhD, Nabil Tabish, MD, MS, Bahram Marami, PhD, Marcel Prastawa, PhD, Daniel Koenigsberg, BS, Clare Bryce, MD, Lana Chahine, MD, et al.

Post-mortem assessment remains the gold standard for a definitive diagnosis of Parkinson's disease (PD). The antemortem diagnosis is challenging due to a clinical heterogeneity and overlap with other disorders. While PD manifests with aggregation of α-synuclein as Lewy bodies and neurites in the central nervous system, this pathology is also evident in the peripheral nervous system. Peripheral Lewy-type α-synuclein aggregation (αSyn) is present in early PD, suggesting its utility as a biomarker. We have previously confirmed that detection of αSyn in submandibular gland biopsies is sensitive (0.75) and specific (0.90) for early PD. However, current approaches require laborious and time-consuming assessment by a highly specialized neuropathologist, limiting the practicality beyond research settings. We constructed and validated a convolutional neural network (CNN), and deployed it for detection of αSyn using 285 digital whole slide images (WSI) of α-synuclein stained sections from 95 unique submandibular gland biopsies from patients with PD (n=59) and controls (n=21). A total number of 2653 αSyn objects were annotated. The CNN had the following performance: sensitivity (0.98), specificity (0.99), and precision (0.84). Moreover, the CNN showed sensitivity of 0.97 in detecting αSyn on a test set of WSI. This demonstrates the utility of a CNN as a practical screening tool facilitating the antemortem diagnosis of PD.

Funding: MJFF grant

139

Quantifying social and non-social gaze behavior in primates during a reward localization task.

Joseph Simon, IV and Erin Rich MD/PhD.

Nash Family Department of Neuroscience, Icahn School of Medicine, New York, NY

In social neuroscience, experimental designs have focused predominantly on prosocial and antisocial behaviors, leaving open the question of how social information affects non-social behaviors. To address this, I've created a task contrasting reward-seeking behavior informed by social and nonsocial cues. Monkeys were trained to saccade to one of two identical green squares to obtain juice reward. Cues included monkey faces or arrows on complex backgrounds, and were used to indicate which target was correct. Cues were shown for 1 second, after which the green squares appeared. The subject had 3 seconds to select a target. Training sessions included four trial blocks. Three blocks were composed of either monkey faces or arrows, and the fourth contained all cues randomly interleaved. To control for potential bias to images, eyes and faces were independently flipped along the horizontal axis, keeping the integrity of the image, but changing gaze direction. We found that accuracy for both social and nonsocial cues was greater than chance level, and slightly higher for the non-social arrows. Additionally, there was no correlation between accuracy and amount of time viewing cues. Overall, these data show that monkeys can use social information to inform decision-making. Furthermore, this experimental design allows for neurophysiological recording experiments to explore the role of social information in non-social reward-seeking decisions.

Funding: FBI seed fund

140

Profiling of tau hyperphosphorylation in FFPE post-mortem human brains

Cheick Sissoko1, Soong Ho Kim1, Kurt Farrell1, Rao Mendu2, Srinivas Chakravartula2, John Crary1

1) Department of Pathology, Nash Department of Neuroscience, Friedman Brain Institute, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai 2) Mass Spectrometry Laboratory, Center for Clinical Laboratories, Mount Sinai Hospital

Background: Tauopathies are neurodegenerative disorders with a range of clinical and motor symptoms characterized by aberrant accumulation and hyperphosphorylation of tau. Understanding the post-translational modification patterns of tau may provide critical insights in the mechanisms of tau aggregation, cell-to-cell propagation and developing therapeutics. We examined the nexopathic nature and evolution of the molecular profile of pathological tau by identifying phospho-epitopes across different brain regions and disorders.

Methodology: Formalin-fixed paraffin-embedded tissue samples from individuals diagnosed with Alzheimer's disease, progressive supranuclear palsy, chronic traumatic encephalopathy, and primary age-related tauopathy (n=3 per group) were analyzed using a Q Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer LC-MS/MS system to precisely locate phosphorylated sites on tau. Data were analyzed using Proteome Discover 2.1 then interpreted and further validated by immunohistochemistry and immunoblot.

Results and Conclusion: We report the first investigation using mass spectrometry of tau phosphorylation in fixed human brain tissue. Preliminary results show our data is consistent with the scientific literature on fresh tissue and immunochemistry. Additionally, we observed potential novel phospho-sites, as well as trends across each tauopathy and brain regions. Our data underline the great potential and feasibility of FFPE for tau proteomics phenotyping.

141

Understanding the neurobiological mechanisms of FOXP1 syndrome using patient-derived iPSCs

Sofia Stathopoulos1,2, Nan Yang3, Joseph Buxbaum1,2

1Department of Psychiatry, Icahn School of Medicine, Mount Sinai, NY.

2Seaver Autism Center for Research and Treatment, Icahn School of Medicine, Mount Sinai, NY.

3Department of Neuroscience, Icahn School of Medicine, Mount Sinai, NY.

Autism spectrum disorder (ASD) is characterized by phenotypic and genetic heterogeneity. Haploinsufficiency of the forkhead-box protein P1 (FOXP1) gene leads to FOXP1 syndrome, a neurodevelopmental disorder with complex manifestations including ASD. Human neuronal models are a proxy to study the mechanisms of FOXP1 syndrome. Induced pluripotent stem cells (iPSCs) retain the genetic background of the individual they derived from and can differentiate into induced neurons (iNs). This study aims to improve our understanding of FOXP1 syndrome using iNs and identify candidate cellular phenotypes that could be used to identify potential therapeutics.

Our approach is to:1) generate high-quality excitatory iNs derived from FOXP1 patients/sibling pairs, by transiently expressing proneuronal factor Ngn2 in iPSCs;2) capture the electrophysiological phenotype of the iNs using patch-clamp; and,3) identify FOXP1-associated transcriptomic and chromatin landscape signatures by RNA seq, ATAC-seq and CUT & tag.

Excitatory iNs from FOXP1 patient/sibling pairs were successfully generated. Studies from patch-clamp recordings, RNAseq, ATAC-seq and CUT&Tag assays are ongoing. These will allow us to identify electrophysiological, transcriptomic and epigenetic signatures associated with FOXP1 haploinsufficiency. This will be the first report of hiPSCs and iNs for FOXP1 syndrome.

This work was supported by the Seaver Foundation; Sofia Stathopoulos is a Seaver Postdoctoral Fellow.

142

Identification of novel modification gCaMKIIQ285dopaminylation in brain

A.F. Stewart1, R.M. Bastle1, R. Thompson3, S. Fulton1, A. Lepack1, L. Farrelly1, Y. Lu1, H. Molina4, T.W. Muir3, I.S. Maze1,2

1Dept. Neuroscience, 2Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029-5674, 3Dept. Chemistry, Princeton University, Princeton, NJ 08544, 4Proteomics Resource Center, Rockefeller University, New York, NY 10065-6399

Background: Monoamines are traditionally regarded as chemical signals that act extracellularly on surface bound receptors in brain. However, recent work from our lab demonstrates that non-vesicular monoamines have a receptor-independent mechanism via transamidation onto glutamine residues of proteins.

Methods: We selectively isolated dopaminylated proteins in brain utilizing a novel endogenous chemical tagging method to specifically immunoprecipitate dopaminylated proteins. Following chronic heroin self-administration in rats, immunoprecipitations coupled to mass spectrometry identified novel dopaminylated proteins, including multiple isoforms of CaMKII. We further characterized CaMKII dopaminylation utilizing in vitro enzymatic assays coupled to mass spectroscopy, to identify glutamine 285 as selective sites of dopaminylation on gCaMKII. Furthermore, utilizing genetically modified cell lines we have observed a deficit of gCaMKII nuclear translocation and subsequent pCREB activation following dopamine treatment and subsequent chemical stimulation.

Results: gCaMKIIQ285dop is upregulated following one day abstinence from heroin self-administration. In vitro data suggests gCaMKIIQ285dop may affect nuclear localization and pCREB signaling. pCREB deficits were rescued by blockade of dopaminylation at Q285.

Conclusion: These data represent not only a possible novel mechanism of regulation of CaMKII, but also a possible novel receptor-independent of dopaminergic transmission.

143

Modeling sporadic progressive supranuclear palsy in a novel collection of iPSC lines

Kevin Strang1,2,3,4, Megan Iida1,2,3,4, Kristen Whitney1,2,3,4, Hadley Walsh1,2,3,4, Kurt Farrell1,2,3,4, Samuel Powell1,3,4,5, Michael Deans1,3,4,5, Ruth Walker1,3,4,5, Steve Frucht, Giulietta Riboldi, Kristen Brennand1,3,4,5, John Crary1,2,3,4

Departments of Neuroscience1, Pathology2, Loeb Alzheimer's Disease Center3, Friedman Brain Institute4, Genetics & Genomics5, Neurology6, Icahn School of Medicine at Mount Sinai

Background: Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized clinically by parkinsonian symptoms and neuropathologically by accumulation of hyperphosphorylated protein tau in the brain. While sporadic tauopathy outweighs familial tauopathy in prevalence, most research models incorporate autosomal dominant mutations. A model of sporadic PSP using human iPSC-derived neurons would be useful for disease modeling.

Method: Skin-derived fibroblasts from clinically- and autopsy-diagnosed PSP patients were collected (n=9) and reprogrammed into iPSCs using Sendai virus. Cells were differentiated into cortical glutamatergic neurons via lentiviral transduction of neurogenin 2. Three PSP patient-derived iPSC lines, one MAPT mutation-carrying control, and two negative controls were transduced and differentiated. Lines were characterized using RNA sequencing, immunofluorescence and biochemical analysis of disease markers. Additionally, alterations in candidate causal factors derived from parallel genetic and transcriptomic studies were assessed.

Result/conclusions: Viral transduction of patient-derived iPSCs into neurons results in MAP2 and tau positive neurons. The lines are being analyzed for differences in gene expression and phenotypic markers of neurodegeneration at 10 weeks. Utilization of neuronally-differentiated iPSCs derived from clinically and pathologically diagnosed sporadic PSP patients is vital to studying a disease that mostly presents sporadically.

144

Emotional Content Modulates Brain and Behavior Impact of Tobacco Graphic Warning Labels in Adolescents

An-Li Wang1, **Yuanqi Sun**1, James Padley2, Daniel Langleben2

1 Icahn School of Medicine at Mount Sinai 2 University of Pennsylvania

Background: Previous behavioral studies show that Graphic Warning Labels (GWLs) are more effective in motivating smoking cessation among adolescents than text warnings. However, little is known about how the adolescent brain processes health information and whether the emotional content of GWLs modulates the information processing. We conducted a functional magnetic resonance imaging (fMRI) study to address these questions.

Methods: Over a 4-week period, participants were exposed daily to GWLs previously rated high or low on the emotional reaction (ER) scale (High ER vs. Low ER). Brain responses to GWLs were recorded using fMRI before and after the exposure period. Their memory for GWLs' images and texts was tested respectively.

Results: High ER GWLs induced greater brain response in bilateral Amygdala, compared to Low ER GWL. The medial frontal activation in response to GWLs increased over 4-week exposure. Images from High ER GWLs were better recalled than these from the Low ER GWLs. There was no difference in the recall of text. The text recall was positively correlated with bilateral amygdala activities induced by High ER GWLs.

Conclusions: These preliminary findings show that neural activities in the brain region mediating executive functions increased after 4-week exposure. Unlike adults, the emotional salience of GWLs did not facilitate cognitive processing of textual warnings in adolescents.

Funding:NIH/NICHD K99-HD084746

145

Altered synaptic properties of hypothalamic oxytocin neurons are accompanied by reduced oxytocin release in a Shank3-deficient rat model

Keerthi Thirtamara Rajamani et al.

Department of Psychiatry and Seaver Autism Center

Mutations in SHANK3 gene are a leading cause of Phelan-McDermid syndrome and account for 1-2% of autism spectrum disorder (ASD) cases. Using a rat model carrying a mutation in the Shank3 gene, we previously reported deficits in long-term social recognition memory and synaptic plasticity in the hippocampal and medial prefrontal cortex circuitry that could be reversed by acute oxytocin treatment. Based on these findings, we hypothesize that these deficits are driven by impairments in the oxytocin system. We examined synaptic properties of fluorescently labeled oxytocin neurons using in vitro electrophysiology and found that Shank3-/- rats had lower amplitude distributions in both miniature and spontaneous excitatory postsynaptic potentials, suggesting altered synaptic plasticity. Using immunohistochemistry, we quantified total number and signal intensity of labeled oxytocin neurons, and found no overall change in their number, but observed reduced intensity of oxytocin signal in Shank3-/- rats. Finally, we quantified oxytocin using in vivo microdialysis specifically during social interaction, as this has been previously shown to stimulate oxytocin release. We found elevated oxytocin levels during social interaction in wild type but no change in the Shank3-/- rats, suggesting impaired oxytocin release. Our findings suggest that Shank3 mutation impairs processing and release of oxytocin and alters synaptic properties of oxytocin neurons.

Funding: Beatrice and Samuel A. Seaver Foundation, NIMH-R01MH116108

146

Joshua Torres

High School / Undergraduate Student

Hof Lab, Nash Family Department of Neuroscience

Major Depressive Disorder(MDD) is a neurological disorder that affects 3 million America and it is a leading cause of suicide. There is little understanding of its mechanisms and there aren't aren't any biomarkers for identifying suicidal patients. In an effort to better understand the disorder and find biomarkers, we used the high resolution of 7 Tesla(7T) MRI imaging to study the insula and its subregions. We specifically chose the insula because it has been associated with reduced functional connectivity and grey matter volume in depression We used Spatial K , a segmentation tool currently being developed, and 7T images to compare the volumes of the insula and it's subregions to clinical values for depression and suicidality in patients with MDD and healthy controls. There wasn't enough significant data to make any conclusions but Spatial K showed potential to be a powerful segmenting tool. Most of the segments it produced were clean and in-line with the subregions discussed in the literature. More study of the insula and use of Spatial K may lead to the discovery of biomarkers for suicidality that can be used to give patients the treatment they need.

147

Chemogenetic actuator drugs impair prefrontal cortex-dependent working memory in rhesus monkeys

Nicholas A. Upright and Mark G. Baxter

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

Background: The most common chemogenetic neuromodulatory system, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), uses a non-endogenous actuator ligand to activate a modified muscarinic acetylcholine receptor that is no longer sensitive to acetylcholine. It is crucial in studies using these systems to test the potential effects of DREADD actuators prior to any DREADD transduction, so that effects of DREADDs can be attributed to the chemogenetic system rather than the actuator drug.

Methods: We investigated working memory performance after injections of three DREADD actuators - clozapine, olanzapine, and deschloroclozapine - in male rhesus monkeys tested in a spatial delayed response task before any DREADD transduction took place.

Results: Administration of 0.2 mg/kg clozapine, 0.1 mg/kg olanzapine, and 0.3 mg/kg deschloroclozapine impaired working memory function in some monkeys. Performance at 0.1 mg/kg clozapine and 0.1 mg/kg deschloroclozapine did not differ from mean performance after vehicle in any of the four subjects.

Conclusions: These findings underscore the importance of within-subject controls for DREADD actuator drugs to confirm that effects following DREADD receptor transduction are not due to the actuator drug itself, as well as validating the behavioral pharmacology of DREADD actuator drugs in the specific tasks under study.

148

Blood microRNAs as a biomarker for stress susceptibility or resilience and treatment response

Y.Y. van der Zee1,2, O. Issler2, A. Ramakrishnan2, K. Alvarez2, J. W. Murrough1, B. Rutten1, E. J. Nestler2.

1Maastricht University, The Netherlands

2Icahn School of Medicine at Mount Sinai

Introduction: There is an urgent need for objective biomarkers for diagnosing depression, assigning treatment, and assessment of treatment response. MicroRNAs (miRNAs) are small noncoding RNA molecules, which can be detected in body fluids and have emerged as potential biomarkers of disease conditions, including depression.

Methods: We profiled the expression levels of circulating blood miRNAs from mice that was collected before and after exposure to Chronic social defeat stress (CSDS), as well as after either imipramine or ketamine treatment. To probe the involvement of a subset of these miRNAs in depression in human patients, RT-qPCR was conducted on blood samples of treatment-resistant depressed patients and healthy controls before and after treatment with ketamine.

Results: We observed robust differences in blood miRNA signatures between resilient and susceptible mice after an incubation period but not immediately after exposure to stress. Furthermore, treatment with ketamine, but not imipramine, re-established baseline miRNA expression levels in mice that responded to the drug, but not in non-responders. Analysis of candidate miRNAs in human blood samples validated a subset of targets identified in mice as candidate biomarkers to aid depression diagnosis and predict ketamine treatment response.

Conclusion: This study identifies candidate miRNAs that warrant further investigation as biomarkers for depression treatment response.

149

Modulating microglial states in neurodegeneration through BET proteins

Sarah Veugelen1, Josefa Sullivan1, Sahil Agrawal1, Pinar Ayata1, Ana Badimon1, Hayley Strasburger1, Rab Prinjha2, Uwe Schaefer3, Alexander Tarakhovsky3, Anne Schaefer1

1)Mount Sinai, 2)GlaxoSmithKline, 3)Rockefeller University

Background: Neurons are the most vulnerable cell type in the brain and their endurance is of critical importance to organism survival. Therefore, it is necessary to understand the mechanisms that contribute to loss of specification and lead to neuronal dysfunction and death. Recent studies have implicated microglia as important contributors to neurodegeneration. These cells display high levels of plasticity and exist in diverse functional states. This allows them to rapidly respond to brain injury or inflammation but must also be tightly maintained to ensure brain health. In peripheral macrophages, the bromodomain and extra-terminal domain (BET) proteins provide the epigenetic switch that regulates these functional states. We propose that BET proteins are also key in regulating this in microglia and that BET inhibition can reverse an aberrant inflammatory state.

Method: We use pharmacological and genetic approaches to delineate the contribution of BET proteins to microglial inflammatory states.

Results: We found that pharmacological inhibition of BET proteins prevents the induction of an inflammatory state in microglia by selectively downregulating genes implicated in the interferon response pathway and confirmed our findings in an in inducible model of Alzheimer's Disease.

Conclusion: BET proteins regulate the switch between different microglial functional states and their inhibition represents a novel therapeutic strategy to suppress the pro-inflammatory microglial state during neurodegeneration.

B.A.E.F., NIH and GSK

150

The functional impact of structural variation in the human brain

Vialle RA, Lopes KP, Crary JF, Raj T

Departments of Neuroscience and Pathology, Loeb Center for Alzheimer's disease, Mount Sinai, New York

BACKGROUND: Structural variants (SVs) are an essential source of genetic diversity and have been linked to many diseases. However, their contribution to molecular traits in the brain and its impact on neurodegenerative diseases remains unknown. The Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD) consortium provides an extensive collection of multi-omics data that allows us to identify SVs and characterize their functional impact. This includes deep whole-genome sequencing (WGS) from 1,860 subjects from four aging and AD cohorts (ROS/MAP, MSBB, and Mayo Clinic).

METHOD: Here, we developed a rigorous computational pipeline integrating seven different SV discovery tools plus merging and genotyping strategies to identify high confidence SVs present in all cohorts.

RESULTS: We identified previously known SVs at MAPT locus and identified several novel suggestive associations to neuropathology traits. We integrated multi-omics data derived from CHIPseq, RNAseq, and Proteomics experiments to the access quantitative trait loci associations of common SVs with histone acetylation (SV-haQTL), splicing (SV-sQTL), gene expression (SV-eQTL), and protein expression (SV-pQTL).

CONCLUSION: Overall, we present the most comprehensive map of structural variation in aging cohorts, providing a valuable resource for understanding the functional impact of SVs in neurodegenerative and neuropsychiatric diseases.

FUNDING: This project is supported by grants from the NIH National Institute on Aging.

151

The Role of Resilience and Wellness in Suicide Prevention

A. Vitale; S. Alter; L. Byma; A. Feder; E. Podolak; R. Yehuda; F. Haghighi, et al

JJPVA Medical Center; Mount Sinai School of Medicine

Introduction: The Resilience and Wellness Center (RWC) is an innovative program focused on suicide prevention. The RWC attempts to address stigma associated with engaging in mental healthcare by augmenting traditional treatments with complementary and integrative health interventions. This program provides an opportunity to enhance life skills through Whole Health intervention, including: meditation, yoga, music therapy, exercise/dance, etc.

Methods: Veteran participants attend 14 different life skill classes 3 hours/day, 5 days/week over 4 weeks. Assessment batteries are administered pre-post program attendance and include validated questionnaires such as the Beck Depression Inventory (BDI), Beck Hopelessness Scale (BHS), and Patient Health Questionnaire-9 (PHQ-9). Pre-post comparisons of outcome were performed across all subjects/cohorts using two sample t-tests.

Results: To date, 14 Veteran cohorts have completed the program, totaling 131 participants. Although 14 cohorts have attended, data is presented here for 9 cohorts. For suicide attempters, significant improvements were observed in depression, measured by the BDI ($p \leq .001$), the PHQ-9 ($p \leq .001$). We also assessed at hopelessness and found a large improvement in score ($p < .002$).

Conclusions: These data underscore the importance of developing and sustaining novel interventions for engaging Veterans at risk of suicide. The RWC provides an alternative treatment paradigm for at risk veterans who may struggle with traditional mental health treatments. This intervention is promising, showing significant improvements in health quality.

152

Microglia and macrophages promote corralling, wound compaction and recovery after spinal cord injury via Plexin-B2

Xiang Zhou 1,5,*, **Shalaka Wahane** 1,*, Marie-Sophie Friedl7, Michael Kluge7, Caroline C. Friedel7, Kleopatra Avrampou1, Venetia Zachariou1,3, Xijing He5,6, Roland H. Friedel 1,2,#, and Hongyan Zou 1, 2,

1 Nash Family Dept. of Neuroscience, 2 Dept. of Neurosurgery, Friedman Brain Institute, 3 Dept. of Pharmacological Sciences, 4 Dept. of Genetics and Genomic Sciences, Mount Sinai Center for Transformative Disease Modeling, Icahn Institute for Data Science and Genomic Technology, New York, NY, USA, 5 Dept. of Orthopedics, Xi'an Jiaotong University, 6 Xi'an Medical Center,China, 7 Institut für Informatik, LMU Munich, Germany

Tissue repair after spinal cord injury (SCI) requires mobilization of immune and glial cells forming a protective barrier that seals the wound and facilitates debris clearing, inflammatory containment, and matrix compaction. This process involves corralling, wherein phagocytic immune cells become confined to necrotic core surrounded by astrocytic border. We elucidate a temporally distinct gene signature in injury-activated microglia/macrophages (IAM), which engages axon guidance pathways. Plexin-B2 is upregulated in IAM, which is required for motosensory recovery after SCI. Plexin-B2 deletion in myeloid cells impairs corralling, leading to diffuse tissue damage, inflammatory spillover, and hampered axon regeneration. Corralling begins early and requires Plexin-B2 in both microglia and macrophages. Plexin-B2 promotes microglia motility, steers IAM away from colliding cells, and facilitates matrix compaction. Our data thus establish Plexin-B2 as an important link that integrates biochemical cues and physical interactions of IAM with the injury microenvironment during wound healing.

153

Identifying novel structural variants at the 17q21.31 MAPT locus in progressive supranucelar palsy using targeted long-read sequencing

Ricardo Vialle1,4, **Hadley Walsh**1,2,4, Alicia Casella1,2,4, Megan Iida1,2,4, Kurt Farrell1,2,4, Kathryn Bowles1,3,4, Alan Renton1,3,4, Melissa Smith3, Robert Sebra3, Towfique Raj1,3,4, Alison Goate1,3,4, John Crary1,2,4

Departments of Neuroscience1, Pathology2, Genetics & Genomics3, Loeb Alzheimer's Disease Center4, Icahn School of Medicine at Mount Sinai

Background: The 17q21.31 MAPT locus is associated with sporadic tauopathies in the absence of an exonic mutation, including progressive supranucelar palsy (PSP) among others. This locus contains a number of large cytogenetic rearrangements (e.g., duplications, deletions and inversions) that hinder fine-mapping of disease risk.

Methods: Targeted single molecule real-time sequencing (SMRT-seq) of the 17q21.31 locus was performed in a cohort of PSP cases (n=9) and controls (n=20) on DNA isolated using NimbleGen sequence capture probes using the PacBio platform. These data were aligned using NGMLR, structural variants were identified using SVIM and results analyzed in R and Integrative Genomic Viewer.

Results/conclusions: We obtained an average of 353k reads across 29 samples with an average read length of 5kb. 41 variants were called on average per case. These variant calls ranged in size from 52 to 944,000 bp, including 22 inversions, 15 insertions, 38 duplications, and 29 deletions across all samples. Of these, we identified 6 variants with novel associations with PSP. Pending further validation and replication in larger cohorts, these variants may help elucidate the mechanism underlying disease risk in PSP derived from the MAPT locus.

154

Peripheral biomarkers and sequelae of operational blast exposure

Wang, Z., Haghighi, F., Ge, Y., et al.

Mount Sinai School of Medicine

Background: To study blast-related neurotrauma we have undertaken human studies involving military personnel exposed to repeated blasts and examined corresponding whole genome transcriptional profiles.

Methods: The study enrolled 31 male participants (age 30.2 ± 7.4 years) during a 3 day data collection cycle including baseline (day 1), pre- and post- breaching (day 2), and follow-up (day 3) at a U.S. Army training site. Blood samples were obtained from every time point. All subjects have a previous history of exposure to blast, and 17 of them self-reported at least one lifetime history event of TBI. We performed transcriptional profiling via RNA-seq and correlated gene patterns with daily symptoms e.g. headache, dizziness, etc., and neurocognitive performance.

Results: We identified transcriptional changes associated with acute blast exposure as well as that persist over twelve hours. We found that UBA6, which signals proteasomal degradation in response to cellular stress, showed elevated expression acutely following blast in those with a history of TBI as compared to a decrease in expression in those without; and gene GADD45G to be differentially expressed, which has been reported associated with peripheral nerve injury in animal models.

Conclusions: This study represents a systematic investigation of transcriptional regulatory changes associated with symptoms of acute blast exposure. It underscores the importance of taking into account prior lifetime history of TBI, blast symptomology in identification of robust peripheral biomarkers of blast responsivity.

155

The landscape of multiscale transcriptomic networks and key regulators in Parkinson's disease

Qian Wang, Yuanxi Zhang, Minghui Wang, Won-Min Song, Qi Shen, Andrew McKenzie, Insup Choi, Xianxiao Zhou, Ping-Yue Pan, Zhenyu Yue & Bin Zhang

Department of Neurology and Neuroscience, Friedman Brain Institute Department of Genetics and Genomic Sciences-Mount Sinai Center for Transformative Disease Modeling Icahn Institute of Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY 10029

Genetic and genomic studies have advanced our knowledge of inherited Parkinson's disease (PD), however, the etiology and pathophysiology of idiopathic PD remain unclear. Herein, we perform a meta-analysis of 8 PD postmortem brain transcriptome studies by employing a multiscale network biology approach to delineate the gene-gene regulatory structures in the substantia nigra and determine key regulators of the PD transcriptomic networks. We identify STMN2, which encodes a stathmin family protein and is down-regulated in PD brains, as a key regulator functionally connected to known PD risk genes. Our network analysis predicts a function of human STMN2 in synaptic trafficking, which is validated in Stmn2-knockdown mouse dopaminergic neurons. Stmn2 reduction in the mouse midbrain causes dopaminergic neuron degeneration, phosphorylated α-synuclein elevation, and locomotor deficits. Our integrative analysis not only begins to elucidate the global landscape of PD transcriptomic networks but also pinpoints potential key regulators of PD pathogenic pathways.

The work is supported by NIH grants P50NS0947331, U01AG046170, RF1AG057440, and R01NS060809

156

ANALYSIS OF PARKINSON'S DISEASE SUBTYPES VIA CLUSTER ANALYSIS

Kristen Watkins[1,2], Giulietta Riboldi[3], Towfique Raj[2]

[1]ISMMS, [2]Friedman Brain Institute, [3]NYU Langone

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder. PD's highly heterogenous presentation has prompted research efforts to uncover clinical subtypes in order to improve disease management and inform clinical trial subject selection. This study aims to examine whether unbiased cluster analysis of PD motor and nonmotor symptoms reveals distinct disease subtypes.

Method: MSMD data was collected via chart review. PPMI data was downloaded from the LONI database. Correlations between traits, hierarchical clustering of traits, and non-hierarchical kmeans clustering of subjects via Principal Component Analysis were performed.

Results: In the MSMD cohort (n=85), fluctuations and dyskinesias clustered ($p = .02$). Non-hierarchical clustering of subjects revealed three clusters: (i)enriched in fluctuations, dyskinesias, freezing of gait, and depression; (ii)enriched in dyskinesias and fluctuations; (iii)milder symptoms. In the PPMI cohort (n = 371), the following traits clustered: (i)depression and anxiety ($p < .01$), (ii)disease duration and tremor ($p = .04$), (iii)bradykinesia and rigidity ($p = .02$), (iv)cognitive assessment scores ($p = .05$). Clustering of subjects revealed three clusters: (i)atremulous PD and worse psychiatric and autonomic symptoms; (ii)tremulous PD and older onset, worse cognition; (iii)milder symptoms. Comparing the cohorts is difficult due to differences in disease duration and medication usage.

Conclusions: Multiple clinical subtypes were found in both cohorts. Further characterizing these subtypes and incorporating molecular profiling can help with personalized treatment for PD in the future.

Funding: ISMMS Student Investigator Reward

157

Modeling frontotemporal dementia with MAPT V337M mutation in iPSC-derived brain organoids

Kristen Whitney*, Kevin Strang*, Megan Iida, Kurt Farrell, Aaron Bell, Hadley Walsh, John Crary, Tau Consortium Stem Cell Group

Pathology, Neuroscience, Friedman Brain Institute, Loeb Center for Alzheimer's Disease

Background: Frontotemporal dementia with MAPT mutation is a neurodegenerative disease characterized by accumulation of abnormal hyperphosphorylated tau protein (p-tau). Patients with the MAPT V337M mutation display behavior and personality changes, aphasia and dementia. There is a critical need for cellular models that recapitulate tauopathy mechanisms. Induced pluripotent stem cell patient-derived organoid models have emerged as a powerful tool, with the advantage of recapitulating the human genetic environment in a cellular system.

Methods: Forebrain organoids were produced in collaboration with the Tau Consortium Stem Cell Group. Organoids were generated from iPSCs derived from MAPT mutation carriers and compared to isogenic controls (n=7 lines) at 2, 4, 6, and 8+ months. Organoids were processed, stained immunohistochemically using a panel of neurodegenerative markers, imaged, and analyzed using semi-quantitative and quantitative assessments (positive pixels). Ultrastructure was assessed using electron microscopy.

Results/conclusion: Organoids displayed a morphological and cytoarchitectural pattern consistent with neurodevelopment. MAP2/CTIP2+ neurons were evident and predominated at earlier time points with ALDHL1/GFAP+ astrocytes becoming more abundant at later time points. IBA1 was negative. Immunohistochemistry revealed marked expression of p-tau, but other markers of neurodegeneration (amyloid, a-synuclein and TDP-43) were negative. Future studies characterizing pathologically relevant p-tau epitopes and other cellular changes will advance the utility of brain organoids for modeling tauopathy.

158

Comparing the transcriptome and epigenome of living and postmortem human brain specimens

Lillian Wilkins, Emily Moya, Lisa Linares, Brian Kopell, Alexander Charney

Genetics and Genomic Sciences, Psychiatry, Neuroscience, Neurosurgery

Background: Our understanding of the molecular underpinnings of neuropsychiatric traits is largely based on studies using postmortem human brain specimens. Molecular comparisons between these and brain specimens harvested from living people are lacking, thus an unmet need in neuroscience. Here we profile the transcriptome and epigenome of living and postmortem human brain specimens for comparative analyses.

Methods: Living brain samples (N=49) were collected during deep brain stimulation surgery. Postmortem samples (N=51) were collected from the Columbia Brain Bank (BB), Harvard BB, and Miami BB. All specimens were from the dorsolateral prefrontal cortex. Protocols for small input library preparation were optimized and RNA-seq performed. For a subset of the specimens (10 living, 10 postmortem) we are now performing FACS using NeuN to isolate neuronal and glial cell populations followed by ATAC-seq.

Results: Approximately one third of all genes are differentially expressed between living and postmortem brain specimens. Genes upregulated in living and postmortem are enriched for neuronal and immune pathway annotations, respectively. ATAC-seq data generation is underway; preliminary analyses will be presented at the retreat.

Conclusion: We show differences in gene expression between living and postmortem human brain specimens and seek to understand how epigenomes differ between these states. This has broad importance for the field given the ubiquitous use of postmortem specimens in studying the neurobiology of neuropsychiatric traits.

Funding: ISMMS

159

Expression quantitative trait loci show temporal specificity in the pre-frontal cortex

Hannah Young, Amanda Dobbyn, Alanna Cote, Eli Stahl, Laura Huckins

Departments of Genetic and Genomic Sciences and Psychiatry, ISMMS

Background: Due to limited tissue availability, efforts to characterize the expression quantitative trait locus (eQTL) architecture of the human brain have examined post-mortem bulk tissue comprising multiple cell types from subjects of all ages. Age-associated changes in gene expression for a subset of genes and in cellular composition have been identified in the pre-frontal cortex (PFC), suggesting that one eQTL search across all ages is insufficient to properly explain the dynamic regulatory architecture of the brain across development.

Methods: Genotype information and post-mortem PFC RNA-seq data from five datasets consisting of a total of 1586 individuals aged 30 to 108 years were used to map cis eQTLs. Individuals were stratified into seven age bins of 10-year increments (30-39, 40-49, …, 90+) and MatrixEQTL was run separately for each bin. A forward stepwise conditional analysis was performed to identify independent eQTLs. Co-localization between the age-specific eQTLs and psychiatric and neurologic trait GWAS loci will be assessed using coloc.

Discussion: This is to our knowledge the most comprehensive analysis of genetic regulation in the brain across the human lifespan and the most well-powered eQTL study for many of the specific age periods investigated. Age-specific eQTLs could provide insight into the age of onset or progression of psychiatric disease, especially for disorders that manifest during or change throughout adulthood.

Funding: NIMH

160

Multiplexed CRISPR targeting of schizophrenia risk genes

Alex Yu1,2,3,4,5, Aiqun Li1,2,3,4, Minghui Wang5,6, Bin Zhang5,6, Panagiotis Roussos2,3,5, Kristen J Brennand1,2,3,4,5

1Department of Neuroscience; 2Department of Psychiatry; 3Friedman Brain Institute; 4Icahn Institute of Genomics and Multiscale Biology, 5Department of Genetics and Genomic Sciences 6Mount Sinai Center for Transformative Disease Modeling

BACKGROUND: Genetic studies increasingly reveal many neurodegenerative and psychiatric disorders to be complex polygenic conditions. The growing list of disease-associated genes requiring functional validation necessitates rapid screening protocols. Guide-RNA libraries targeting multiple genes can be used with CRISPR-based systems to offer a high-throughput screening method.

METHOD: To assess the viability of the technique, we first assembled a gRNA library targeting ten schizophrenia risk genes. After evaluating the gRNA distribution using MiSeq next-generation sequencing, we transduced human induced pluripotent stem cell (hiPSC)-derived neurons with the gRNA library and CRISPR. Finally, we leveraged Expanded CRISPR-compatible Cellular Indexing of Transcriptomes and Epitopes by Sequencing (ECCITE-seq) to simultaneously detect unique gRNAs and transcriptomes in single cells.

RESULTS: We optimized a protocol for assembling gRNA libraries and used MiSeq to confirm a similar abundance between individual gRNAs. We have generated clonal human induced pluripotent stem cell (hiPSC) lines stably expressing all CRISPR components to reduce variability in our screen.

CONCLUSION: With gRNA library multiplex screening, we explore the impact of ten schizophrenia genes on the global transcriptome. We intend to immediately apply this method to screen dozens of risk genes associated with Alzheimer's disease and other complex genetic brain disorders.

FUNDING: NIH, University

161

Temporal proximity and valence link memories encoded close in time

Yosif Zaki1, Zachary Pennington1, Zhe Dong1, Kanaka Rajan1, Denise Cai1

1Department of Neuroscience, ISMMS

The compilation of memories, collected and aggregated across a lifetime, defines our human experience. How are memories dynamically updated and integrated across time and experience? Our study suggest that a shared neural ensemble may link distinct memories encoded close in time. Using in vivo calcium imaging (with open-source Miniscopes in freely behaving mice), a TetTag activity-dependent cell tagging system, chemogenetics and novel behavioral designs, we tested how hippocampal networks temporally link memories separated across hours to days. We found that contextual memories encoded close in time are linked by directing storage into overlapping hippocampal ensembles, such that the recall of one memory can trigger the recall of another temporally-related memory. Increasing the negative valence of a memory extends the temporal window for linking memories retrospectively. This transfer of fear from an aversive memory to a previously formed safe memory can be abolished by inhibiting the reactivation of the neural ensemble of the safe memory during the consolidation of the aversive memory. Current work is focused on uncovering network dynamics that support fear learning and give rise to context-specific retrieval of memory. These results shed light on the neural substrates underlying how memories are integrated and segregated in the brain.

Funding: McKnight Memory and Cognitive Disorders Award, Klingenstein-Simons Fellowship, Brain Research Foundation Award, NARSAD Young Investigator Award, Friedman Scholar Award, NIMH-1DP2MH122399-01, NIH-R01-MH120162, NSF-1926800

Posters

To View All Posters: http://ow.ly/sR4J50zmPOc

Aaron Das
Agathe de Pins
Alanna Cote
Angelo Lontok
Ann-Nicole Frimpong
Anthony Lacagnina
Ashley Cunningham
Catherine Elorette
Cheick Sissoko
Christine Ginalis
Christopher McLaughlin
Ciorana Roman Ortiz
Darpan Chakraborty
Emma Lehmann
Esther Cheng
Halle Ronk
Hannah Grosman
Iya Prytkova
Jacqueline
Jaroslav Bendl
Jocoll Burgess
Joshua Torres
Katherine Keller
Katherine LeClair
Katherine Meckel
Kaustubh Kulkarni
Kenny Chan
Kristen Watkins
Kristen Whitney
Kurt Farrell
Lillian Wilkins
Maddie O'Brien
Manon Herbinet
Marija Borozan
Mathilde Pruvost
Michael Deans
Moya_Emily
Nick Upright
Pengfei Dong
Qian Wang
Rebecca Hofford
Ricardo Vialle
Sabina Bayshtok
Sarah Banker
Sarah Neuner
Shaik RB
Syed Faraz Kazim
Tzu-Yi Chen
Vyoma Sahani
Yasemin Schmitt
Yuanqi Sun
Zachary Nelson

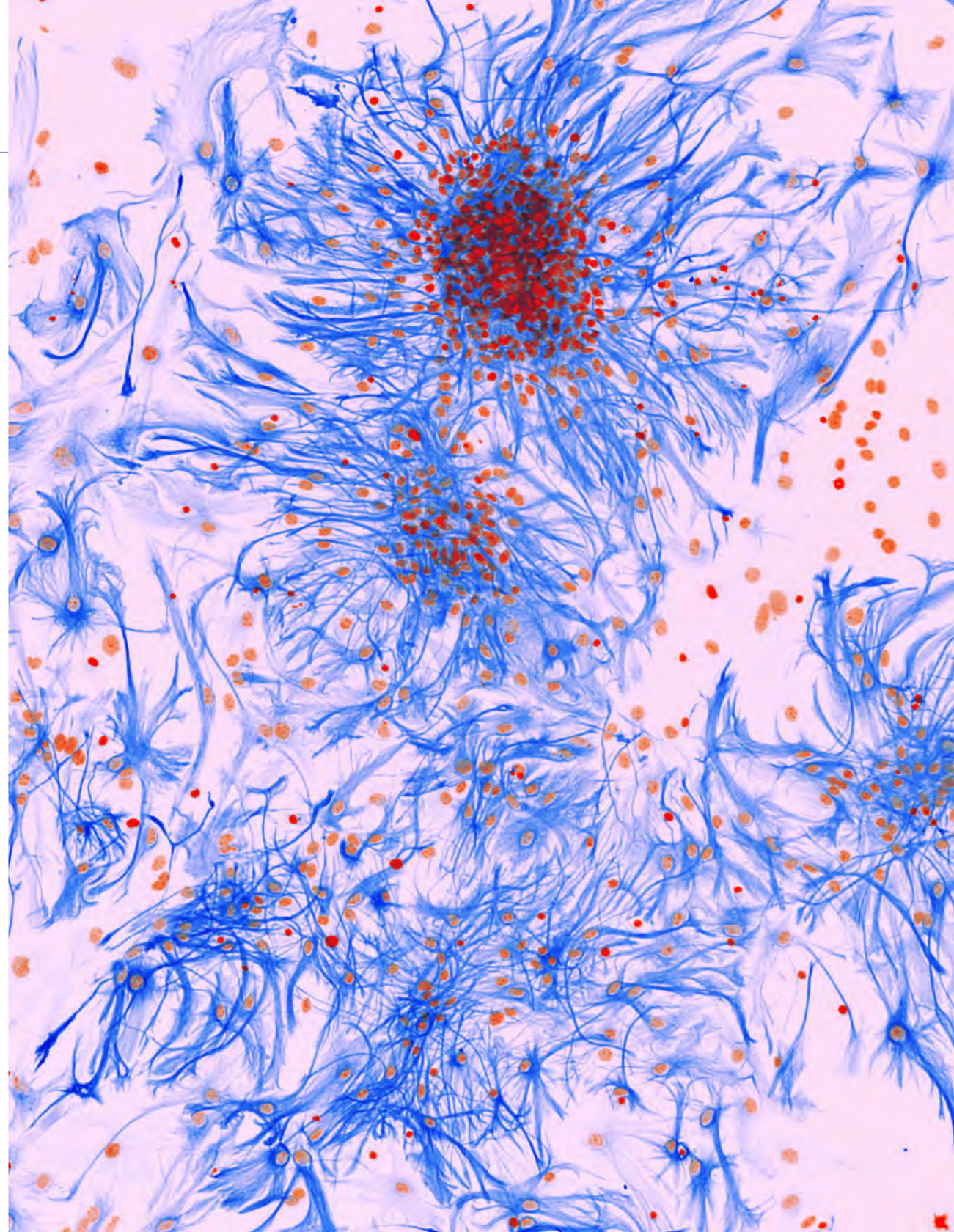


Image by Shalaka Wahane, PhD, Nash Family Department of Neuroscience

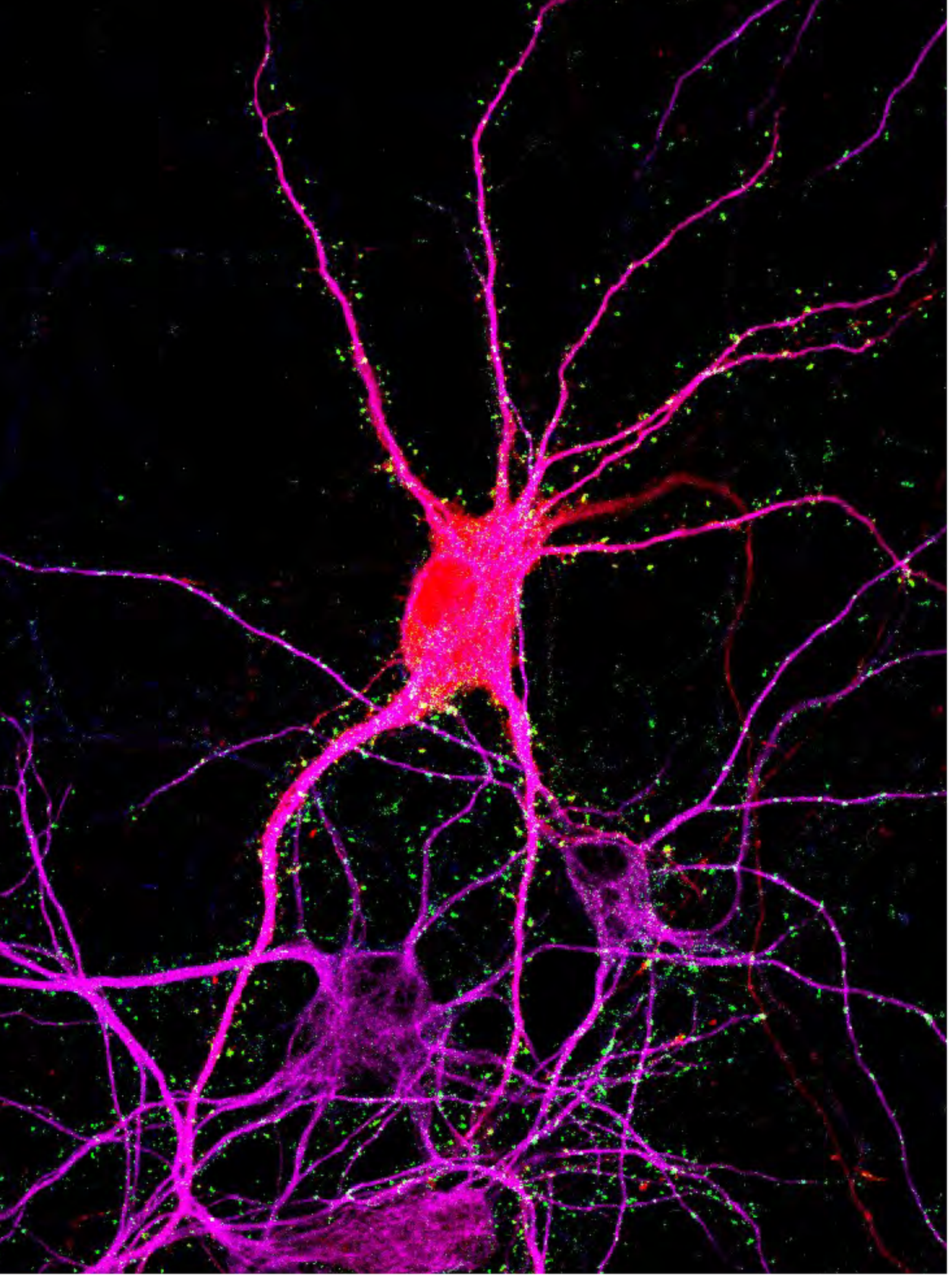


Image by Devina Ung, PhD, Andrea Boitnott and Danielle Mendonca, Department of Psychiatry

Neuroscience Graduate Training Program

The Neuroscience graduate program on the whole had a great year. The program is strong and vibrant. In 2019, 12 students successfully defended their thesis--we wish them all the best in their careers moving forward. This fall, we received 354 applications to the program--another whopping 40% increase in total applications over the previous year (and that was a 45% increase over its previous year). This number (354) is about 1/3 of the total PhD applications (spanning all training areas) the graduate school received. At the time of this writing, it is too early to know final decisions on the part of all of the applicants, but I'm optimistic that we will have another outstanding, diverse, multi-talented class of the highest caliber. The success of the program reflects, in large part, the quality of our students, and that is a direct product of the admissions process. I am particularly grateful for the efforts big and small by faculty and students to make the Admissions process so successful. To you, I say thank you! I especially want to acknowledge the tireless work by the Neuro ad hoc screening committee of Mark Baxter, Ming-Hu Han, Vanna Zachariou, Daniela Schiller, Nan Yang, Betsy Cropper and Steve Salton. And a particular shout-out to Nick Upright, who had a large hand in organizing new admissions events and has now served selflessly two years in a row on the mind-numbing, day-long Institutional admissions committee. You're the best Nick, really.

Training grants. Last year, we were at a crossroads with our three T32 training grants--two of them were up for renewal and the third had to be repackaged as a new submission. At the time of this writing, I am cautiously optimistic, based on impact scores and discussions with program officers, that the T32 on aging and the T32 supporting year 1 and 2 students will be renewed. The reviewer comments on the third one--from NIMH--were straightforward and should not be too difficult to deal with, but will require resubmission. All of this bodes well for re-establishing our training grant support. Nevertheless, we need to be creative in coming up with ways to support an increasing number of neuroscience students in the face of the graduate school cap on overall PhD class size. Status quo means that if we grow in size each year, other training areas cannot (the converse is also true.....).

Curriculum. Two changes are coming, both of which are in the planning phases right now. The first is going to be a new course led by Mark Baxter and Erin Rich tentatively titled "Neural Data Science" to be taught in Spring 1 and 2 sessions for Year 2 students. This course will be mandatory for all Neuroscience PhD students. The idea for this course sprung from a requirement of the Year 1/Year 2 T32 training grant requiring courses in neural computation that go beyond statistics. Mark and Erin are establishing a course that will combine Mark's current Data Analysis for Behavioral Neuroscience course (Spring 1) with a second component (Spring 2) that will build and expand on Mark's course by first focusing on basic analyses of time series data, such as spike trains, imaging data, oscillatory brain data (LFPs, EEG, ECoG), and will then emphasize topics such as population coding and functional connectivity measures. The course will then deal with advanced analysis of large neural data sets, covering data mining techniques and best practices, basic classification methods from machine learning, and introducing neural network models and how they scale up to advanced artificial intelligence systems. The timing for such a course couldn't be better-- our current students and those we aim to recruit are increasingly computationally sophisticated. In order to recruit or retain students with the appropriate skillsets, we must be able to support and challenge them with relevant coursework. Thank you to Mark and Erin for taking this on.

The other curriculum-relevant change will be the introduction of a standard set of criteria--spanning all MTAs--for judging the quality and adequacy of thesis proposal exams and defining more precisely the relationship between mentor and student in developing the written document. The idea for such a standardized set of criteria arose principally from other training area faculty and students who felt that there was a persistent unevenness in the quality of thesis proposal exams both across, and within, training areas. The exact format this will take is still being worked out, so stay tuned.

George W Huntley

Stay Connected. Follow Us.

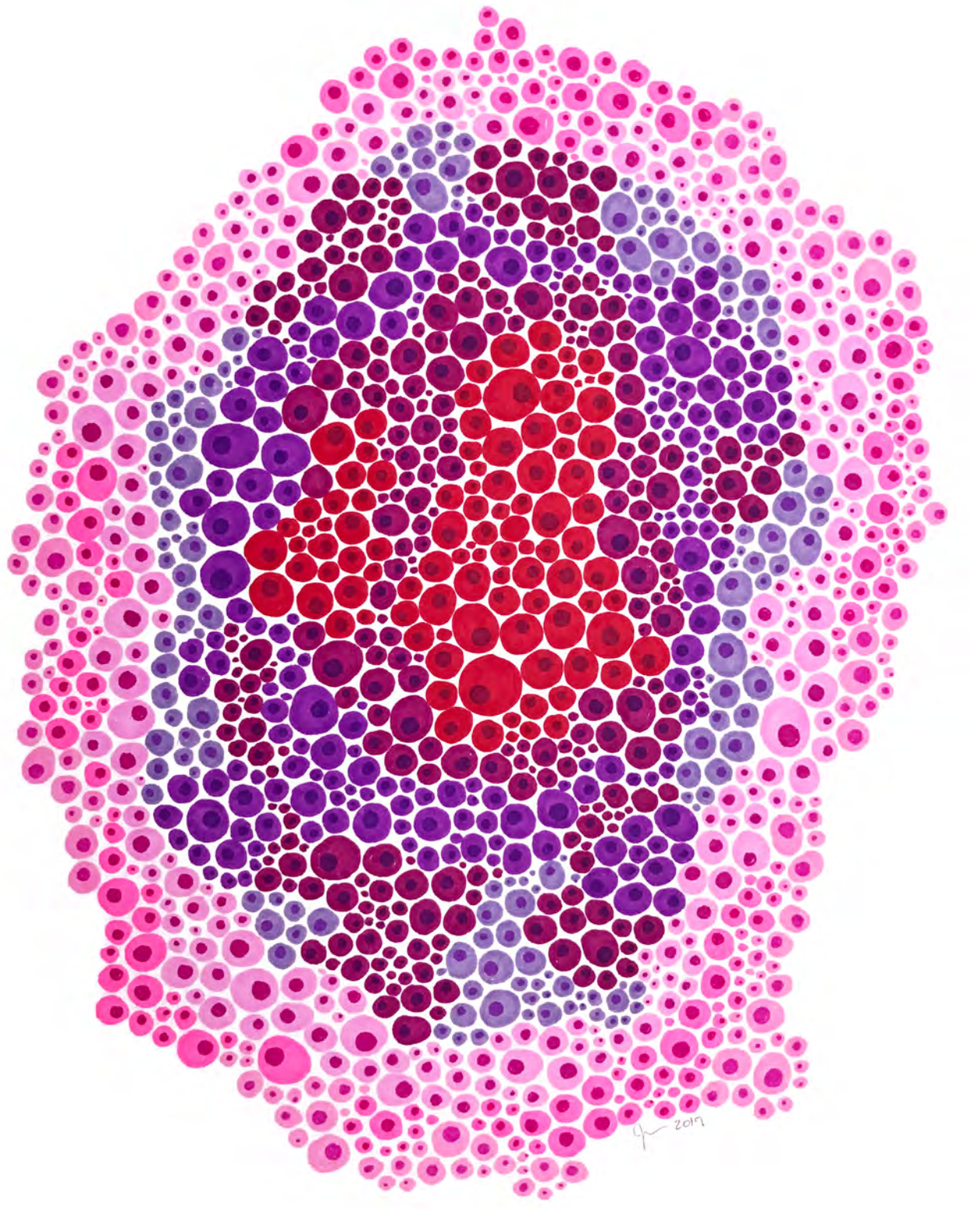


Image by Jessica Johnson, Genetics and Genomic Sciences

For more information about The Friedman Brain Institute's upcoming events and lectures, please visit www.mountsinai.org/fbi

CELEBRATING COLLABORATION

*Feel free to **Like, Comment, Tweet, Retweet, Favorite, Friend, Share, etc...!!***

@SinaiBrain
@MountSinaiNYC
@IcahnMountSinai
@GradSchoolSinai
@MountSinaiPsych
@MountSinaiNeuro
@MSHSNeurology
@SeaverAutism
@MountSinaiDBS
@SinaiTBI
@IcahnInstitute
@IcahnDAC
@SinaiNeuro
@IcahnCMIN
@MtSinaiPostdocs
@SinaiGenetics
@ComeBeBraiNY
@dana_fdn
@SfNtweets

#FriedmanBrainInstitute
#NashNeuroscience
#DiverseBrains
#neuroscience
#MSNseminars
#sinaiBAW
#brain
#ArtoftheBrain
#ENDALZ
#Addiction
#AutismBrainNet
#Stroke
#epigenetics
#depression
#MultipleSclerosis
#schizophrenia
#stemcells
#Autism