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2017 for
the Ninth Annual
Neuroscience
Retreat

Cover image by Stefan Fuertinger, PhD, and Kristina Simonyan, MD, PhD

2016

The 8th Annual Neuroscience Retreat

FRIEDMAN BRAIN INSTITUTE

and the **Neuroscience Training Area**

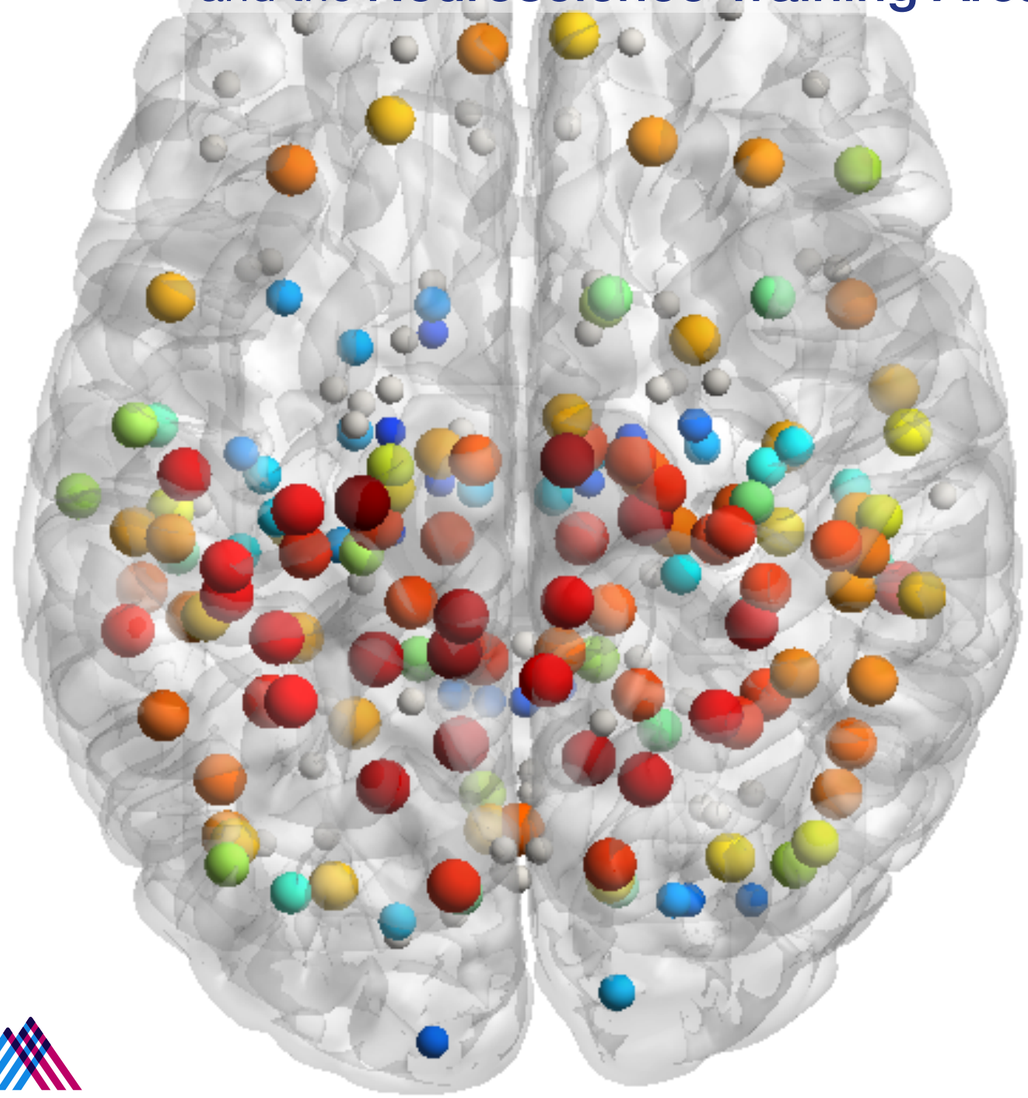

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Image by Paul A. Slesinger, PhD

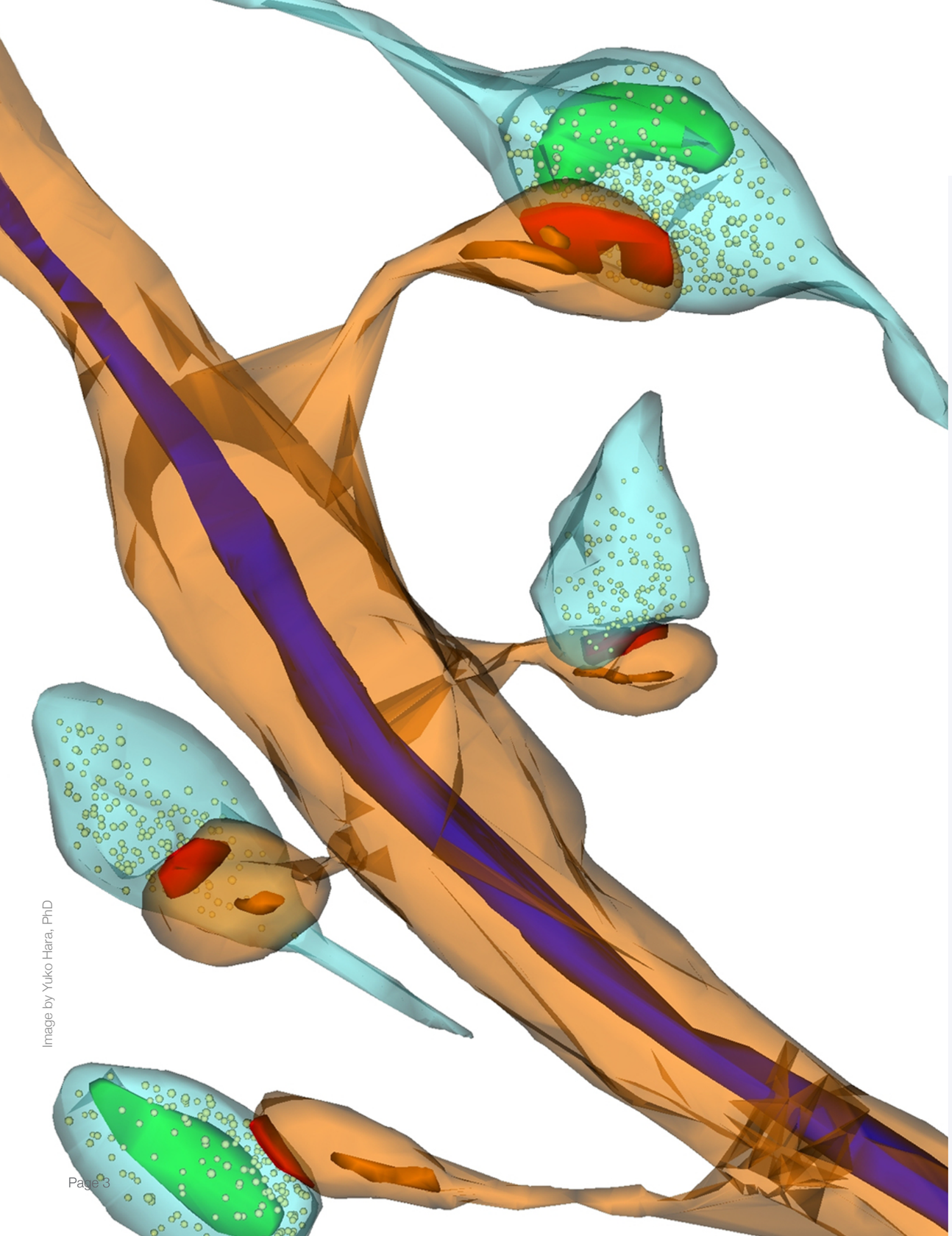

Image by Yuko Hara, PhD

THE FRIEDMAN BRAIN INSTITUTE

CONTENTS

THE FRIEDMAN BRAIN INSTITUTE
AGENDA

REGISTRATION and BREAKFAST

8:45 a.m.

Sign in and Register (Lobby)
Poster setup (Library, 3rd fl.)
Breakfast (Room 20, 2nd fl.)

OPENING REMARKS and ANNOUNCEMENTS (Hosack Hall)

9:30 a.m

Scott Russo, PhD (Neuroscience)

9:35 a.m

Eric Nestler, MD, PhD (Friedman Brain Institute)

10:05 a.m

George W. Huntley, PhD (Neuroscience)

KEYNOTE ADDRESS

10:15 a.m. - 10:50 a.m.

Miriam Merad, MD, PhD
(Oncological Sciences, Medicine, Hematology and Medical Oncology)
"*Macrophage-neuronal crosstalk in the CNS and the periphery*"

BREAK 10:50 a.m. - 11:10 a.m.

SESSION ONE

11:10 a.m.

Chair - Daniela Schiller, PhD (Neuroscience and Psychiatry)

11:15 a.m.

Ian Maze, PhD (Pharmacology)
"Histone monoaminylation in the developing and adult brain: novel mechanisms of 'epigenetic' plasticity"

11:30 a.m.

Ping-Yue Pan (Neurology)
"Synaptojanin1 mediates a novel signaling pathway in Parkinson's disease pathogenesis"

11:45 a.m.

Vasiliki Mitsi (Neuroscience)
"RGS4 modulates chronic stress and responses to fast-acting antidepressants"

12:00 p.m.

Richard O'Connor (Pharmacology)
"Role for hypothalamic projections to habenula in obesity"

12:15 p.m.

Catherine Pena (Neuroscience)
"Early life stress enhances susceptibility to depression via long-lasting transcriptional alterations within reward circuitry"

LUNCH

12:30 p.m. - 1:30 p.m.

Room 20, 2nd floor

SESSION TWO

1:30 p.m.

Chair - Muhammad Parvaz, PhD (Psychiatry)

1:35 p.m.

Anne Schaefer, MD, PhD (Neuroscience)
"Polycomb repressive complex 2 (PRC2) protects adult neurons against neurodegeneration"

1:50 p.m.

Milo Smith (Neuroscience)
"Inflammation suppresses developmental neuroplasticity"

2:05 p.m.

John Fullard (Psychiatry)
"Cell-type specific open chromatin profiling in human postmortem brain provides insight into genetic regulatory mechanisms and schizophrenia."

2:20 p.m.

Virginia Gao (Neuroscience)
"Astrocytic β2-adrenergic receptors mediate long-term memory formation"

2:35 p.m.

Erin Bobeck (Pharmacology)
"A novel neuropeptide-receptor system, BigLEN-GPR171, regulates drug reward"

RECEPTION and POSTER SESSION

Library, 3rd fl.

2:50 p.m.

Poster Session and Reception Begin

4:50 p.m.

"Studying the Brain", Story Collider Live Show
Three true, personal stories about the study of neuroscience.

5:20 p.m.

Award Ceremony
Best Poster, Best Oral Presentation, "Call for Images Award" and 2016 BRAIN Award

5:30 p.m.

Reception Ends

Image from the Casaccia Lab

Ping-Yue Pan
Department of Neurology

Synaptojanin1 mediates a novel signaling pathway in Parkinson's disease pathogenesis

Background: PARK8/LRRK2 represents the most frequent genetic cause for familial Parkinson's disease (PD) with unclear pathogenic mechanisms. More recently, three independent studies (including one from our group), has reported a rare recessive mutation in PARK20 known as SYNJ1 from families with early onset Parkinsonism, however, its pathogenic role in PD has yet to be characterized.

Methods: We use BAC transgenic animal models, biochemistry and state-of-art optical methods.

Results/Conclusions: We find evidence linking synaptojanin1 (encoded by SYNJ1 gene) and LRRK2 protein functions at the nerve terminals of midbrain dopamine neurons. PD-linked LRRK2 G2019S mutation Results in slowed synaptic vesicle (SV) endocytosis in PD-vulnerable dopamine neurons. Using mass spectrometry, we have identified that LRRK2 phosphorylates synj1 T1205 in vitro. Missense mutation of T1205 reduces synaptojanin1's function in vitro and in cells. Combining these two genetic alterations leads to more severely impaired SV trafficking. Furthermore, transgenic mice carrying both SYNJ1+/- and LRRK2 G2019S mutations display reduced exploratory behavior as well as impaired motor skills and short steps, reminiscent of clinical PD. Our study demonstrates a convergence of signaling pathways for two PD genes, who's functional interplay may underlie synaptic vulnerabilities in dopamine neurons in early PD pathogenesis.

Funding: Cote Early Investigator Award (PD14-00011) and Internal Research Grant (PDF-IRG-1447) from the Parkinson's Disease Foundation (PDF), R21 grant from NINDS (1R21NS095155-01).

Vasiliki Mitsi
Department of Neuroscience

RGS4 modulates chronic stress and responses to fast-acting antidepressants

Background: Depression is a debilitating disease, often associated with cardiovascular disorders. Understanding the key intracellular mechanisms underlying depressive states is essential for the development of more efficient treatment. RGS4 is a signal transduction molecule that modulates the function of GPCRs via interactions with heterotrimeric G-proteins. Our previous work highlighted the role of RGS4 in the efficacy of various antidepressants.

Methods: We applied genetic mouse models for global or conditional deletion of RGS4 gene. We use the Chronic Unpredictable Stress (CUS) paradigm, along with biochemistry, brain imaging, echocardiography and RNA-sequencing.

Results: Chronic stress downregulates RGS4 expression in the mouse mPFC, and also in the heart atria. Using the CUS paradigm we show that ablation of the RGS4 gene increases vulnerability to depression-like behaviors and promotes functional and structural changes in the heart. fMRI imaging reveals that knockout of RGS4 affects cortical activity during stress. Conditional deletion of RGS4 in the mPFC facilitates responses to ketamine, via a mechanism that involves adaptations in metabotropic glutamate receptor function, and mTOR signal transduction. Furthermore, RNA-sequencing analysis on mPFC tissue following chronic stress and/or ketamine treatment provided novel information on the impact of RGS4 on gene expression adaptations.

Conclusion: Our data point to RGS4 as an essential modulator of depression-related maladaptations and stress-induced cardiovascular abnormalities and provide novel information on the cellular mechanisms underlying the actions of fast-acting antidepressants.

Funding: NARSAD, NINDS

Richard M. O'Connor
Department of Pharmacology and Systems Therapeutics

Role for hypothalamic projections to habenula in obesity

Background: Rates of obesity are increasing worldwide while pharmacotherapies that safely reduce body weight in obesity remain elusive. The development of obesity in rats is associated with the emergence of a profound brain reward deficit. The lateral hypothalamus (LH) plays a critical role in energy homeostasis and reward sensitivity. Precisely how LH influences brain reward function and the value of food remains unclear. The lateral habenula (LHb) has been described as a "preference center" which exerts a negative influence over motivated behaviors through inhibition of midbrain dopamine neurons. A major input to the LHb originates in the LH. We tested the hypothesis that LH projections to LHb play an important role in food preference and food-related motivation.

Methods: To target the LHb-LH pathway, we delivered a retrograde AAV2/5-Cre-eYFP virus into the LHb. A Cre-inducible diphtheria toxin (DTA) was delivered to the LH, ablating LH neurons that project to LHb. Separately we delivered Cre-inducible "excitatory" (hM3Dq) DREADD to LH allowing for stimulation of the LH-LHb circuit.

Results/Conclusions: Lesioning of the LH-LHb pathway in rats decreased the motivational value of food. Conversely stimulating the LH-LHb circuit increased the willingness of rats to work for food rewards and increased home-cage chow consumption. These findings identify the LH-LHb pathway as an important brain circuit involved in feeding.

Funding: NIH

Catherine Peña
Department of Neuroscience

Early life stress enhances susceptibility to depression via long-lasting transcriptional alterations within reward circuitry

Background: Early life stress (ELS), including abuse and neglect, affects more than 3 million US children each year and is among the strongest non-genetic lifetime risk factors for developing depression. Hallmark symptoms of depression, including social avoidance and anhedonia, implicate the ventral tegmental area (VTA) and brain reward circuitry in depression, yet how ELS impacts development of reward circuitry and vulnerability to depression remains largely unknown.

Methods: Male and female mice were standard-reared or exposed to ELS during a sensitive window, and half of each group faced an additional adult stressor. Depression-like behaviors were quantified and RNA-seq was performed in VTA. Target genes were then bi-directionally manipulated in VTA.

Results: ELS enhances vulnerability to depression-like behavior only after additional adult stress. ELS induces long-lasting transcriptional alterations in VTA that may prime the brain to respond to additional stress. The transcription factor orthodenticle homeobox 2 (Otx2) is implicated as an upstream regulator of enduring transcriptional changes in VTA. Over-expression of Otx2 in VTA rescues, and local knock-out of Otx2 recapitulates, the effects of ELS on vulnerability to depression-like behavior.

Conclusions: We have identified a novel molecular target mediating the impact of ELS on long-lasting vulnerability to depression-like behavior.

Funding: NIH and HDRF (EJN).

Milo R. Smith
Department of Neuroscience

Inflammation suppresses developmental neuroplasticity

Background: Developmental neuroplasticity is essential for shaping proper brain function and the high prevalence of developmental disorders demand deeper study to determine how diseases may disrupt neuroplasticity.

Methods: We developed and applied an integrative bioinformatics approach to systematically match plasticity to 436 disease signatures, to yield a ranked list of diseases most likely to dysregulate plasticity signature genes. We applied a novel Disease Leverage Analysis across the ranked disease list to identify shared pathophysiology that may disrupt developmental plasticity.

Results/Conclusions: By inferring shared pathophysiology of diseases signatures that match to plasticity signatures, we predicted inflammation would inhibit developmental plasticity and experimentally validated its suppression of juvenile cortical plasticity. Our findings suggest systemic inflammation in children may have unexpected negative consequences on the neurodevelopment trajectory by disrupting neuroplasticity.

Funding: Funded by Traineeship, NIDCR-Interdisciplinary Training in Systems and Developmental Biology and Birth Defects T32HD075735 (M.R.S), Mindich Child Health and Development Institute Pilot Fund (J.T.D. and H.M.), P30 NIEHS Grant P30ES023515 (J.T.D and H.M.), R01EY024918 (H.M.), R01EY026053 (H.M.), Knights Templar Eye Foundation (H.M.), March of Dimes (H.M.), Whitehall Foundation (H.M.), R01DK098242 (J.T.D), and U54CA189201 (J.T.D).

John F. Fullard
Department of Neuroscience

Cell-type specific open chromatin profiling in human postmortem brain provides insight into genetic regulatory mechanisms and schizophrenia.

Background: Open chromatin provides access to DNA binding proteins for the correct spatiotemporal regulation of gene expression. Mapping chromatin accessibility has been widely used to identify the location of cis regulatory elements (CREs), including promoters and enhancers. CREs show tissue- and cell-type specificity and disease-associated variants are often enriched for CREs in the tissues and cells relevant to disease.

Method: We applied ATAC-seq to neuronal and non-neuronal nuclei, isolated from frozen postmortem tissue, to generate cell-type specific maps of open chromatin regions (OCRs) in the human brain.

Results: >50% OCRs are differentially accessible between neurons and non-neurons, showing enrichment with known cell-type markers and CREs. Relative to non-neurons, neuronal OCRs display higher evolutionary conservation and are enriched in distal regulatory elements. Transcription factor footprinting analysis reveals differences in the regulome between cell types and ascribes mechanistic roles to a number of schizophrenia GWAS risk variants.

Conclusion: Studying the chromatin landscape gives insight in to the regulation of gene expression in different cells of the brain and has identified the potential mechanism of action of numerous disease-associated genetic risk variants.

Funding: NIH/VA/FBI/Icahn Institute for Genomics and Multiscale Biology

Virginia Gao
Department of Biomedical Sciences

Astrocytic β2-adrenergic receptors mediate long-term memory formation

Background: Emotionally relevant experiences form strong, long-lasting memories by critically engaging noradrenaline, which mediates and modulates the consolidation of these memories. Noradrenaline acts through adrenergic receptors (ARs), including βARs, the differential anatomical and cellular distribution of which suggests that they play distinct roles in memory processing. However, much about their specific contributions and mechanisms of action remains to be understood, despite the fact that blockers of these receptors, such as propranolol, are already being investigated in the clinical setting for treatment of anxiety disorders.

Methods: We used a contextual, fear-based learning paradigm to model emotional memory formation in rats. To interrogate the role of hippocampal βARs, we used intracranial injections of drugs or cell-type specific viruses targeting these receptors. Finally, we used Western blot analysis to examine the downstream molecular mechanisms.

Results: We show that astrocytic but not neuronal β 2ARs in the hippocampus are required for memory consolidation. These hippocampal β2ARs but not β 1ARs are coupled to the training-dependent release of lactate from astrocytes, which is necessary for long-term memory formation as well as underlying molecular activations of markers of long-term plasticity and memory.

Conclusions: We conclude that β2ARs expressed in astrocytes and not neurons are the essential mediators of the effect of noradrenaline on long-term memory formation. This key metabolic role of astrocytic β2ARs may represent a novel target mechanism for stress-related psychopathologies.

Funding: NIMH/NRSAF30 (VG), NIMH/R01 (CA)

Erin N. Bobeck
Department of Pharmacology and Systems Therapeutics

A novel neuropeptide-receptor system, BigLEN-GPR171, regulates drug reward

Background: Recently we deorphanized GPR171 as the receptor for the abundant neuropeptide, Big-LEN. Virtual screening of a library of small molecules identified compounds that target GPR171. Using these compounds and viral mediated knockdown we found that GPR171 within the hypothalamus regulates feeding. Despite high expression of the neuropeptide and receptor throughout the reward circuit, their role in reward behaviors is unknown.

Methods: Drug reward was assessed using conditioned place preference (CPP) following lentiviral shRNA-mediated knockdown of GPR171 in particular brain regions. A drug (GPR171 agonist, antagonist, or morphine) was repeatedly paired to one chamber and vehicle to another. Preference was determined measuring time spent in each chamber without drug. Following morphine CPP, alterations in GPR171 mediated signaling was determined using HitHunter cAMP assay.

Results/Conclusions: We found high expression of GPR171 in the basolateral amygdala, prefrontal cortex and hippocampus. Mice treated with morphine CPP, show enhanced BigLEN or GPR171 agonist mediated signaling in the prefrontal cortex. Knockdown of GPR171 in the basolateral amygdala caused a reduction in morphine CPP. In addition, GPR171 selective ligands produce no preference or aversion on their own, but GPR171 antagonist reduces morphine CPP. Together, these Results suggest a role for GPR171 in drug reward.

Funding: NIH grants NS026880 and DA019521 to L.A.D and a NIDA T32 DA007135 to E.N.B.

Abstracts

1

Transcription factor ΔFosB regulates aggressive behavior in male mice in a cell-specific manner.

H. Aleyasin[1], S. A. Golden[1,2], M. Flanigan[1], A. Takahashi[1,3], C. Menard[1], J. Mutler[1], E. A. Heller[1], M. Pfau[1], G. E. Hodes[1], M. Heshmati[1], L. K. Bicks[1], J. Tai[1], S. J. Russo[1]

[1] Icahn School of Medicine at Mount Sinai, New York, New York, USA,

[2]National Institute on Drug Abuse (NIDA), USA, [3]University of Tsukuba, Ibaraki, Japan

Background: A number of studies implicate reward circuitry as an important modulator of aggressive behavior. However, little is known about the molecular mechanisms modulating such behavior. Here we explore the role of ΔFosB, a transcription factor and master regulator of reward-motivated behaviors in male aggression in mice.

Methods: Old and sexually experienced male mice physically interact with novel young, sexually naïve C57BL/6 mice in their home cage (R/I test). R/I interactions are recorded and scored for aggressive behavior. To modify ΔFosB we inject viral vectors into the ventral striatum.

Results/Conclusion: We demonstrate a clear association between the level of ΔFosB in the ventral striatum (VSt), and the intensity of aggressive behavior. We show that ΔFosB is specifically increased in D1R expressing MSNs of VSt in aggressor mice. D1 MSN-specific induction of ΔFosB expression reinforces aggressive behavior in mice measured by R/I test. These data strongly support a cell-specific pro-aggressive role of ΔFosB in the VSt. Altogether our findings help understanding the molecular basis for motivational aspects of aggressive behavior in mice.

Funding: This research was supported by NIH

2

Tracing of central nervous system projections to the pancreas

Alexandra Alvarsson, Mitchell Bayne, Sarah Stanley

Diabetes, Obesity and Metabolism Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, and Laboratory of Molecular Genetics, Rockefeller University, 1230 York Avenue, New York, NY 10065

Background: Glucose-sensing neurons of the central nervous system respond to blood glucose levels and orchestrate counterregulatory responses to hypoglycemia. These neurons appear to constitute distinct neuronal populations that mediate different physiological functions, but previous studies have been hampered by low expression levels of glucose sensors such as glucokinase (Gck). However, a recently generated transgenic mouse with cre-recombinase expression in Gck-expressing neurons (Gck-cre/Rosa-tdTomato mice) allows the mapping of Gck expression. We here used a pseudorabies virus expressing GFP (PRV-GFP) as a retrograde trans-synaptic tracer in Gck-cre/Rosa-tdTomato mice to map glucose-sensing neurons projecting to the pancreas, a key organ in homeostatic regulation.

Methods: PRV-GFP (5x100 nl) was injected throughout the pancreas of Gck-cre/Rosa-tdTomato mice via a Hamilton syringe. Five days after PRV-GFP injections the mice were perfused and the brains dissected, sectioned and mounted for quantification using an optical microscope. The numbers of PRV-GFP infected neurons and neurons with overlapping Gck and GFP labelling were quantified manually.

Results/Conclusion: Neurons with overlapping Gck and PRV-GFP labelling were identified in several hypothalamic regions, indicating that these regions harbor glucose-sensing neurons that project to the pancreas.

Funding: NIH

3

Brain region-specific microglia specification

Pinar Ayata, Ana Badimon, Joe Scarpa, Brianna Ramirez, Josefa Sullivan, Immanuel Purushothaman, Fan Zhang, Li Shen, Bojan Losic, Anne Schaefer
Friedman Brain Institute, Department of Neuroscience, Icahn School of Medicine at Mount Sinai
Department of Genomics, Icahn School of Medicine at Mount Sinai

Microglia have a dual role in the regulation of neuron function: releasing chemokines or trophic factors that support the neuron fitness, and removing non-functional neurons or synapses. They execute these functions within functionally distinct brain microenvironments. Given the heterogeneity of neurons in these microenvironments, we hypothesized that microglia in different brain regions need to utilize distinct sets of surface and signaling molecules that allow them to best serve their neighboring neurons.

Using microglia-specific translating ribosome associated mRNA profiling and single-nuclei RNA sequencing, we found that microglia obtained from the striatum and from the cerebellum express distinct sets of genes that are associated with discrete microglia functions. The heterogeneity in the transcriptional program of microglia is maintained by the function of the Polycomb repressive complex 2 (PRC2). This is evident in PRC2-deficient microglia, which lose their region-specific transcriptional signature. To investigate if the brain region-specific microglia specifications can be reinstated, we pharmacologically eliminated microglia and examined transcriptional signatures of the regenerated microglia.

This study provides a new perspective on microglia specification, maintenance, and glia-mediated neurodegeneration.

Pinar Ayata's salary is 100% supported by the DP2 MH100012-01 (Schaefer) "Cognate microglia-neuron interaction and its role in inflammation".

4

Postnatal Microglia Depletion Causes a Reversible Autism-Like Disorder in Mice

Ana Badimon and Anne Schaefer

Icahn School of Medicine at Mount Sinai

Background: Microglia are the brain's resident immune cells responsible for synaptic pruning and circuit formation, making them essential during brain development when neuronal connections are established. Disruption of normal microglia function has been linked to various neurodevelopmental diseases, including autism spectrum disorders (ASD). Immune dysfunction and synaptic abnormalities have been implicated in ASD, so we pharmacologically deplete microglia without inducing immune activation to determine if loss of homeostatic microglia function is sufficient to induce an ASD-like phenotypes in mice.

Methods: Microglia survival is dependent on activation of Colony Stimulating Factor 1 receptor (CSF1R). Pharmacological microglia depletion at birth is achieved via administration of a CSF1R inhibitor to the lactating mother. Complete loss of microglia was confirmed by immunostaining. Behavior was analyzed using three-chamber sociability, rotarod, and open field assays.

Results: We found that the loss of microglia neuroprotective function is sufficient to result in altered brain connectivity and associated behavioral abnormalities as seen in ASD. Postnatal microglia depletion is associated with decreased weight gain and motor deficits as early as 4 weeks of age. Microglia-depleted mice display ASD-like impairments in social interaction. Ceasing inhibitor treatment at 3 months of age allowed for rapid microglia repopulation, and resulted in the rescue of both the motor deficits and sociability deficits over time. The unexpected reversibility of the phenotype suggests that the ASD-related neuronal circuits show microglia-dependent plasticity in the adult mouse brain.

Funding: NIAT32AG049688-01

5

Patterns of resting-state functional connectivity alterations in isolated focal dystonias.

Giovanni Battistella[1], Pichet Termsarasab[1], Ritesh A. Ramdhani[1], Stefan Fuertinger[1], Kristina Simonyan[1,2]*

Departments of [1]Neurology and [2]Otolaryngology, Icahn School of Medicine at Mount Sinai

Background: The pathophysiology underlying task specificity in isolated focal dystonia remains elusive. Although recent neuroimaging studies demonstrated regional changes in brain connectivity, it remains unclear whether focal dystonia may be considered a disorder of abnormal networks. We examined topology as well as the global and local features of large-scale functional brain networks across different forms of isolated focal dystonia, including patients with task-specific (TSD) and nontask-specific (NTSD) dystonias.

Methods: Resting-state fMRI images were acquired in 18 NTSD, 15 TSD, and 15 healthy volunteers (HV). Data were analyzed using Independent Component Analysis (ICA, MELODIC-ICA, FSL), and graph theoretical analysis.

Results: Compared with HV, patients showed altered network architecture characterized by abnormal expansion or shrinkage of neural communities, such as breakdown of basal ganglia–cerebellar community, loss of a pivotal region of information transfer (hub) in the premotor cortex, and connectivity reduction within the sensorimotor and frontoparietal regions. TSD were further characterized by significant connectivity changes in the primary sensorimotor and inferior parietal cortices and abnormal hub formation in insula and superior temporal cortex, whereas NTSD exhibited abnormal strength and number of regional connections.

Conclusions: Our results suggest that isolated focal dystonias represent a large-scale disorder and provide evidence that the two subclasses of primary focal dystonia are associated with different pathophysiological mechanisms.

Funding: NIDCD,NIH R01NS088160/R01DC011805 to KS.

6

Impact of weekend admissions on mortality and discharge disposition in acute ischemic stroke (AIS).

Siddharth Bhesania, Janki Patel, Hardikkumar Shah, Bijal Patel, Harsh Patel, Karan Patel, Maria Suprun, John Doucette, Urvish Patel

Icahn School of Medicine at Mount Sinai

Background: Stroke is the second most common cause of death worldwide. There are few documented studies showing “weekend effect” on mortality in AIS for other country cohorts but there is no large population-based study done in the USA to quantify mortality rate and discharge status.

Method: In the Nationwide Inpatient Sample database (2000-2011), hospitalizations for AIS, identified by ICD-9-CM codes. We performed weighted analysis using chi-square, student’s t-test, Cochran-Armitage trend test, and Wilcoxon rank-sum test. Multivariate survey logistic regression was performed to find out mortality and discharge disposition(DD-discharge to Skilled nursing facility/Intermediate care facility) for the weekend. We had adjusted our outcomes for age, gender, race, hospital region, academic status, primary payer, and Charlson’s Comorbidity Index (CCI).

Results: A total of 5224074 hospitalizations for AIS were identified, of which 1183211(22.65%) hospitalizations occurred on weekend. The mortality trend decreased from 7.19%(2000) to 4.59%(2011). Crude analysis showed lower in-hospital mortality (1.53%vs.4.38%;p=0.01) and DD (15.2%vs.42.99;p

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White matter abnormalities in distinct phenotypes and putative genotype of spasmodic dysphonia

Serena Bianchi, Giovanni Battistella, Kristina Simonyan

Icahn School of Medicine at Mount Sinai

Background: Spasmodic dysphonia (SD) is a form of focal dystonia characterized by involuntary spasms of the larynx impairing speech production. Two types of SD have been described, abductor (ABSD) and adductor (ADSD). In the former, the vocal folds hyper-abduct, making the voice breathy and weak; in the latter, the vocal folds adduct, making the voice strained or strangled. While the etiology of SD is unknown, evidence suggests that, similar to other dystonias, SD may have a hereditary basis. Neuroimaging studies have shown that SD is associated with structural and functional abnormalities in regions underlying sensorimotor control. However, little is known regarding the neuroanatomical correlates of SD phenotypes (ABSD, ADSD), and its hereditary predisposition.

Methods: We conducted Tract-Based Spatial Statistics analyses (TBSS) on diffusion data to assess differences in white matter integrity, as measured by fractional anisotropy (FA), between: 1) ABSD (N=37) and ADSD (N=37) patients; and 2) SD patients with (familial, N=29) or without (sporadic, N=30) a family history of dystonia.

Results: Differences in FA between ABSD and ADSD patients were observed in the right retrolenticular internal capsule, SMA, orbital IFG, right/left cingulum and left STG. Differences in FA between familial and sporadic patients were found in right IFG.

Conclusion: These findings suggest that different neurological profiles underlie SD phenotypes and putative genotype.

Funding: R01DC01805 grant to KS from NIDCD, NIH.

8

Association between estradiol and posttraumatic stress disorder in men and women military veterans

ME Bowers[1], JD Flory[1,2], D Abu-Amara[4], CR Marmar[4], and R Yehuda[1,2,3]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA,
[2]James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA,
[3]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA,
[4]Steven and Alexandra Cohen Veterans Center for Posttraumatic Stress and Traumatic Brain Injury, Department of Psychiatry, NYU Langone School of Medicine, New York, NY, USA

Background: Posttraumatic stress disorder (PTSD) is twice as prevalent among women as men, raising questions about the contribution of biological factors that are differentially organized according to sex/gender, such as gonadal hormones, to PTSD risk. Estradiol has previously been associated with emotion, fear learning, and psychopathology in women. Men also synthesize estrogens, although typically at lower levels compared to women, and, therefore, they have been understudied in relation to behavior and psychopathology.

Method: Plasma estradiol levels were assayed using ELISA in 160 men and in 35 women military veterans, grouped according to presence or absence of PTSD.

Results: A significant main effect of group revealed that veterans with PTSD had lower levels of plasma estradiol overall compared to veterans without PTSD.
Conclusion: The data highlight the idea that although biological factors, including hormones, may be differentially organized according to gender, these factors may still have the same directional relationship with disease states and behavior.

Funding: Department of Defense

9

Using iPSCs to develop a drug-screening platform for the treatment of Phelan-McDermid Syndrome

Andrew Browne, Elodie Drapeau Ph.D., Joseph D. Buxbaum Ph.D.

Icahn School of Medicine at Mount Sinai

Background: Autism spectrum disorder (ASD) has high heritability and a prevalence of nearly 1% worldwide, but heterogeneity has made identifying the underlying etiology difficult. Focusing on monogenic disorders with high penetrance for causing ASD can allow for the identification of pathways common to other forms of ASD. Shank3 is one such gene that our lab has studied extensively for which haploinsufficiency produces Phelan-McDermid Syndrome (PMS) with most patients having ASD. Existing models of Shank3 deficiency have found post-synaptic membrane deficits, where Shank3 serves as a scaffolding protein.

Methods: Using blood samples collected at the Seaver Autism Center, we are generating induced pluripotent stem cells (iPSCs) from patients with PMS and unaffected siblings and differentiating them into neural cells. RNA sequencing will be performed on these neural cells and used to identify candidate drugs with anti-correlated expression signatures.

Results: Twelve patient/sibling pairs have been reprogrammed and iPSCs that pass quality control are being differentiated into neural cells with first third of samples currently being validated with immunolabeling. RNA sequencing of these neural cells will provide insight into the biological pathways implicated in PMS and could help to identify candidate drugs for repositioning, while a comparison with other ASD and PMS models could lead to the identification of convergent disease pathways.

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High Body Mass Index Impacts Disease Course in Multiple Sclerosis through Epigenetic Modifications in Monocytes

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Background: A high Body Mass Index (BMI) (≥25) is prevalent among individuals with Multiple Sclerosis (MS) and can potentially influence disease course by impacting axonal damage, the main biological correlate of long-term disability.

Methods: Magnetic resonance imaging, flow cytometry of whole blood samples, DNA methylation analysis on the Illumina 450K Methylation Array, and lipidomic profiling via Mass Spectometry were conducted on MS patients. Spinal cord sections from high fat diet fed mice induced with Experimental Autoimmune Encephalitis (EAE) were used for immunohistochemistry. Immunocytochemistry was performed on THP-1 cells treated with 15-hydroxycoisatetraenoic acid (15-HETE).

Results/Conclusion: MS patients with a high BMI (≥25) showed reduced gray matter volume and DNA methylation changes in peripheral monocytes related to cell migration, suggesting that axonal damage could result from increased cytotoxic attack by monocytes. These **Results** were validated in a mouse model, which revealed a direct association between monocytic infiltration into the CNS and clinical outcome. In patients with a high BMI, we also detected reductions in plasma 15-HETE which altered Tet2 activity and DNA hydroxymethylation levels in THP-1 cells, pointing to a putative mechanism for BMI-dependent modulations in DNA methylation. These findings have great implications for the use of dietary interventions as a therapeutic strategy for Multiple Sclerosis.

Funding: NIH

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A Role for H3K9me3 in the Maintenance of Neuronal Cell Identity

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Background: The human epigenome includes numerous histone post-translational modifications that confer varied chromatin states to modulate gene expression. Akin to the activation of lineage-determinants in establishing cellular identity, increasing evidence suggests an importance for epigenetic silencing of lineage-irrelevant factors in maintenance. Thus, we explored the involvement of the globally repressive mark, histone 3 tri-methyl lysine 9 (H3K9me3), in cell-type-specific neuroepigenomic regulation.

Methods: Four mouse brain cortices were sorted into neuronal and glial populations using fluorescence-activated nuclei sorting. Following MNase digestion, chromatin immunoprecipitation with anti-H3K9me3 antibody was performed to isolate bound DNA fragments. Samples were ultimately submitted for high-throughput sequencing. Using BowTie2, retrieved sequencing files were aligned to the mouse reference genome; diffReps was used to annotate differential regions between the two subsets.

Results: Neuronal and glial H3K9me3 ChIP-seq tracks showed appreciable differences in genome-wide distribution. Further breakdown into genomic element categories revealed distinct patterns distinguishing the two populations. Of note, nearly half (101) of 222 published ‘reprogramming-resistant regions’ overlapped with regions of relative neuronal enrichment of H3K9me3, while only 28 overlapped with regions of relative depletion.

Conclusion: Take together, the above data suggest a role for H3K9me3 as an early deterrent of neuronal regression to pluripotency.

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A survey of somatic variation in human neurons and glia

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Background: Genetic studies over the past several decades have identified several types of somatic variation in human brain tissue. The functional consequences of such variation remain unclear, but for diseases it is believed to be causal. Here, we further investigate patterns of somatic variation in the brain by comparing SNVs in neurons and glia.

Methods: Post-mortem specimens were obtained from the dorsolateral prefrontal cortex and temporal muscle of 5 cases with schizophrenia and 5 controls matched for age, gender and ancestry. Neurons and glia were isolated from each cortical specimen using FACS, and whole-exome sequencing was performed on the neurons, glia and temporal muscle of each individual. The resulting data was processed and subjected to quality control procedures using an in-house somatic calling pipeline.

Results/Conclusion: After quality control processing, 9 individuals (5 cases and 4 controls) and 27 exomes (neurons, glia and muscle from each individual) remained for analysis. We identified 310 high-confidence somatic variants (188 variants in case exomes, 122 in control exomes). We found a total of 65 variants that were present in both the neurons and glia of an individual, 99 variants that were specific to neurons, and 81 specific to glia. These preliminary findings suggest that cell types in the human brain are characterized by unique and shared somatic variants.

Funding: NIH, VA, FBI, GGS

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A novel mechanism of nicotine addiction: interplay of nicotine intake and MHb-IPN circuitry

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Background: Nicotine is the major rewarding component in cigarette. Nicotine is also toxic and can damage brain. It has been shown that systemic injection of high dose nicotine caused a massive degeneration in Medial Habenula-Interpeduncular nucleus circuitry in rats brain.
Although how nicotine affects this circuitry when it`s volitionally taken by animal and human smoker is unknown.
Method: Nicotine self-administration in rodents, diffusion MRI, T1 MRI, degeneration silver staining, western blot, immunohistochemistry

Results: By using the diffusion MRI and T1 imaging , we find that self-administration of nicotine results in a reduced FA value of fasciculus retroflexus and a smaller medial habenula volume in rats, implicating a damage of the MHb-IPN circuitry. This is confirmed by degeneration silver staining, which shows damage of fasciculus retroflexus. Furthermore, we also find that human smokers have a smaller habenula volume compared to non-smokers. Interestingly, selective lesions of Mhb-IPN circuitry increase nicotine intake in rats. Finally, we try to understand how nicotine damage the MHb-IPN circuitry.

Conclusion: Overall, our data clearly suggest that volitional intake cause damage of MHb-IPN circuitry and dysfunction of this circuitry in return to cause more nicotine intake. This feed forward mechanism may implicate in the mechanism of nicotine addiction in smokers.

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What is the Nature of the Verbal Memory Deficit in Bipolar Disorder?

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Background: Verbal memory (VM) impairments in Bipolar Disorder (BD) has not been systematically studied. We investigated components of verbal learning in a sample of BD patients, their unaffected siblings (UAS), and healthy controls (HCs).

Method: The CVLT was administered to 75 BDs, 75 UAS and 119 HCs. Learning and memory processes were subdivided: Attention (Trial 1), Learning [Total Recall 1 to 5, Learning Slope and Learning strategy (Semantic and Serial Clustering)] and Memory (Short Delay Recall, Long Delay Recall Percent Retention, and Recognition Hit Rate).

Results: BDs vs HCs were impaired in Learning (Total Recall 1 to 5, $p<0.001$; Slope, $p=0.048$) and Memory Retrieval (Short Delay Recall, $p<0.001$; and Long Delay Recall, $p<0.001$; Percent Retention, $p=0.037$). There were no significant differences (BD vs. HC) with regard to basic attentional capacity (Trial 1; $p=0.095$) nor did BDs show evidence of inefficient learning (semantic and serial clustering $p=0.135$ and $p=0.075$ respectively). UAS vs. HCs were impaired on both learning (Trial 1 to 5, $p=0.016$; Slope $p=0.022$) and memory measures (Short Delay, $p=0.030$).

Conclusion: BDs and UAS showed VM deficits in both encoding and retrieval processes however, UAS benefited from semantic cueing whereas BD patients did not and therefore may use compensatory strategies. VM impairments seem to be related to genetic risk and may serve as useful endophenotypes.

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Identification of a novel thalamic circuit that controls compulsive nicotine intake

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Background: Nicotine is the principal reinforcing component in tobacco smoke responsible for addiction. Here, we investigated how the value of nicotine is processed in brain and which circuits may contribute to the emergence of compulsive intake.

Methods: Intravenous nicotine self–administration (SA) in rats and mice under various reinforcement schedules and a randomized contingent foot shock paradigm were used to measure compulsive-like nicotine responding. Designer receptors exclusively activated by designer drugs (DREADDs) were used to manipulate the activity of discrete circuits and cells in brain. Glycoprotein (G)-deleted rabies virus (RVdG) was used to map monosynaptic inputs in brain.

Results: We found that genetic or pharmacological blockade of orexin transmission in rats and mice, respectively, decreased their willingness to work for nicotine. We identified a novel population of neurons expressing orexin-1 receptors (OX1R) located immediately adjacent to lateral habenula (LHb) which we term “Area X”. These Area X neurons are GABAergic. DREADD-mediated stimulation of LHA projecting to Area X dramatically increased the value of nicotine, reflected by nicotine-seeking responses that were resistant to contingently delivered noxious footshocks.

Conclusion: We identify a novel hypothalamo-thalamic circuit that regulates the value of nicotine and compulsive nicotine-seeking responses. Manipulation of activity in this circuit may represent a novel mechanism for medications development in human smokers.

Funding: NIDA

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Borderline personality disorder patients show longitudinal amygdala and anterior insula sensitization to emotional stimuli following initial habituation

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Background: Borderline personality disorder (BPD) is the prototypical disorder of emotion regulation, yet there remains limited understanding of its neurocognitive correlates.

Method: We examined the effect of repeated exposure to emotional images across two sessions separated by about three days upon nodes of the salience network in BPD patients, avoidant personality disorder patients (AvPD), and healthy controls (HC). 26 BPD, 25 AvPD, and 24 HCs viewed 5 presentations of the same set of 10 negative and 10 neutral images in each of two sessions as fMRI data were acquired. Activation in anatomically-defined salience network regions-of-interest (amygdala; anterior insula, AI; and dorsal anterior cingulate cortex, dACC) was investigated.

Results: Right amygdala activity showed a main effect of within-session habituation across groups. However, only BPD patients showed increased right amygdala activation to the images re-encountered on Day 2. A similar pattern was observed in right AI, but not in left amygdala, left AI, or dACC.

Conclusion: These **Results** suggest dissociable processes of acute habituation and delayed sensitization in BPD patients.

Funding: NIMH

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Pre-existing variations in amygdala morphology indicate susceptibility to social defeat stress in mice

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Background: Clinical research has revealed amygdalar dysregulation in patients with depression, indicating that it plays an integral role in mood disorders. Our work has also demonstrated that individual variability in connectivity between the amygdala and cortical regions is associated with divergent behavioral responses to social stress. Thus, investigation of neuronal morphology in the amygdala could lead to a better understanding of how animals are predisposed to susceptibility.

Methods: An acute model of social stress, developed by our lab, was used to separate a naïve population of mice into those that exhibit susceptible and resilient behavior. Microinjections of Alex Flour 568 dye were performed in the amygdala, which allowed us to probe differences in synaptic connectivity and dendritic arborization.

Results/Conclusion: Neuron reconstruction revealed that susceptible mice have greater preexisting dendritic arborizations between 50-90um from the soma compared to the resilient mice. Dendritic spine analysis showed that resilient mice exhibit lower thin spine densities between 50-100um from the soma compared to both control and susceptible mice. This supports the notion that there are differences in amygdalar synaptic plasticity with acute social stress. In conclusion, these **Results** demonstrate a preexisting whole cell difference in the amygdalae of resilient and susceptible mice that may contribute to their divergent behavioral response to acute social stress.

Funding: NARSAD Young Investigator Award

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Neuropathic pain promotes gene expression adaptations in stress and depression related brain regions

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Background: Neuropathic pain, characterized by sensory symptoms such as allodynia and hyperalgesia, is also associated with the development of depression and anxiety. Mounting clinical and preclinical studies indicate neuropathic pain leads to altered activity in brain regions involved in motivation and stress, including the nucleus accumbens (NAc), medial prefrontal cortex (mPFC), and periaqueductal grey (PAG).

Methods: We employed a long-term neuropathic pain model in adult mice which enhanced anxiety- and depression-like behaviors, and performed RNA sequencing in mPFC, NAc, and PAG samples. Ingenuity pathway analysis was performed on differentially expressed genes to identify anxiety and depression related expression patterns. We also employed chronic unpredictable stress to validate our findings on a separate murine model of depression.

Results/Conclusion: Distinct transcriptional profiles emerge across these brain regions in correspondence with chronic pain, but show overlapping effects in signaling pathways and biological functions. We show significant overlap between differentially expressed genes identified in this data set, and genes implicated in depression, anxiety, and pain from previous studies. Multiple genes regulated by neuropathic pain were also regulated by chronic unpredictable stress. Our data shows that neuropathic pain corresponds with network-wide alterations in gene expression which correspond with patterns observed in murine depression models.

Funding: Banting Postdoctoral Fellowships program and NINDS

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Role for Tcf7l2 in regulating nicotinic acetylcholine receptor function and nicotine intake

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Background: Nicotine acts in the brain by stimulating neuronal nicotinic acetylcholine receptors (nAChRs). The positive reinforcing effects of nicotine are related to activation of high-affinity □4□2 nAChRs in the midbrain dopamine system. Conversely, aversive effects of nicotine are regulated by nAChRs containing □5, □3 and/or □4 subunits in medial habenula (MHb) neurons that project to interpeduncular nucleus (IPN), with these subunits highly enriched in the MHb-IPN circuit. The molecular mechanisms that restrict □5, □3 and/or □4 subunit expression to the MHb-IPN system, and the thereby control nicotine intake, are unknown.

Methods: Drug self-administration; electrophysiology

Results/Conclusions: Genetic deletion of Tcf7l2 decreased □5 subunit gene expression in the MHb-IPN system. Moreover, we identified disrupted nAChR-mediated transmission in the MHb-IPN of Tcf7l2 knockout rats, measured using 86Rb+ efflux from and various electrophysiological techniques. Finally, we found that Tcf7l2 knockout rats consumed significantly more nicotine than their wildtype counterparts. Together, these data establish a key role for Wnt signaling, mediated through the transcription factor TCF7L2, in regulating the function of □5 subunit-containing nAChRs in the MHb-IPN system. Moreover, Wnt/Tcf7l2 signaling in this system appears to play a key role in controlling the motivational properties of nicotine.

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A functional 3'UTR polymorphism (rs2235749) of prodynorphin alters microRNA-365 binding in ventral striatonigral neurons to influence novelty seeking and positive reward traits

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Background: Genetic factors impact behavioral traits relevant to numerous psychiatric disorders and risk-taking behaviors. Here, we explored the relationship of genetic variants of the prodynorphin (PDYN) gene, which is enriched in the striatonigral/striatomesencephalic pathway, a key neuronal circuit implicated in positive behavioral choice and action.

Methods: We used a multidisciplinary approach to dissect the relationship between genetic background and gene expression, microRNA regulation as well as behavior in human subjects and translational animal models.

Results/Conclusion: Our data revealed that rs2235749 modifies striatal PDYN expression via impaired binding of miR-365 and is significantly associated to novelty- and reward-related behavioral traits in humans and translational animal models. There was an association of rs2235749 with novelty seeking trait and a strong genotype-dose association with positive reinforcement behavior in control subjects, which differed in cannabis-dependent individuals. Using lentiviral miRZip-365 constructs selectively expressed in Pdyn-neurons of NAcSh, we demonstrated that the Pdyn-miR-365 interaction in the NAcSh directly influences novelty seeking exploratory behavior and facilitates self-administration of natural reward. Overall, this translational study suggests that genetically determined miR-365-mediated epigenetic regulation of PDYN expression in mesolimbic striatonigral/striatomesencephalic circuits possibly contributes to novelty seeking and positive reinforcement traits.

Funding: NIH

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A novel compound promotes A□ clearance and rescues Alzheimer's disease-related cognitive defi-cits by reducing brain synaptojanin1 expression

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Background: Currently no treatment is available to slow or stop Alzheimer Disease (AD).We recently characterized the functional roles of a PIP2 degrading enzyme synaptojanin1 (synj1) in AD.

Method: We searched for novel drugs/compounds targeted at reducing synj1 levels using Cmap screening combined with in vitro validation studies using wild-type and ApoE4 cortical cultures.We performed dose-curve analysis of top hits in neuronal cultures,and investigated the effects of selected compounds in vivo using APP/PS1 transgenic and ApoE4 knock-in mouse models.

Results: A L-type Ca2+channel blocker nimodipine reduced A□ and synj1 protein levels in a dose-dependent manner in wild-type and ApoE4 neuronal cultures. One month nimodipine administration significantly reduced synj1 and A□ brain content, and improved cognitive functions in ApoE4 knock-in and APPswe/PS1ΔE9 AD transgenic mouse model. We next designed and synthesized nimodipine structural analogs to explore the possibility of reducing Ca2+channel inhibition and potentiating synj1 lowering effects. One structural analog (Synatocpd #9) exhibited an increased potency at lowering synj1 and A□40/42 levels, with attenuated Ca2+channel blockade effects compared to nimodipine. We are currently testing Synatocpd #9 in vivo using APPswe/PS1ΔE9 mice to determine whether 3months of daily injection can lower brain synj1 expression, A□ levels, and ameliorate AD-related neuropathological and cognitive deficits.

Conclusion: Our studies may lead to new therapeutic strategies development for AD, directed at modulating brain phospholipid homeostasis.

Funding: Alzheimer Association, Department of Veteran Affairs RR&D SPiRE,NIH.

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Functional Region of Interest Optimization for Small Structures Like the Habenula

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Neuroscience, TMII, Radiology, Psychiatry; ISMMS

Background: Small subcortical structures such as the habenula (Hb) play critical roles in mood, movement, and reward, but their size has limited in vivo study. As fMRI resolution improves, the best approach for maximizing BOLD sensitivity to small structures remains underexplored. Here, we evaluate several image analysis strategies for optimizing Hb ROIs in fMRI space.

Method: We acquired nine anatomical and resting-state functional (2.1x2.1x2.1mm, 15min) 3T MRI datasets. Individual anatomical Hb ROIs were objectively segmented following Kim et al. (NeuroImage, 2016). We compared five ways of selecting fMRI voxels after downsampling these ROIs to functional resolution: unoptimized (i.e. nearest-neighbor interpolation only), volume-matched (i.e. matched to segmented Hb volume), maximum regional correlation, maximum homotopic correlation, and maximum pairwise correlation. BOLD sensitivity was estimated by the ratio of low-frequency (<0.1Hz) to high-frequency (≥0.1Hz) power spectra and compared using paired-samples t-tests (uncorrected due to the small sample size of this exploratory evaluation).

Results: Low/high-frequency power ratios were significantly increased for homotopic ($p=0.040$) and pairwise ($p=0.033$) optimized ROIs compared to unoptimized ROIs; significant differences among optimized ROIs were also detected.

Conclusions: Combining individual-specific anatomical and voxel-wise timeseries information significantly increased low-frequency power within our Hb ROIs, suggesting improved BOLD sensitivity for subsequent fMRI analyses. While caution is warranted, this approach holds promise for improving BOLD sensitivity in studies of small neural structures.

Funding: Le Foundation

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Histone monoaminylation: a novel mechanism of 'epigenetic' plasticity

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Background: Alterations in gene expression promote adaptations implicated in a wide variety of human diseases. More recently, histone mechanisms have been shown to regulate transcriptional programs contributing to neurological disorders; our understanding of how these mechanisms mediate persistent patterns of transcriptional dysfunction remains limited. Monoamines in brain play a critical role in neuronal plasticity, with alterations in monoamine production being implicated in the development and treatment of numerous brain disorders. Although vesicular packaging of monoamines is essential for neurotransmission, recent data have demonstrated the additional presence of 'reserve' pools of extravesicular monoamines in the nucleus of monoaminergic neurons; it remains unclear, however, whether nuclear monoamines may play roles independent of neurotransmission. Monoamines have previously been shown to form covalent bonds with certain cytoplasmic proteins via transamidation by the TGM2 enzyme. We hypothesized that nuclear proteins may similarly be modified to control distinct aspects of their function.

Methods: We employ a variety of biochemical, biophysical and molecular approaches to fully delineate the function of histone monoaminylation.

Results/Conclusions: We have identified histone proteins as robust substrates for monoaminylation in vivo. Our data indicate that H3 monoaminylations act to facilitate binding of adjacent H3K4me3 interacting proteins, while simultaneously allosterically inhibiting the actions of DNMT3A to promote genic activation in monoaminergic cells.

Funding: NARSAD Young Investigator Award, MQ Fellowship, Sloan Research Fellowship.

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Characterization of hiPSC-neurons from psychosis patients with neurexin-1 deletions

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Background: Neurexin-1 (NRXN1) is a highly alternatively spliced presynaptic cell-adhesion protein essential for synaptic function. Heterozygous intragenic deletions in this gene are strongly associated with schizophrenia and autism spectrum disorder. We aim to investigate the functional consequences of NRXN1 deletions using human induced pluripotent stem cell (hiPSC) derived neurons.

Methods: We have reprogrammed skin samples from four individuals carrying NRXN1 deletions, one related control and three unrelated controls into hiPSCs. For each individual, three hiPSC clones were differentiated into neural progenitor cells (NPCs) and neurons. Total RNA from these samples was collected for Illumina RNA-sequencing and Pacific Biosciences long read SMRT-sequencing. Currently, lentiviral (LV) transduced Cas9-mediated upregulation of NRXN1 in NRXN1 deletion hiPSC neurons is being performed to create isogenic controls.

Results/Conclusion: hiPSC NPCs and neurons were made and characterized from patients with heterozygous NRXN1 deletion and controls. Preliminary analysis of RNA-sequencing data demonstrates differential expression at the gene, transcript and exon level in NRXN1 deletion hiPSC neurons. Pilot SMRT-seq analysis showed expression of multiple full length NRXN1 isoforms, however to catalogue the complete diversity of NRXN1 isoforms a targeted strategy is now being optimized. Future work will be done to restore transcriptional differences in hiPSC neurons using CRISPR-mediated upregulation of NRXN1 to create isogenic controls for functional studies.

Funding: NIH, NYSCF and NARSAD

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Lateral Habenula Orexin Receptor 2 Controls Aggression Reward

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Background: Recent imaging studies in humans suggest that elevated interpersonal aggression in psychiatric patients may result, in part, from the inappropriate activation of reward circuitry in social contexts. Here we investigated the role of lateral habenula (lHb) orexin signaling in aggression and its rewarding components.

Methods: We used a combination of fluorescent in-situ hybridization and immunohistochemistry (IHC) to anatomically characterize the orexin lateral hypothalamus (LH) to lHb circuit. We then used IHC, qRT-PCR, and western blotting to measure LH orexin neuron activation, lHb orexin receptor expression, and OxR2-mediated signaling activation, respectively, in aggressors (AGGs) and non-aggressors (NONs) following exposure to a conspecific. Finally, we performed AAV-shRNA-mediated knockdown of lHb Orexin receptor 2 (OxR2) and determined the effects of this manipulation on aggression and aggression conditioned-place preference.

Results: Following exposure to a conspecific, AGGs displayed increased LH orexin mRNA and protein and increased lHb OxR2 mRNA compared to NONs. In addition, AGGs displayed greater cFos activaton of orexin-positive neurons than NONs following exposure to a conspecific. AAV-shRNA-mediated knockdown of OxR2 in the lHb functionally decreased aggression and aggression conditioned-place preference.

Conclusion: Our findings support a novel functional role for LH-lHb orexin signaling via OxR2 in aggression and aggression reward.

Funding: NIH

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Constructing a comprehensive map of long non-coding RNAs in brain using integrated transcriptomic approaches

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Background: Long non-coding RNAs (lncRNAs) are implicated in gene transcriptional regulation, and likely play a role in neurodevelopmental disorders. We have established a lncRNA enrichment approach that is used in combination with both short-read and long-read RNA-sequencing technologies.

Methods: Our lncRNA capture-sequencing (SeqCap) method targets and preferentially sequences lncRNA transcripts in a sample and our custom analysis pipeline annotates and classifies novel transcripts uncovered by our experimental technique to link isoforms to gene biotypes.

Results/Conclusions: We have generated short-read lncRNA-SeqCap for five prefrontal cortex post-mortem brain samples, as well as astrocytes, neural progenitor cells and neurons derived from iPSCs of a single individual. Capture efficiency of spiked-in external RNA controls indicated an average 1,000-fold enrichment of captured transcripts when comparing the pre- and post-capture libraries, as measured by qPCR. We further combined long-read sequencing with lncRNA-SeqCap to identify full-length transcripts in the SH-SY5Y cell line, which showed an average 100-fold enrichment of target expression levels post-capture. Analysis has revealed many novel lncRNA as well as protein-coding isoforms, and has uncovered evidence of interleaved transcripts arising from a combination of both gene biotypes. Our protocol allows us to construct an improved map of lncRNA gene structures that will serve as valuable resource to the field.

Funding: Seaver Foundation and NIMH

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RGS20 actions in the mouse Periaqueductal Gray modulate sensitized responses in models of inflammatory pain.

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Background: Chronic pain conditions affect millions of people whereas their therapeutic management could highly benefit from the understanding of the cellular adaptations chronic pain conditions promote in the CNS. The Periaqueductal gray (PAG) is one of the key brain regions involved in modulation of nociceptive transmission and descending inhibition of nociceptive pathways. We investigate the role of Regulator of G-protein Signaling-20 (RGS20), in behavioral and biochemical adaptations to inflammatory pain. RGS proteins modulate the duration and direction of GPCRs signal transduction, and have been shown to control physiological responses.

Methods: Complete Freund's Adjuvant (CFA) model of inflammatory pain, knockout mouse models, RNAsequencing, Voltammetry, Western blot

Results: Global deletion or conditional knockdown of RGS20 in PAG, lead to prolonged sensitized behaviors in response to hindpaw inflammation. RNAseq data reveal that chronic inflammatory pain-like states promote a number of adaptations in the PAG, including changes in the expression of molecules involved in serotonin synthesis and release. Voltammetry studies in the rostral ventral medulla RVM), reveal that RGS20 knockout(RGS20KO) mice have a lower readily releasable serotonin pool resulting in lower levels of stimulated release. Consistent with these findings, the loss of inhibitory descending control leads to increased c-fos activation in the spinal cord.

Conclusion: Our studies reveal a crucial role of RGS20 in the PAG in nociception and point to RGS20-regulated pathways as promising targets for the treatment of inflammatory pain.

Funding: NINDS

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Transient Visual Evoked Potentials in Idiopathic ASD

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Background: There is a critical need to identify biomarkers and objective outcome measures that can be used to understand underlying neural mechanisms in autism spectrum disorder (ASD). Visual evoked potentials (VEPs) offer a noninvasive technique to evaluate the functional integrity of visual pathways while probing for disease pathophysiology.
Method: Transient VEPs (tVEPs) were obtained from 32 children with ASD and 32 typically developing (TD) children. A conventional contrast-reversing checkerboard condition was compared to a novel short-duration condition, which was developed to enable objective data collection from severely affected populations who are often excluded from electroencephalographic (EEG) studies.

Results: Children with ASD showed significantly smaller amplitudes compared to TD children at two of the earliest critical VEP components, P60-N75 and N75-P100, which reflect primarily excitatory and inhibitory postsynaptic activity, respectively. There were no group differences in response latency among groups. All time-domain analyses persisted when the ASD group was divided by IQ. Findings were consistent across both stimulus conditions. Ninety percent of children with ASD completed the short-duration condition compared to 70% for the standard condition.

Conclusion: The current study establishes the utility of a short-duration tVEP test for use in children at varying levels of functioning and describes neural abnormalities in children with idiopathic ASD.

Funding: This study was funded by the Seaver Foundation and Autism Speaks (PI: Siper).

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Whole brain connectomics for the establishment of behavioral response to social defeat stress

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Background: The brain is a singular organ composed of regions performing specialized roles. Thus, research focusing on the function of the brain in its entirety can provide us with novel means for understanding and treating neuropsychological disorders.

Methods: Using a mouse model, we developed an acute model of social stress that allowed us to observe susceptible and resilient divergent behavioral response at a one-hour timepoint. To observe correlative activity of various regions through the brain, we performed immunohistochemistry for cFos, an immediate early gene, on populations of susceptible and resilient animals. To probe the morphological substrate, we injected a retrograde GFP virus into the amygdala and analyzed the synaptic architecture of circuit-specific cells.

Results/Conclusion: We found greater whole-brain correlative cFos activity in low-cFos expressing cells of resilient animals. However, when we focused on high-cFos expressing cells, we observed the emergence of an amygdala-driven network only in susceptible animals. We also uncovered that susceptible animals have greater stability in specifically in prelimbic cells that are activated by social stress. Together, this may be indicative of lower constitutive activity in the brains of susceptibility allowing for the amygdala to seize control of the network when it is stimulated by stress.

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Common Genetic Variants Indicate a Role of microRNAs in the Etiology of Schizophrenia

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Background: microRNA regulate expression of targeted genes post-transcriptionally and studies point to a role of such molecules in schizophrenia. We therefore systematically explored the role of microRNA in schizophrenia in the setting of common genetic variants, by identifying microRNA that are regulators of schizophrenia genes and functional genetic variants relating to microRNA.

Method: We used schizophrenia genetic risk variants identified by the Psychiatric Genomics Consortium and predicted targets of microRNAs in a gene set approach to find microRNA that are regulators of schizophrenia genes. Further, genetic variants altering microRNA binding sites, the microRNA stem-loop, the mature microRNA, and eQTLs affecting microRNA abundance were examined.

RESULTS: We found miR-9-5p targets to show the strongest disease association along with evidence for involvement of additional microRNAs including miR-137. Interestingly, for the two aforementioned microRNA, the regulated target genes as well as the microRNA host genes show an association with schizophrenia. Further, a functional schizophrenia risk variant changing the target site of miR-1/206/613 in NT5C2 was identified and experimentally validated.

CONCLUSION: The novel implication of miR-9-5p is schizophrenia is of particular interest, as this neurodevelopmental microRNA has a regulatory loop with the fragile X mental retardation homolog FXR1, and regulates dopamine D2 receptor density, with both of these genes located in schizophrenia-associated loci.

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Role for nucleus accumbens neuroligin-2 in major depressive disorder and stress resiliency

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Neuroligin-2 (NLGN-2) is a postsynaptic cell adhesion protein that plays an integral role in the inhibitory synapse. Mutations in the neuroligin gene family have been associated with neuropsychiatric disorders; however, very little is known about NLGN-2. We performed transcriptional profiling of the neuroligin gene family in postmortem nucleus accumbens (NAc) of depressed patients. We reverse translated these findings in the social defeat stress model in mice. We further explored the cell-type specific contribution of NAc NLGN-2 to stress resiliency using a Cre-conditional RNA interference approach to knockdown NLGN-2 in either D1-MSNs or D2-MSNs. NLGN-2 gene expression is reduced in the NAc of depressed patients. In stress susceptible mice, NLGN-2 is selectively reduced in D1-MSNs. Knockdown of NLGN-2 in NAc D1-MSNs mediates susceptibility to social defeat stress and decreased dominance behavior. NLGN-2 knockdown in NAc D2-MSNs causes increased dominance behaviors, promoting stress resiliency.

These findings establish a novel, bidirectional role for NAc NLGN-2 in behavioral resilience, providing a molecular basis for the development of cell-type specific depression therapies.

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microRNA-206 regulates schizophrenia-related behaviors in mice

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Background: Schizophrenia (SZ) is a debilitating disorder characterized by psychosis, emotional dysfunction, and cognitive impairments. SZ is associated with deficits in parvalbumin (PV) expressing interneurons in prefrontal cortex (PFC), and mutations in the PV interneuron-enriched microRNA-206 are associated with SZ. Thus, miR-206 may regulate cortical PV interneurons and thereby influence behaviors relevant to SZ.

Methods: miR-206 knockout (KO) mice were created by homologous recombination in embryonic stem cells. Behavioral tests included open field, a delayed non-matched-to-place (DNMTP) operant task, prepulse inhibition, and fear conditioning. Miniature IPSCs (mIPSCs) were recorded from PFC pyramidal neurons. For immunofluorescence studies, fixed brain sections were stained with antibodies against GAD67 and PV.

Results: miR-206 KO mice were grossly normal. KO mice had impaired prepulse inhibition and increased anxiety-related behaviors in response to stressful stimuli. Female miR-206 KO mice were slower to learn a DNMTP operant task, while male KOs omitted more trials, indicative of dysfunctional prefrontal cortical circuitry. Consistent with a role for miR-206 in regulating cortical GABAergic function, mIPSC frequency was decreased in PFC pyramidal neurons of KO mice.

Conclusions: miR-206 appears to be critical for proper inhibitory cortical transmission. Loss of miR-206 causes SZ-related behavioral deficits, including sensorimotor gating impairment, cognitive dysfunction and anxiety-like behaviors.

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Smell shapes social judgment

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Background: Once associating another person with an unpleasant smell, how do we perceive and judge this person from that moment on? Given that disgust elicits the immediate urge to keep away, disgust associations in a social context may similarly urge a mental distance.

Method: We recruited 17 healthy volunteers and used olfactory conditioning and a social attribution task during fMRI.

Results: Participants reported a range of negative feelings after olfactory conditioning, including disgust, anger, and anxiety ($P = 0.001$). The aversive smell activated the bilateral amygdala and right insula ($P < 0.05$, corrected). Participants showed more frequent trait attributions ($p < 0.05$) as well as deactivations of the vmPFC together with regions involved in theory of mind and empathy ($p < 0.05$, corrected).

Conclusion: Our findings extend the emerging "meaning-centered" view of the vmPFC by showing that a disgust association can be strong enough to decontextualize perceived behavior. By way of association, smell "sticks" to a person and may shape our social judgment.

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Fear memory reactivation and reconsolidation: The role of context

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Background: Fear memories can be diminished by conducting extinction during the reconsolidation time window, and this effect is specific to the reactivated conditioned stimulus. However, real-life events are usually associated with several different cues, and each cue can potentially trigger reconsolidation. We introduced a technique to target all multiple cues associated with an event that causes fear.

Methods: The experiment was conducted over the course of three days. Day1: The participants underwent fear conditioning to two different cues in a same context. Day2: There were three groups of participants. One group was reminded of the context, another group was reminded of one of the conditioned stimuli, and a third group received no reminder. Ten minutes after the retrieval trial, all participants underwent the extinction session. Day3: All three groups were presented again with the conditioned stimuli without the unconditioned stimulus to test spontaneous fear recovery, followed by a reinstatement test.

Results/Conclusion: Presentation of the context before extinction prevented the return of fear to the different conditioned stimuli associated with the same aversive outcome. This finding suggests that extinction following context retrieval may have a potential impact on therapeutic approaches to prevent the return of fear.

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Predicting gene expression in the dorso-lateral pre-frontal cortex

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Background: Understanding of the genetic aetiology of psychiatric disease has advanced greatly through the use of genome-wide association studies, although the biological implications of identified variants are not always clear. More understanding could be gained by identifying disease-associated changes in gene expression; however, these studies are sparse and subject to multiple confounding factors.

Recent studies have developed methods to impute tissue-specific gene expression levels from genotype. We have developed gene-expression predictors for the dorso-lateral pre-frontal cortex (DLPFC). These will be applied to existing large-scale GWAS for genic association analyses.

Methods: Imputed genotype and DLPFC RNA-seq data were obtained through the CommonMind Consortium project. This dataset encompassed 668 individuals and 16,242 genes.

For each gene, a prediction model was created using either associated eQTLs or SNPs local to the gene (+/- 1Mb). Predictors were created using elastic net regression and Bayesian sparse linear mixed models, and tested using ten-fold cross-validation.

Results/Conclusion: To date, predictors have been created for 4191 genes with at least two eQTLs. 2175 genes (52%) were predicted well ($R2 > 0.1$), while 94% of genes achieved $R2>0.01$.

This is the first model to predict gene expression in the DLPFC, a region of substantial interest in psychiatric research. These data are considerably larger than used in previous studies, which may result in higher prediction accuracy.

Funding: NIMH CommonMind Consortium

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Neuronal deletion of Kmt2a/Mll1 Histone Methyltransferase in Ventral Striatum is Associated with Defective Spike-Timing Dependent Striatal Synaptic Plasticity, Altered Response to Dopaminergic Drugs and Increased Anxiety

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Background: Methylation of H3 lysine 4 by regulators such as Lysine methyltransferase 2a (Kmt2a)/Mixed-lineage leukemia 1 (Mll1) **Results** in enrichment at promoters/enhancers, but molecular and cellular phenotypes in subcortical areas are not understood.

Methods: Mice carrying loxP sites flanking exons 3 and 4 of Kmt2a/Mll1 were bred with CamKIIα-Cre mice for conditional knockout. These mice were used for diurnal, stimulant, and D1-agonist induced locomotor activity, and electrophysiological recording of striatum. Quantitative RNA assays were also performed. A second cohort of Mll12lox/2lox mice were injected with AAV8-GFP-Cre in ventral striatum for behavioral testing of anxiety and depression.

Results: Neuronal ablation of Kmt2a/Mll1 in adult ventral striatum is associated with excessive nocturnal activity and blunted responses to stimulant and dopaminergic agonist drugs. Slice recordings revealed a near-complete loss of spike timing-dependent long-term potentiation. Striatal transcriptome sequencing in adult mutants identified 262 Kmt2a-sensitive genes, mostly downregulated. Behavioral tests showed increased anxiety in multiple paradigms.

Conclusions: Therefore, Kmt2a regulates synaptic plasticity in striatal neurons and provides an epigenetic drug target for anxiety and dopamine-mediated behaviors.

Funding: NIH

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Probing neural circuits that underlie individual alcohol drinking behaviors

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Background: Addiction to alcohol abuse is marked by the transition from casual consumption of alcohol to pathological consumption behaviors. This transition is known to recruit distinct neural circuits involved in reward, stress and executive control. Interestingly, alcohol abuse demonstrates variability in individual consumption behaviors. Here, we sought to determine how the initial recruitment of the mesocorticolimbic reward circuit modulates variable alcohol drinking behaviors using a genetically identical mouse model.

Methods: Inbred C57BL/6J male mice were exposed to a 24-hour two-bottle choice alcohol drinking paradigm to establish two drinking groups: low alcohol drinking or high alcohol drinking mice. Using neural circuit-probing electrophysiological, optogenetic and voltammetric techniques, we investigated how projection-specific dopaminergic neurons originating from the ventral tegmental area (VTA) were altered between the alcohol drinking groups.

Results: We discovered that low alcohol drinking mice have increased activity in dopamine neurons that project to the nucleus accumbens (NAc) when compared to ethanol naïve or high alcohol drinking mice. These cellular adaptations are observed with specific intrinsic ion channel adaptations and are also observed to causally modulate alcohol drinking behaviors. We also observed differential dopamine release in the NAc between the alcohol drinking groups.

Conclusion: These data suggest that pathological neuroadaptations of the VTA-NAc circuit underlie individual alcohol drinking behaviors.

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Role for granulocyte colony stimulating factor in the rewarding effects of cocaine

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Background: There is growing evidence showing that dysregulation of the immune system plays a role in the pathophysiology of psychiatric disorders. Recently, evidence has begun to accumulate that cocaine alters immune signaling in ways that may drive pathological use behaviors. We used broad serum profiling to determine which inflammatory proteins are altered by cocaine exposure in rodents, and used those **Results** to interrogate how those proteins modify behavior. We identified granulocyte colony stimulating factor (G-CSF) as a cocaine-regulated protein that alters cocaine-mediated behaviors.

Methods: Serum from animals receiving high dose self- or experimenter-administered cocaine, was analyzed for 24 cytokines chemokines and growth factors using quantitative multiplex analysis. For behavioral experiments, animals were pre-treated with systemic injections of G-CSF protein, and alterations in conditioned place preference (CPP) and locomotor sensitization were measured.

Results/Conclusions: Serum analysis demonstrated multiple immune factors were modulated by cocaine, however only G-CSF was elevated in both self- and experimenter-administered cocaine, and serum levels of G-CSF showed linear correlation with levels of locomotor sensitization and self-administration, respectively. Behaviorally, animals pre-treated with G-CSF demonstrated increased locomotor sensitization and CPP for cocaine. These experiments provide evidence that alterations in this peripherally derived cytokine play an important role in regulating cocaine-related behaviors.

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Regulation of Lateral Hypothalamic Midbrain Circuitry in Social Defeat Stress

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Background: The lateral hypothalamus (LH) mediates stress and reward processing and projects heavily to the ventral tegmental area (VTA), a region key to the development of susceptibility or resilience to social stress.

Methods: We use the chronic social defeat stress (CSDS) paradigm, a model of depression that produces mice that are resilient or susceptible to the defeat stress. To characterize the circuitry underlying depression behaviors, we use electrophysiology, optogenetic and viral manipulations, and behavioral testing.

Results: Our electrophysiological recordings reveal increased firing activity in LH-VTA neurons of susceptible mice, compared to control and resilient mice. This observed hyperactivity in susceptible behaviors is recapitulated in stress-primed animals using optogenetics to induce increased firing in ChR2-expressing LH-VTA neurons. Hypocretin, a neuropeptide exclusively produced in the LH, induces susceptible behaviors in stress-primed animals when microinfused into the VTA. Since hypocretin activates both dopaminergic and GABAergic neurons within the VTA, we will elucidate the LH input to VTA microcircuitry in the context of CSDS.

Conclusions: Our results suggest that the LH is involved in modulating susceptible behaviors in the VTA in CSDS. Due to the heterogeneity of the VTA cellular population, we will need to further characterize the LH-VTA circuitry underlying depression behaviors.

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Mutation of Vps11 causes a new class of Leukoencephalopathy and impaired autophagy

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Background: Genetic leukoencephalopathies (gLEs) are a group of heterogeneous disorders characterized by white matter abnormalities affecting the development of the central nervous system. Actually, ~50% of gLEs are of unknown etiology and therefore particularly challenging to diagnose.

Methods: Using whole exome sequencing (WES) and basic techniques in molecular and cellular biology, we identified and characterized the function of a new Vps11 variant.

Results/Conclusion: Our WES analysis identified homozygosity for a missense variant, VPS11: c.2536T>G (p.C846G), as the cause of a novel gLE syndrome in five individuals from three unrelated Ashkenazi Jewish families. We find that C846G variant causes aberrant ubiquitination of Vps11 and increases its turnover without disturbing its secondary structure. Our data show that autophagic activity is impaired in Vps11-deficient cultured cells and homozygous Vps11-C846G patient-derived lymphoblastoid cells. Using RFP-GFP-LC3 reporter assay, we determined that Vps11 depletion reduces autophagy flux by promoting accumulation of immature autophagosomes and reducing formation of autolysosomes. Our study reveals the pathogenic mechanism of a new gLE syndrome, thereby facilitating its diagnosis, and unveils Vps11 mutant-mediated dysfunctional autophagy as a potential drug target for the treatment of this disorder.

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Development of Cell-Based Neurotransmitter Fluorescent Engineered Reporters (CNIFERs) for Real-Time in vivo Detection of Neuropeptides

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Background: Although neuropeptides are essential participants in the regulation of neural activity, the mechanisms, dynamics and consequences of neuropeptide release in vivo remain largely unexplored. We are developing biophotonic tools to monitor the release of neuropeptides in awake animals. CNiFERs are clonal HEK293 cells engineered to express a specific GPCR that, when stimulated, triggers an increase in intracellular [Ca2+] that is detected by a FRET-based Ca2+ sensor. Thus, CNiFERs provide a direct and real-time optical read-out of local changes in neurotransmitter/peptide levels.

Methods: CNiFERs, aimed to detect somatostatin (STT) and vasoactive intestinal peptide (VIP), were created by lentiviral transduction of HEK293 cells. Transduced cells were single cell-sorted and expanded. Clonal CNiFERs were screened for sensitivity and specificity by a high-throughput plate reader. Selected clones were further characterized in vitro with multiple presentation of the agonist to test potential desensitization.

Results/Conclusion: We have created CNiFER clones with nanomolar sensitivity to their respective agonists (STT EC50=15nM, VIP EC50=350nM). Importantly, each neuropeptide CNiFER has little or no non-specific response to a panel of other neuromodulators. These new CNiFERs provide a unique means to monitor neuropeptide release in vivo in real-time and can be combined with other optical methods, such as optogenetics and calcium imaging, to study the function of neuropeptides in cortical microcircuits.

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Quantitative comparison of graph theoretical measures of simulated and empirical functional brain networks

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Background: Whole-brain computational models have shown promise in enriching our understanding of mechanisms contributing to the formation and dissolution of resting-state functional patterns. It is therefore important to determine the degree to which computational models reproduce the topological features of empirical functional brain networks. Here, we focused on the performance of the Kuramoto model as it is considered most representative model of coupled phase oscillators.

Methods: Simulated resting-state functional connectivity (FC) was generated using the Kuramoto model constrained by empirical structural connectivity. The simulated FC matrix was tuned to best fit empirical FC matrix. We quantified the difference, in terms of relative error, in graph theoretical measures between the simulated and empirical functional networks.

Results: The averaged relative differences in graph measures were found to be 2–77% over the entire range of connection densities and 0.1–22% over a range of 37–50% connection densities. We found that simulated functional data can be used with confidence to model graph measures of global and local efficiency, characteristic path length, eigenvector centrality, and resilience.

Conclusions: This study demonstrates the value of computational models in assessing whole-brain network connectivity, and provides a method for the quantitative evaluation and external validation of graph theory metrics derived from simulated data that can be used to inform future study designs.

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Potential roles for histone dopaminylation in cocaine-induced plasticity

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Background: Drug addiction is a debilitating disease that is characterized by loss of control over drug intake. While drug addiction remains a devastating health and societal issue, few advances have been made in the treatment of this disorder. Although the molecular mechanisms mediating addiction remain unclear, there is now emerging evidence that drugs of abuse promote alterations in cell-type specific gene expression patterns in brain, thereby 'high jacking' normal cellular functions to promote aberrant forms of behavioral plasticity. We have recently identified a novel set of histone posttranslational modifications (PTMs) that are enriched within monoaminergic neurons – e.g., H3 glutamine 5 dopaminylation (H3Q5dop) in ventral tegmental area (VTA) dopaminergic neurons – and we hypothesize that chronic cocaine exposure may impact these PTMs to promote pathological phenotypes associated with drug abuse.

Methods: Here, we employ a wide array of biochemical, biophysical, molecular and behavioral approaches in a well-established rat model of cocaine self-administration.

Results/Conclusions: Our results indicate that extended, but not restricted, access to cocaine followed by extended periods of withdrawal promotes increased diffusion of dopamine into the nucleus of VTA neurons, heightened cytoplasmic-nuclear shuttling of the H3Q5 dopaminylase (Tgm2) and potentially altered genome-wide patterns of H3Q5 dopaminylation, thereby indicating a putative role for this novel PTM in drug induced plasticity.

Funding: 2014 NARSAD Young Investigator Award, MQ Research Fellowship, 2016 Sloan Research Fellowship in Neuroscience

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Representational similarity of social landmarks in the human brain

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Background: Social relationships can be complex and and change constantly and yet we quickly track the social positions of others as a matter of basic survival. In a previous study, we asked how the human brain represents and organizes social relationships. We made use of a "choose-your-own-adventure" game and functional magnetic resonance imaging to find that the hippocampus tracks changes in social relationships in a two-dimensional map along the power and affiliation axes. Here we present new evidence on how information about specific individuals encountered in social interactions is represented in the brain.

Methods: Participants played the leading role in a virtual social game and interacted with different characters while in an fMRI scanner. Each interaction was characterized by a change along either the power or affiliation dimensions. We now use representational similarity analysis (RSA) to analyze the multi-voxel patterns of brain activity in the hippocampus and test them against the predictions of different representational models.

Results/Conclusion: We expect that the patterns of hippocampal activity will be more similar to the patterns predicted by a model encoding individual positions on the 2D social map compared to a model encoding individual identities.

Funding: Klingenstein-Simons Foundation Award in the Neurosciences

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MODULATING THE EPIGENOME OF THE IMMUNE SYSTEM TO TREAT TRAUMATIC SPINAL CORD INJURY

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Axon regeneration is a critical component of sensory and motor function recovery following spinal cord injury (SCI). The resulting inflammatory response is considered an important determinant of the extent of axonal regeneration achieved following SCI. Microglia play a central role in this inflammatory response following their differentiation into M1 or M2 subtypes, which possess pro-inflammatory or pro-regenerative properties, respectively. Unfortunately, the local SCI environment favors M1 differentiation, which is harmful to tissues and inhibits axon regeneration. Recently, it has been discovered that histone modifications play a role in monocyte differentiation. Previous studies in our lab have elucidated that HDAC3 is highly expressed in M1, but not M2 cells after SCI. Additionally; our data indicate low H3ac in M1 cells in contrast to elevated H3K9ac and H3K27ac in M2. This led us to hypothesize that HDAC3 functions as an epigenetic brake for M2 gene expression and that HDAC3 inhibition may favor axon regeneration. Through preliminary studies involving the treatment of an SCI model with an HDAC3 inhibitor, RGFP966, we found that the M2 cell density was significantly elevated. Furthermore, in another SCI model, administration of HDAC3 inhibitor resulted in improved functional recovery. These data suggest that histone modifying enzymes may be promising pharmacological targets for regulating functional polarization of M1 and M2 cells.

Funding: NIH

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Increased kinase activity of the Parkinson's disease-linked LRRK2-G2019S mutation drives excessive excitatory synaptic activity in developing striatum

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Background: Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) contribute to Parkinson's disease (PD). Causal mechanisms are unknown, but mutations in the kinase domain follow disease heritability implicating altered kinase activity. The most common LRRK2 mutation, G2019S, increases kinase activity. How this impacts PD-related circuits is poorly understood. LRRK2 expression levels rise during synaptogenesis and are highest in striatal spiny projection neurons (SPNs).

Methods: We used LRRK2 G2019S and D2017A (kinase-dead) knockin mice to determine how LRRK2 kinase activity affects developing striatal circuits.

Results/Conclusion: By P21, G2019S SPNs exhibited a significant increase in frequency of sEPSCs compared to wildtype in both direct- and indirect-pathway SPNs. There were no differences in glutamatergic activity between wildtype and D2017A SPNs, indicating a selective effect of G2019S. Acute exposure to LRRK2 kinase inhibitors normalized activity, indicating that the excessive excitation is directly mediated and kinase-dependent. Dendritic spine-head widths on G2019S SPNs were abnormally large, which was matched by an abnormal range of postsynaptic responses. Isolating striatum from neocortex ex vivo normalized excessive G2019S sEPSC frequency, suggesting that abnormal corticostriatal activity is involved. These findings indicate the G2019S mutation imparts a unique gain-of-abnormal-function to striatal circuits during development and may fundamentally modify circuit structure and function.

Funding: NIMH, MJFF, APDA.

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Role of blood-brain barrier permeability and tight junction protein claudin-5 in vulnerability to social stress and major depressive disorder.

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Multiple clinical studies suggest that heightened peripheral inflammation contributes to major depression disorder pathogenesis. It has been hypothesized that circulating inflammatory molecules are released following chronic stress, penetrate the blood brain barrier (BBB), and affect neural circuits mediating stress vulnerability and depression.

In this study we investigated the effect of chronic social defeat stress (CSDS), a mouse model of depression, on BBB permeability and regulation of tight junction protein Cldn5.

We found that after 10-day CSDS, Cldn5 mRNA and protein expression is reduced in the nucleus accumbens (NAc) of stress-susceptible animals when compared to resilient mice and unstressed controls. In fact, lower permissive acetylation and enhanced repressive methylation was measured along the Cldn5 gene promoter in stress-susceptible mice. We found a similar decrease of Cldn5 mRNA in the NAc of depressed patients. In mice, chronic down-regulation of Cldn5 expression induced social avoidance and depression-like behaviors. MRI scans revealed higher penetration of a gadolinium-based contrasting agent in stress-related brain regions of defeated animals suggesting reduced BBB integrity. By understanding how chronic stress affects the BBB we may be able to augment current antidepressant treatment or design new therapeutic strategies.

NIH

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Partial correction of metabolic and behavioral phenotypes of Alzheimer's APP/PSEN1 mice by gene targeting of diabetes/Alzheimer's-related Sorcs1

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Background: Type 2 diabetes (T2D) increases the risk for Alzheimer's disease (AD). SORCS1 encodes a protein-sorting molecule genetically linked to both T2D and AD.

Method: to study Sorcs1 effects, we assessed memory, glucose homeostasis, and brain biochemistry and pathology in wild-type, Sorcs1 -/-, APP/PSEN1, and Sorcs1 -/- X APP/PSEN1 mice.

Results: Male mice with either the APP/PSEN1 or Sorcs1 -/- genotype displayed earlier onset and impairment in learning behavior and glucose homeostasis. Behavioral and metabolic abnormalities in male mice were not exacerbated when the two disease model mice (Sorcs1 -/- models T2D; APP/PSEN1 models AD) were crossed. However, female Sorcs1 -/- X APP/PSEN1 mice exhibited worse metabolic dysfunction than Sorcs1 -/- knockouts and worse memory than wild-type mice. Deletion of Sorcs1 from APP/PSEN1 mutant mice did not change brain total or oligomeric amyloid-beta peptide.

Conclusions: There was a trend for gene targeting of Sorcs1-/- to partially mitigate the metabolic and amyloid pathologies. These **Results** indicate that crossing AD and T2D model mice may not always cause exacerbation of both the amyloidosis and the metabolic phenotype and highlight unexpected pitfalls of creating mixed models of disease.

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Late Adolescent Shift from Local to Distributed Monosynaptic Inputs onto Fronto-Posterior Cortical Projection Neurons

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Background: Visual attention, the cognitive ability that enhances perception of selected stimuli, develops postnatally and is disrupted in neurodevelopmental disorders such as autism. A direct "top-down" projection from the anterior cingulate cortex (ACC) to primary visual cortex mediates visual attention and requires adolescent development. However, little is known about this projection's input sources, and if inputs undergo developmental modifications.

Methods: An intersectional viral genetic technique was employed to map the monosynaptic inputs onto top-down cells in adolescence and adulthood. Whole brain maps were generated. Inputs were characterized by cell type in regions of interest.

Results/Conclusion: Cortical areas contributed the majority of monosynaptic inputs onto top-down cells. Local inputs from the ACC and secondary motor area comprise the large source; other cortical contributions include the retrosplenal, prelimbic, and infralimbic cortex. Non-cortical regions provide distributed inputs from the basal forebrain, dorsal thalamus, and hypothalamus. Approximately 75% of basal forebrain neurons are cholinergic. Comparison of the adult and adolescent whole brain maps revealed a larger number of inputs from local cortical regions during adolescence lost in adulthood. No age-related differences were observed in other cortical and non-cortical areas. This result suggests that local pruning during late adolescence causes a relative shift in input weight from local to distal brain regions between adolescence and adulthood to establish effective top-down control of attention.

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Relationships between perceived stress, spatial reasoning, and the representation of social space in the hippocampus

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Background: The hippocampus is a fundamental region for both episodic memory and spatial navigation in the human brain. Tavares et al., 2015 found that the human hippocampus also represents social interactions as a map of 'social space', measured by power and affiliation relative to an individual's social positioning. To understand how this neural mechanism relates to known cognitive functions, we looked at relationships between spatial reasoning ability, stress sensitivity, and hippocampal activity during social interactions.

Methods: Perceived stress and spatial IQ were quantified using self-report questionnaires, and correlation analyses were performed with fMRI data from 18 subjects who undertook a social game task (Tavares et al., 2015).

Results/Conclusion: Social performance measured by hippocampal activity showed a negative correlation with perceived stress. Surprisingly, this same measure was not correlated with spatial IQ. We also found no significant correlation between perceived stress and activity of the posterior cingulate cortex (PCC), which represents social distance in the same fMRI paradigm. These findings point to a potential mechanism by which stress may influence social functioning.

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Verbal memory deficits in bipolar disorder.

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Background: Verbal memory (VM) is a consistently-large cognitive deficit shown in bipolar disorder (BD) that is linked to poorer outcomes. Despite its importance, past studies have found mixed **Results** regarding VM intricacies, leading some to propose learning strategies may account for VM deficits. Better understanding intricacies of VM deficits and the role of learning strategies could help pinpoint where VM breaks down and inform cognitive remediation targets. This study compared VM in BD and healthy control (HC) samples, controlling for demographic and illness characteristics. We also examined whether learning strategies mediated relations between diagnosis and VM.

Methods: We assessed VM in 113 affectively-stable BD patients and 106 HC participants. We compared BD and HC on VM intricacies including attention, learning, memory, and learning strategy domains, while controlling for demographics, premorbid IQ, lifetime mood episodes, and current bipolar symptoms.

Results: BD performed significantly worse on attention, learning, memory and learning strategies. However, except for learning strategies, BD patients' poorer performance fell within normal limits (< -1 SD). Further, learning strategies significantly mediated relations between diagnosis (HC vs. BD) and VM.

Conclusion: Results suggest VM deficits are related to inadequate use of learning strategies and cognitive remediation efforts in BD should focus on teaching and practicing these strategies.

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Efficient Cas9-mediated induction of neuronal differentiation of human induced pluripotent stem cells

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Background: Studying how cells of the nervous system develop is crucial to understanding normal brain development and how it goes awry in disease conditions. The generation of hIPSCs from somatic cells has enhanced the study of brain development by allowing modeling of normal development and human diseases in vitro using hIPSC-derived neural cells from healthy individuals and patients. Current Methods for generating neural cells from hIPSCs are cumbersome and involves introduction of exogenous transcription factors. Our goal is to develop and validate a programmable and multiplex-able system for inducing expression of gene targets within their indigenous chromosomal **Background** in order to efficiently generate specific neural cell types.

Methods: Using a nuclease-null CRISPR/Cas9- protein fused to transcriptional activation domains, we are inducing expression of transcription factors essential for differentiation of neural cells into specific lineages. Starting with hIPSCs derived from healthy individuals, we are generating glutamatergic, GABAergic and dopaminergic neurons by CRISPR/Cas9-induced expression of transcription factors already published for these cell types.

Results/Conclusion: We demonstrate that CRISPR/Cas9 technology provides a programmable and rapid method for inducing gene expression and generation of neural cell types. Using this method, we can rapidly and efficiently direct the differentiation of hIPSCs and delineate transcription networks necessary for defining specific hIPSC differentiation choices.

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Abstracts

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Differentiation of basal forebrain cholinergic neurons from iPSCs harboring familial Alzheimer's mutation PSEN2N141I

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Background: Mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the amyloid precursor protein (APP) are associated with autosomal dominant, early onset familial AD.

Methods: We have optimized an in vitro protocol to generate human basal forebrain cholinergic neurons (BFCNs) from iPSCs. Our immediate goal is to characterize BFCNs and intermediate neural progenitors (NPCs) differentiated from iPSC reprogrammed from skin cells of subjects affected by PSEN2 N141I mutation and controls. After induction of BFCN differentiation, we have analyzed: (1)rates of cell death; (2)capacity to generate Tuj1+/FOXG1+/ChAT+ neurons in vitro; (3)expression of genes/proteins of interest related to neuronal differentiation or inflammation; and (4)generation of soluble and oligomeric Aβ40/42.

Results/Conclusion: We have found potential alterations in the inflammatory apparatus of PSEN2 mutant NPCs and we are currently characterizing the pathways implicated. Our ultimate goal is to employ the molecular, transcriptomic, and electrophysiological properties of these cells in the development of novel diagnostics and/or therapeutics for AD.

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The Effects of Cigarette Smoking Behavior and Psychosis History on General and Social Cognition in Bipolar Disorder.

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Background: Several studies have documented the prevalence and effects of cigarette-smoking on cognition in psychosis disorders; fewer have focused on bipolar disorder (BD). The current study assessed the influence of cigarette smoking on general and social cognition in a BD cohort, accounting for illness features with a focus on psychosis history.

Methods: We assessed smoking status in 105 euthymic BD patients, who completed a comprehensive battery including both social and general cognitive measures. We compared smokers vs. non-smokers on cognitive performance and tested for effects of psychosis history, premorbid intellectual functioning, substance use, and current affective symptoms.

Results: Within the BD non-psychotic subgroup (n = 45), smokers generally outperformed non-smokers; in contrast, for BD subjects with a history of psychosis (n = 41), non-smokers outperformed smokers. This pattern was noted more globally using a general composite cognitive score and on social/affective measures assessing patients' ability to identify emotions of facial stimuli and solve emotional problems.

Conclusion: These **Results** suggest there may be at least partially divergent underlying neurobiological causes for cognitive dysfunction in BD patients with and without psychosis in relation to cigarette-smoking behavior.

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The mGluR2 receptor antagonist BCI-838 reverses anxiety-related behavioral traits in a rat model of blast-related mTBI.

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Background: Blast-related mild traumatic brain injury (mTBI) has been common in the recent conflicts in Iraq and Afghanistan. We previously showed that rats subjected to repetitive low-level blast exposure displayed anxiety-related behavioral traits that were present many months after blast exposure validate like post-traumatic stress disorder (PTSD) model. Pharmacological inhibition of the mGluR2 receptor with BCI-838 has shown pro-neurogenic, pro-cognitive, and anxiolytic/anti-depressant effects in rodents. The aim of this study was to investigate whether administration of BCI-838 could enhance brain function and reverse anxiety/stress related behaviors in a rat model of blast-related mTBI.

Methods: Rats were subjected to three 75 kPa blast exposures while under anesthesia following which they were treated daily with BCI-838 during a 2-months and tested on a variety of cognitive and anxiety/stress related behavioral tasks.

Results: BCI-838 did not affect cognitive performance in novel object recognition. However BCI-838 reversed anxiety in the open field, light/dark escape and zero maze compared to controls.

Conclusions: BCI-838 reverted anxiety-related behaviors in a rat model of blast-related mTBI and could represent a potential pharmacological therapy for veterans suffering PTSD symptoms following blast-related mTBI.

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Role of leukocyte-derived microRNAs in stress-induced inflammation and depression

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Background: We have previously identified inflammatory status as an important mediator of behavioral response to repeated social defeat stress (RSDS), a paradigm that produces susceptible and resilient phenotypes. As microRNAs (miRs) are important regulators of inflammation, we sought to examine their role in mediating inflammatory and behavioral response to RSDS.

Methods: Mouse blood was collected following RSDS and leukocyte populations were isolated via fluorescence-activated cell sorting. Leukocyte miR and mRNA expression was profiled via quantitative real time PCR. miR-25 knock out (KO) bone marrow chimeric mice were generated and subjected to RSDS.

Results: We find that, in both susceptible and resilient mice, RSDS produces an increase in circulating neutrophils coupled with a decrease in B cells. T cells and Ly6chigh monocytes are selectively decreased and increased, respectively, only in susceptible mice. Within the Ly6chigh monocyte cell population, several miRs are differentially regulated in susceptible and resilient mice. miR-25, a miR with known roles in inflammatory signaling and myelopoiesis, is upregulated in susceptible mice. Mir-25 KO chimeric mice display enhanced behavioral resilience.

Conclusions: Our **Results** suggest a role for miRs as regulators of stress-induced inflammation and depression, and identify miR-25 as a novel potential therapeutic.

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Exploring the 3D landscape of chromatin across neural differentiation

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Background: The human genome has traditionally been studied as a linear entity, ignoring how three-dimensional looping interactions that bring together distal non-coding regulatory elements and proximal promoters may modulate gene expression. Even with innovations in chromosome conformation capture techniques, the 3D neuroepigenome remains largely underexplored. By identifying cell-type-specific chromatin architectural changes, we may be able to better elucidate the hitherto unknown roles of non-coding variation in the risk for psychiatric disorders.

Methods: In situ Hi-C is performed on human induced pluripotent stem cell-derived neural progenitor cells, glutamatergic neurons, and astrocytes, owing to the difficulties in obtaining sufficient amounts of genetically matched, pure populations of these cell types from postmortem tissue. Briefly, in situ Hi-C involves crosslinking chromatin within intact nuclei, genome-wide restriction, biotinylation of cut ends, and re-ligation, thereby capturing physical interactions between distant genomic loci and creating “chimeric” fragments. Subsequently, the samples undergo library preparation and are paired-end sequenced on the Illumina MiSeq and HiSeq platforms. The data are processed bioinformatically to arrive at contact maps.

Results/Conclusion: First, by comparing an experimental sample to one that lacks the crucial ligation step, we show a drastically reduced number of chimeric reads and a contact-depleted map in the negative control. Second, even with low read counts (5-8 million/sample) cell-type-specific interaction domains are beginning to emerge.

Funding: NIH

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Cell-type specific total transcriptome, connectome, and function of nucleus accumbens somatostatin interneurons reveals multi-scale regulation of sensitivity to cocaine

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Background: Forebrain Somatostatin Interneuron (SstIN) loss has been observed in post-mortem brains of people with psychiatric diseases ranging from depression and bipolar disorder to Alzheimer's. In the last decade, the role of SstINs in cortex and hippocampus has been well established and highlights the profound impact a small population of interneurons can have on the plasticity of neural circuits. However, little is known about the role of SstINs in the Nucleus Accumbens (NAc) or in substance abuse disorders. Since SstINs in the NAc have the same embryonic origin as cortical and hippocampal SstINs, the MGE, we hypothesized that these cells play a critical role in regulating plasticity underlying NAc dependent, cocaine-evoked behaviors.

Methods: We employed a cell-type specific, multi-scale approach to characterize NAc SstINs in vivo. First, we used FACs combined with next-generation RNA sequencing and sequenced the total transcriptome of NAc SstINs from individual SstIN reporter mice after I.P. cocaine. Next, we used a novel modified conditional alphaherpes virus to perform retrograde circuit tracing and label the afferent connectome of Nac SstINs. Finally, we used optogenetics to determine the functional role of NAc SstINs during cocaine locomotor and CPP testing.

Results/Conclusion: Our experiments identify cell-type specific genome wide transcriptional changes induced by cocaine and provide a circuit based mechanism for the function of NAc SstINs at the micro- and mesoscales in vivo.

Funding: NIDA, NIMH

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Sorting Nexin 27 in midbrain dopamine neurons regulates addictive behavior

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Background: G-protein gated inwardly-rectifying potassium (GIRK) channels activated by GABA-B receptors mediate a slow inhibitory postsynaptic current (sIPSC) that profoundly influences neuronal firing. However, the role of GIRK channels in psychostimulant abuse is poorly characterized. Sorting Nexin 27 (SNX27) is an adaptor protein that maintains surface expression of GIRK channels in VTA dopamine (DA) neurons, and SNX27 knockout from DA neurons increases acute locomotor response to a single dose of cocaine. Here, we hypothesized that SNX27 knockout in DA neurons will enhance locomotor sensitization to chronic cocaine. We also compared the effect of the SNX27 knockout on GABA-B-GIRK currents in SNc and VTA DA neurons.

Methods: Mice lacking SNX27 in DA neurons (SNX27_TH_KO) were tested for locomotor sensitization to IP 3.75 mg/kg cocaine. AAV5.EF1a.DIO.eYFP virus was injected into the dorsal striatum (DS) or nucleus accumbens (NAc) of SNX27_DA_KO and control mice, and whole-cell patch-clamp recordings were obtained from eYFP-positive VTA DA neurons.

Results/Conclusion: SNX27_TH_KO mice exhibited locomotor sensitization at a dose of cocaine (3.75 mg/kg) that failed to elicit sensitization in control mice, suggesting enhanced sensitization. Furthermore, GABA-B-GIRK currents were reduced in both VTA DA and SNc neurons in SNX27_DA_KO. Thus, SNX27 regulation of GABAB-GIRK currents in DA neurons plays a critical role in the behavioral response to chronic cocaine.

Funding: NIH

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Nicotinic Activation of Somatostatin Inhibitory Neurons by Lypd6-nAChR□2 System Restores Cortical Plasticity in Adulthood

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Background: Experience-dependent cortical plasticity declines into adulthood, posing a challenge for recovery of function. While the role of Parvalbumin (PV)-interneurons on plasticity has been extensively studied, contributions of other GABAergic neurons such as those expressing somatostatin (SST) had largely been ignored. Here we aimed to identify the first SST-based molecular and circuit mechanisms of plasticity. Neuromodulation of SST-interneurons by nicotinic signaling may represent one such mechanism. We tested the role of Lypd6, an endogenous positive nicotinic modulator enriched in SST-cells, on adult visual cortex plasticity.

Methods: Cell-type specific viral manipulations of Lypd6 gene expression and chemgeentic modulation of neuronal activity were coupled with in vivo extracellular electrophysiological recordings to assess cortical plasticity.

Results: Lypd6 decreases its expression in adult primary visual cortex in concert with declining ocular dominance plasticity. Viral overexpression of Lypd6 specifically in adult SST cells reactivated plasticity through the □2 nicotinic acetylcholine receptor by increasing SST interneuron activity, which in turn inhibited PV interneurons – a key early trigger-like event of plasticity in the juvenile cortex. Lypd6-based plasticity was normalized by chemogenetic activation of PV-interneurons, highlighting a key role of SST->PV disynaptic inhibitory circuits.

Conclusion: Identification of the first SST- and nAChRα2-specific plasticity regulator provides novel therapeutic targets for disorders with limited recovery due to diminished plasticity and psychiatric disorders with SST interneuron-deficits.

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Diffusion Kurtosis Imaging of white matter (WM) damage progression in Primary Progressive Multiple Sclerosis (PPMS)

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Background: Diffuse WM injury is prominent in PPMS pathology and is a potential biomarker of disease progression. DKI allows the quantification of non-Gaussian water diffusion, offering more detailed characterization of WM damage, in comparison with traditional diffusion tensor imaging (DTI) metrics (fractional anisotropy (FA) and mean diffusivity (MD)).

Methods: PPMS patients (N=20) underwent two MRI (3.0T) sessions one year apart, including T1-weighted and DKI scans. DKI was pre-processed using DKE and Tract-Based Spatial Statistics using FSL. Voxelwise nonparametric permutation inference tests corrected for sex and age were used to compare baseline and follow-up diffusion metrics in whole-brain WM tracts.

Results/Conclusion: Although no differences were found between baseline and follow-up in FA or MD, mean kurtosis (deviation from Gaussian behavior in all directions) and axonal water fraction (ratio of intra-axonal water over total water) were significantly reduced at follow-up in the corpus callosum and anterior thalamic radiation. DKI of the WM was able to capture a subtle reduction in myelin density and axonal loss, undetected by conventional DTI metrics, suggesting higher sensitivity and specificity of DKI in assessing diffuse tissue damage

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Experience-dependent survival of pre-existing new spine is gated by Lynx1

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Background: Newly formed spines usually retract within days without transforming into stable spines. However, to what extent genetic and environmental factors regulate this key process is totally unknown. Identification of mechanisms that gate the conversion of new spines into stable spines would provide conceptually novel strategy for restoring function. Here we examined to what extent exposure to new experience impacts the survival of pre-existing new spines and whether Lynx1, a nicotinic brake for functional plasticity, modulate this key process.

Methods: By chronic two-photon imaging in vivo, we observed spine turnover of apical dendrites of layer5 pyramidal neurons in adult visual cortex of Lynx1 knockout mice mated with Thy1-GFPM-line.

Results: In adult Lynx1 knock-out mice, visual deprivation elevated the survival rate of pre-existing young spines formed within 4 days prior to deprivation, but not in WT matched controls. This effect was specific to pre-existing new spines but not observed in spines newly formed during deprivation. Finally, functional properties of survived spines are determined by establishing the first simultaneous time-lapse structural and functional imaging at the single spine levels in vivo.

Conclusions: Our study revealed new spines just formed before the exposure to new experience as key substrates for circuit plasticity, and Lynx1 as the first modulator of experience-dependent survival of pre-existing new spines.

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Deciphering the Functional Effects of Parkinsonism-Causing Genes in the Zebrafish Nervous Model Systems

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Background: The aim of this study is to investigate the normal and aberrant function of PLA2G6 and SYNJ1 genes, mutations of which cause recessive complex Parkinsonism, in the zebrafish neural development. Tl and Tg(olig2:EGFP) zebrafish lines are used for this purpose.

Methods: First, gene expression is examined through both qPCR and WISH. Second, genes are downregulated through Morpholino (MO) and CRISPR/Cas9 techniques, and rescue experiments are carried out by co-injecting MOs and human mRNAs. Third, movement and morphology of zebrafish embryos and affected neurons are determined by microscopic imaging and immunohistochemistry. Lastly, RNA-seq is used to determine the transcritome-wide changes and pathway and network enrichment analyses are carried out for a deeper understanding of the biology underlying disease.

Results: We have successfully downregulated the expression of both zPLA2G6 and zSYNJ1 genes and have recovered the morphological phenotypes and gene expression changes through rescue experiments. We have observed dopaminergic cell loss, loss and altered localization of motor neurons, widespread axonal loss, and defasciculation of neurons in the trigeminal ganglion in morphants when compared to wild-type embryos. In addition, we have identified several genes implicated in PD pathophysiology, unregulated in zPLA2G6 morphants.
Conclusion, our work suggests an important role of these genes in the development of the central nervous system.

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DANTE-EPI for CSF Suppression in Cervical Spinal Cord BOLD fMRI at 7T

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Background: A major challenge in spinal cord fMRI is physiological noise due to pulsating CSF, which confounds detection of BOLD signal. In this work, we adapt DANTE to reduce CSF signal contamination in spinal cord BOLD fMRI at 7T.

Methods: The DANTE MRI method consists of a train of low-flip angle RF pulses interleaved with gradient pulses, resulting in suppression of moving spins. In this work, DANTE is combined with an echo-planar imaging (EPI) sequence and applied to the cervical spinal cord at 7T.

Results: DANTE with 250 pulses at 15° achieves 95% suppression of CSF signal, while more conservative 150x15° and 150x10° yield 92% and 80% suppression, respectively. These three DANTE conditions, however, result in attenuation of signal in the spinal cord by 42%, 34%, and 26%, respectively. Temporal cross-correlation of resting-state signal in the bilateral spinal cord gray matter improves from r=0.25 (without DANTE) to r=0.80-0.90 (with DANTE).

Conclusions: DANTE prepared EPI with CSF-attenuation/suppression is a promising spinal cord BOLD fMRI acquisition technique at ultra-high field.

Funding: RSNA, NMSS, NIH.

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Rapid Ngn2-induction of excitatory neurons from hiPSC-derived neural progenitor cells

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Background: Human induced pluripotent stem cells (hiPSCs) have been widely utilized in modeling diverse neurological disease and psychiatric disorders. As hiPSCs produce almost endless number of patient-derived neurons that retain the genetic variations potentially attributed to disease etiology, they have been a promising patient-specific platform for high throughput drug screening. However, the use of currently available protocols for obtaining hiPSC-derived neurons is still limited by long-term differentiation timelines and heterogeneous neuronal phenotypes. Neuronal induction, via the exogenous expression of pro-neural transcription factors, has recently proven to rapidly induce functional neurons with high purity from fibroblasts and hiPSCs.

Method: We adapted Neurogenin 2 (Ngn2)-neuronal induction protocol to lentivirally transduce Ngn2 in hiPSC-derived neural progenitor cells (NPCs) and carried out molecular, imaging and neuronal activity analyses.

Result: Transduction of Ngn2 in hiPSC-NPCs accelerates neuronal morphology, synaptic differentiation and neuronal activity. Also, transient Ngn2 expression is sufficient to generate induced-neurons.

Conclusion: Ngn2-neuronal induction accelerates maturation of functional excitatory neurons from hiPSC-NPCs.

Funding: This research is conducted and supported by NIH funding.

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Reliability of Detection of Intracranial Hemorrhage After Endovascular Intervention for Acute Stroke

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Background: Intravenous and intra-arterial reperfusion therapy in ischemic stroke are associated with increased hemorrhage risk. CT scan of the head is routinely performed post-reperfusion, in part to identify such hemorrhage. Distinction between hemorrhage and extravasated contrast on CT can be challenging and diagnostic accuracy is not well-defined.

Methods: Post-procedural imaging and clinical outcomes for 45 endovascular cases at Mount Sinai Hospital between January 1 and September 30, 2015 were reviewed. Interpretation of initial CT scan by a board-certified staff neuroradiologist was compared with the final clinical impression.

Results: 34 patients had CT as the first imaging study. Of these 34 patients, 16 (47%) exhibited hyperdensity. Neuroradiologist interpretation was concordant with final diagnosis in 10 cases (62.5%).
A discordant/uncertain radiologic diagnosis was provided in 6 patients (37.5%): 1 patient (6%) was incorrectly diagnosed with a hemorrhage, and in 5 patients (31%) a diagnosis of hemorrhage vs. contrast could not be provided.

Conclusions: Hyperdensity is frequently seen on CT post-endovascular intervention. This imaging differentiates hemorrhage from contrast in 62.5% of patients.

Funding: None

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Amygdala lesions alter value-related local field responses in orbital and medial Prefrontal Regions

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Background: Reward-guided behaviors require functional interactions between the amygdala and the prefrontal cortex, specifically orbital (OFC) and medial (MFC) divisions. Lesions of the amygdala attenuate reward-value signals of individual neurons recorded from the OFC, but not the MFC (Rudebeck et al., 2013, Neuron). However, single neurons activity only reflect the local processing of an area and a more complete understanding of this network could take advantage of considering population-level activity using local field potentials (LFPs).

Methods: Using both classical and SVM decoding methods, we analyzed LFPs recorded from both OFC and MFC of monkeys engaged in a stimulus-choice task, before and after excitotoxic lesions of the amygdala.

Results/Conclusion: Visual stimuli associated with different reward amounts evoke a response (ERP) in the LFP in both the OFC and the MFC, but the encoding of reward values, in relation to decisions that monkeys made, was mostly observed in the OFC. Synchronization in the gamma band also encoded reward value in the OFC. Following bilateral lesions of the amygdala, both ERP and gamma responses decreased. Spike synchrony in gamma was also altered. These analyses reveal that loss of amygdala input to the OFC/MFC alter both local processing and the overall communication between prefrontal regions.

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The role of central interleukin 1 on individual difference of aggressive behavior

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Background: There are large individual differences in aggressive behavior within a same species; some animals show intensive aggressive behavior during the agonistic confrontations (aggressor) but some rarely show aggressive behavior (non-aggressor). In this study, we aimed to study the neurobiological mechanism of individual difference of aggression, especially focusing on the role of immune system.

Method: Aggressive behavior of CD-1 males toward BALB/c intruder males were characterized by resident-intruder test for 3 days to define aggressors and non-aggressors. Peripheral and central cytokine/chemokine levels were measured from either blood or micropunched brain samples by ELISA. Intracranial drug microinjection was conducted 10 min before the aggressive encounter.

Results: Aggressive encounter caused a phasic increase of interleukin 1 beta (IL-1b) in the blood in both aggressors and non-aggressors, and there was no difference between groups. By contrast, IL-1b level in the midbrain, dorsal raphe nucleus (DRN), was higher in non-aggressors than aggressors. Also, higher expression of receptors for IL-1b was observed in non-aggressors. We found that both intracerebroventricular (i.c.v.) injection and intra-DRN microinjection of interleukin 1 receptor antagonist increased aggressive behavior.

Conclusion: Our data indicate that IL-1 receptor mediated pathway in the DRN has role on aggressive behavior.

Funding: NIMH

69

A circuit level approach to prefrontal-limbic interactions in positive affect.

Sarita Tamang, Clayton Mosher, and Peter H. Rudebeck

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Background: Anhedonia, characterized by loss of positive affect from pleasurable events such as rewards, is a defining symptom of depression. Current theories emphasize that anhedonia effects pleasure from both anticipation and receipt of rewards. Studies of monkeys with lesions of subcallosal anterior cingulate (sACC) indicate that this area is important for sustaining arousal in anticipation, but not the receipt, of rewards. sACC projects to both the ventral striatum (VS) and amygdala indicating that these areas form a circuit, but it is unclear how these areas interact functionally. Our goal here is therefore to determine the dynamics of sACC-amygdala-VS circuit during reward anticipation and receipt.

Methods: We are recording behavior, autonomic responses, and neural activity in sACC, VS, and amygdala in monkeys during Pavlovian and instrumental trace conditioning tasks, designed to dissociate reward anticipation from receipt.

Results: Monkeys showed elevated behavioral (anticipatory licking) and autonomic (pupil size) responses in anticipation of rewards. They are modulated by their subjective preference for the different fluid rewards offered. Single neuron activity and local field potentials reveal that neurons in sACC and amygdala encode animal's preferences, while neurons in VS simply encode presence or absence of rewards. Furthermore sACC and amygdala neurons encode anticipated rewards when no predictive stimuli are present, i.e. during trace intervals.

Funding: NARSAD Young Investigator Award and ISMMS seed funds.

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How social navigation in the human brain shapes social dysfunction

Rita M. Tavares, Qi Lin, Avi Mendelsohn, Daniela Schiller

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Background: Distinct psychiatric diagnoses involve distinct sets of symptoms. However, social dysfunction is prevalent across disorders. Could there be a common neural origin to some of these downstream effects? Abnormalities in networks involving the hippocampus and the precuneus are prevalent in diseases as distinct as mood and personality disorders. We previously identified a neural network that encoded a geometric representation of social space. The fidelity of this representation in the hippocampus predicted lower social avoidance and neuroticism in healthy participants. We also identified a representation of social distance in the precuneus; the accuracy of this representation was correlated with more exploration of social space. Could these mechanisms play a role in psychiatric disorders and explain symptom severity and phenotypes related to social functioning?

Methods: We developed a social game where we quantify social interactions and uncover their neural correlates. In this fMRI paradigm, participants take the lead role and choose how to interact with cartoon characters. We then quantify their choices and plot each character's trajectory in a two-dimensional social map.

Results / Conclusions: We collected preliminary data in a set of patients. We expect that by quantifying social behavior we will be successful in identifying some of the neural and cognitive underpinnings of social dysfunction.

Funding: Klingenstein-Simons Foundation, NIH.

71

Genetic engineering of human glioma cells for Histone2B-GFP labeling with CRISPR/Cas9 technology:

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Background: Glioblastoma (GBM) is the most common malignant brain tumor with a dismal prognosis of less than 2-year median survival. Advances in culture methods have enabled us to establish patient-derived glioma stem cell (GSC) lines that faithfully preserve genomic and physiologic characteristics of GBM.
The CRISPR/Cas technology is ideally suited for genetic engineering of human cells. I am applying CRISPR to target a doxycycline inducible histone-2B-GFP (H2B-GFP) labeling system to the AAVS1 locus, a "safe harbor" for transgene insertions into the human genome. The H2B-GFP labeled GSC will allow me to isolate quiescent glioma cells (which do not dilute the H2B-GFP label) and to characterize their cancer stem cell properties.

Methods: GSC were transfected with three plasmids: A) targeting vector with Tet-ON transactivator M2rtTA; B) targeting vector with tetO-H2B-GFP; C) plasmid expressing Cas9/sgRNA targeting AAVS1. Cells that have integrated both vectors were isolated by Puromycin and Neomycin double-selection. Insertions were confirmed by PCR over 5' and 3' arms.

Results/Conclusion: I am in the process of establishing 4 different H2B-GFP GSC lines. Until now, one of the cell lines has integrated M2rtTa and H2B-GFP in the designed region. In summary, the CRISP/Cas9 system is an efficient method to modify the genome of patient derived cancer cells.

Funding: NIH R21 NS085466

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**EGFR Expression Defines Epigenetically Imprinted Stem Cell Properties
In Human Germinal Matrix and Glioblastoma**

Jessica Tome-Garcia[1,2], Rut Tejero[2], German Nudelman[3], Elena Zaslavsky[3], Raymund L. Yong[4], Robert Sebra[5], Martin Walsh[5], Roland H. Friedel[2], Fiona Doetsch[6], Nadejda M. Tsankova[1,2]

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Background: Increasing evidence implicates neural stem cells (NSC) for the cellular origin of glioblastoma, but the mechanisms of their malignant transformation remain unclear. Signaling through the epidermal growth factor receptor (EGFR) is one of the main pathways controlling NSC proliferation and differentiation. We and others have shown that its dysregulation is involved in glioma potency, although no studies so far have integrated the functional stem cell properties of human EGFR+ cells in brain development and gliomagenesis.

Methods: We performed unique isolation of EGFR+ cells from fresh human germinal matrix and glioblastoma tissues, based on their ability to bind their cognate EGF ligand, and characterized for the first time their downstream functional and molecular properties ex vivo.

Results/Conclusions: The expression of intact EGFR distinguishes a population of NSC and glioblastoma cells with exclusive stem cell properties. Interestingly, developing and neoplastic EGFR+ cells share a unique epigenetic landscape and transcriptional signatures that confer their stem cell properties, which may have important translational implications for future GBM cancer stem cell therapies.

Funding: Mount Sinai Seed Fund

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Experimental investigation of schizophrenia eQTL hits using CRISPR in cerebral organoids

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Background: The CommonMind Consortium(CMC) recently leveraged RNA-sequencing performed on samples from the dorsolateral prefrontal cortex of 258 schizophrenia (SZ) patient and 279 control subjects with genome-wide association data from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) to identify five schizophrenia risk loci which modulate the expression of single genes. Specifically, we will focus on the SZ risk locus on chromosome 15 which includes the single nucleotide polymorphism (SNP) rs4702 and which is associated with modulated expression levels of the gene FURIN. FURIN is a paired basic amino acid cleaving enzyme which is required for processing of pro-BDNF to BDNF in astrocytes.

Methods: HiPSC-derived cerebral organoids are a previously established model of early cortical development. In these organoids we will utilize CRISPR/Cas9 based genome editing at the SZ risk locus to investigate the genetic modulation of FURIN expression in human neural tissue in vitro determined by the eQTL analysis in addition to using a nuclease-null Cas9(dCas9) to perform CRISPR interference (CRISPRi) to knock-down FURIN expression in order to investigate how modulated gene expression affects neurodevelopmental phenotypes.

Results/Conclusions: In an assay of neural migration based on migration of hiPSC-derived neural progenitor cells (NPCs) away from an neurosphere composed of NPCs, knockdown of FURIN expression using a virally delivered shRNA significantly decreased neural migration relative to control.

Funding: NIH, NYSCF

74

PRC2 couples neuronal identity with survival in the adult brain

Melanie von Schimmelmann[1], Philip Feinberg[1], Josefa Sullivan[1], Stacy M. Ku[1,2], Ana Badimon[1], Ming-Hu Han[1,2], Alexander Tarakhovsky[3], Anne Schaefer[1]*

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Background: Understanding the mechanisms that protect neurons against degeneration is significant for the prevention and treatment of neurodegenerative diseases in humans. The Polycomb repressive complex 2 (PRC2) contributes to neuronal differentiation and the establishment of neuron-type specific gene expression patterns during development. We found that PRC2 plays an essential role in the maintenance of postnatal neuronal specialization by coupling neuronal identity to survival in the adult brain.

Methods: We used a neuron-specific CHIP sequencing approach to identify PRC2 target genes in adult striatal neurons in mice. We employed a genetic approach for postnatal neuron-specific ablation of PRC2. Gene expression was analyzed using microarray and striatal neuron-specific TRAP sequencing technologies, and MSN electrophysiological properties and associated behavior was assessed.

Results/Conclusion: We found that PRC2 protects neurons against progressive neurodegeneration. Deficiency of PRC2 in adult neurons abolishes their functional specification and leads to the activation of PRC2 controlled death-inducing genes. These changes in neuronal cell identity and survival lead to the development of fatal Huntington's- or Friedreich ataxia-like neurodegenerative disorders in mice.

Funding: National Institutes of Health (NIH), CURE Challenge Award, the Seaver Autism Center, and NARSAD.

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Cerebral organoids as a method for characterizing 16p11.2 in Childhood Onset Schizophrenia derived iPSCs

Melanie Williams[1], Brigham J. Hartley[1], Kristen Brennand[1, 2]

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Background: CNVs at 16p11.2 are frequently associated with neurodevelopmental diseases. Current evidence has shown that deletions are associated with macrocephaly and an increased risk of developing Autism Spectrum Disorder (ASD), while duplications are associated with microcephaly, ASD, and schizophrenia. Animal models display dosage-dependent changes. In zebrafish models KCTD13 is a major driver of head size associated with 16p11.2. Furthermore, mouse models show differences in gene expression, brain architecture, behavior. Cerebral organoid generation resembles endogenous developmental program. Multilayered aggregates mimic in vivo cytoarchitectural organization and the transcriptional profile of organoids typically reflects fetal cortical development. Several lines of research have shown that organoids can successfully model neurodevelopmental disease phenotypes. We have developed a modified approach to cerebral organoid development that generates embryoid bodies of uniform size, that mimic the in vivo cytoarchitechture for the characterization of the 16p11.2 CNV in childhood onset schizophrenia derived iPSCs.

Methods: In order to generate our cerebral organoids we have adapted a protocol developed by Mariani, 2015, where we use an Aggrewell 800 plate to generate uniformly sized EBs and inhibit dual-SMAD expression with the small molecules LDN193189, and SB431452. We began our differentiation with human iPSC from 16p11.2 carriers, and non-carrier controls.

Results/Conclusion: With this approach we have successfully generated cerebral organoids for further characterization.

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Locus Coeruleus-Ventral Tegmental Area Neural Circuit Mediates Resilience to Social Stress

Hongxing Zhang, Dipesh Chaudhury, Alexander Nectow, Barbara Juarez, Erin Calipari, Song Zhang, Allyson Friedman, Stacy Ku, Marshall Crumiller, Cheng Jiang, Carole Morel, Nikos Tzavaras, Michelle He, Stephen Salton, Eric Nestler, Jeffrey Friedman, Jun-Li Cao, Ming-Hu Han

Department of Pharmacology and Systems Therapeutics

Background: Ventral tegmental area (VTA) dopamine neurons play a key role in determining susceptibility versus resilience to chronic social defeat stress (CSDS). However, its upstream neural circuit mechanisms remain largely unknown. Locus coeruleus (LC) norepinephrine system is implicated in mediating resilience.

Method: Using circuit-probing electrophysiological, optogenetic and molecular profiling techniques, we investigate the functional role and molecular basis of LC-VTA circuit in mediating stress resilience following CSDS.

Results: Electrophysiological recordings showed a hyperactivity of LC-VTA neurons in the resilient subgroup, while these neurons had control-like firing activity in susceptible mice. Optogenetically increasing the phasic firing of LC-VTA neurons in susceptible mice reversed social avoidance behavior, an effect blocked by antagonizing VTA □1 and □3 adrenoceptors that are highly expressed in VTA-nuclues accumbens (NAc) neurons. Optical activation of LC-VTA neurons also induced resilience-like homeostatic plasticity in VTA-NAc neurons that involved a balance between Ih and K+ channel currents. Furthermore, intra-VTA infusion of these adrenoceptor's agonists in susceptible mice normalized pathological hyperactivity, established the Ih and K+ balance, and reversed social avoidance behavior.

Conclusions: These findings elucidate a norepinephrine circuit as a resilience pathway in the brain, and provide new molecular targets for therapeutically promoting resilience.

Funding: NIMH&NSFC

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Role of Lateral Habenula-Ventral Tegmental Area Circuit in Mediating Susceptibility to Social Defeat Stress

Dipesh Chaudhury*, Hongxing Zhang*, **Song Zhang***, Barbara Juarez, Allyson Friedman, Stacy Ku, Carole Morel, Jun-Li Cao, Ming-Hu Han

Department of Pharmacology and Systems Therapeutics

Background: Lateral habenula (LHb) sends substantial projections to the ventral tegmental area (VTA) and is suggested to mediate depressive behaviors. However, its role in chronic social defeat stress (CSDS) remains unclear.

Method: We took advantage of circuit-probing electrophysiological and optogenetic approaches to study the functional roles of LHb-VTA and VTA-medial prefrontal cortex (mPFC) pathways in mediating susceptibility following CSDS.

Results: Our in vitro slice recordings of LHb-VTA neurons showed robust increase in the firing activity of stress susceptible but not resilient mice when compared to control group. Optigenetically mimicking this firing increase (increasing the firing activity of LHb-VTA neurons) in susceptible mice decreased social interaction time, an effect that was blocked when VTA-mPFC neurons were simultaneously activated. Consistently, in vivo single cell recording showed a significant decrease in firing activity of mPFC neurons following optical activation of LHb-VTA neurons, an inhibitory effect that was blocked by intra-VTA infusion of GABA receptor antagonist GABAzine. Furthermore, optigenetically silencing LHb-VTA neurons rapidly reversed social avoidant behavior.

Conclusions: We present a putative mechanism for susceptibility by which LHb synaptic inputs modulate the inhibitory microcircuitry in the VTA. These findings provide further insight into the roles of LHb-VTA and VTA-mPFC neural circuits in mediating susceptibility to social stress.

Funding: NIMH

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Examining the Effect of Increased EPSCs on the Prevalence of Synapsin I and Phosphorylated Synasin I Proteins in Wild Type and G2019S-Mutant Mouse

Yue Zhong, Benson Neuroscience Lab

Icahn School of Medicine at Mount Sinai

The cause of Parkinson's disease (PD) is largely unknown. However, mutations in the Leucine-Rich Repeat Kinase-2 (LRRK2) are found to be the most common cause of inherited Parkinson's disease. Yet, the pathological function of LRRK2 in inducing the genotypes leading to Parkinson's disease is yet to be determined. The most common LRRK2 mutation is the G2019S mutation, which in some populations such as the North African Berbers accounts for 40% of hereditary PD. The G2019S mutation is found in the kinase domain and this alteration leads to a gain-of-function mutation in which there is an increase in the phosphorylation of other proteins. One protein that is thought to interact with LRRK2 is synapsin I, a presynaptic protein involved in the modulation of the release of neurotransmitters. The G2019S mutation has been found to contribute to abnormal synaptic function. Preliminary data show an increase in the frequency of excitatory postsynaptic currents (EPSCs) in medium spiny neurons of the dorsal striatum in G2019S-mutant mice when compared to wild type (WT) mice. Here, we hypothesize that there is a link between increased EPSCs and the G2019S mutation and that the G2019S mutation may result in altered total synapsin I or phosphosynapsin I protein levels. We will analyze levels via immunohisto-chemistry of striatal sections taken from three WT mice and three mice expressing a knock-in G2019S (GSKI) mutation all of which are 21 days old. Results from the experiment show that the total level of synapsin and phosphorylated synapsin level was not significantly different in the WT vs. the G2019S-mutant mice. This suggests that the G2019S mutation does not lead to an increase in the phosphorylation of synapsin proteins. Therefore, the cause for the increase of EPSC's was not due to the synapsin protein.

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MiNDS: Mentoring in Neuroscience Discovery at Sinai

Ana Badimon, **Carla Golden**, and **Josefa Sullivan**

Icahn School of Medicine at Mount Sinai

Backgrounds: MiNDS is a community volunteer initiative based out of the Icahn School of Medicine at Mount Sinai. Our program strives to make neuroscience education more engaging and accessible to empower and inspire students by extending our resources to local East Harlem schools and community centers. Any Mount Sinai affiliate interested in teaching or volunteering can get involved in multiple ways!

Methods: MiNDS promotes interactive and educational neuroscience experiences through on-site and off-site lessons. Our outreach programs include one-time lessons, a 12-week STEM mentoring program with New York Academy of Sciences, and involvement in Brain Awareness Week.

Results: With the support of the Friedman Brain Institute, the Center for Excellence in Youth Education (CEYE), the New York Academy of Sciences, and the Dana Foundation, over 150 volunteers have reached over 800 budding scientists! Please email MiNDatSinai@gmail.com with any questions or if you would like to get involved.

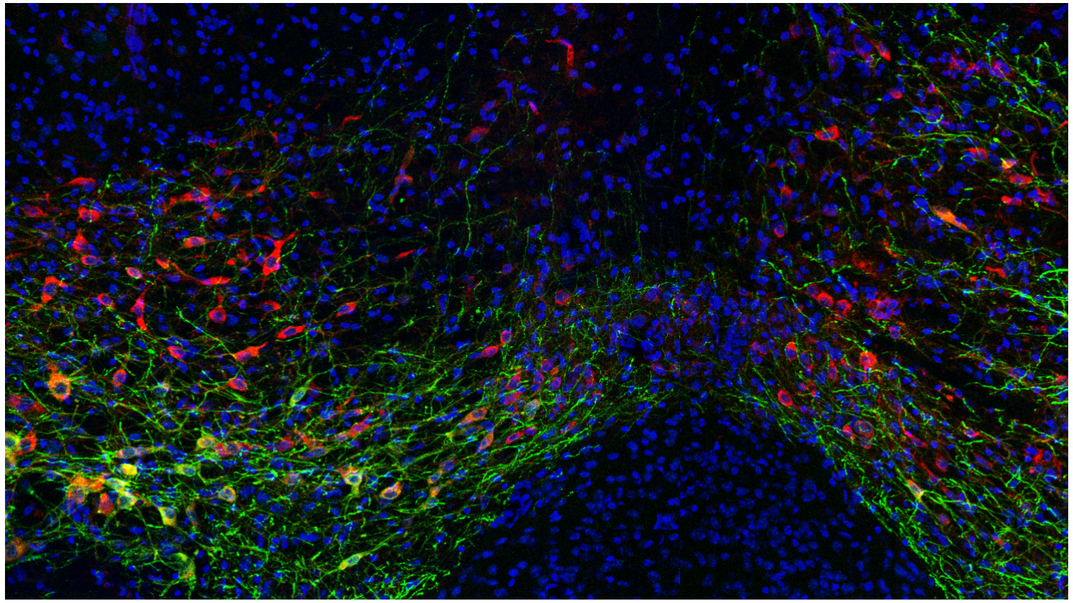


Image by Efrain Ribeiro & Barbara Juarez

Neuroscience Graduate Training Program

Our Neuroscience Graduate Training program finishes another year marked by steady growth in stature and success. With overall numbers of graduate school admissions down at Mount Sinai, and across the country generally, in comparison with previous years, the Neuroscience program this year received a record number of applications. We are excited to welcome 11 outstanding Ph.D students for Fall, 2016 representing a variety of backgrounds and interests. Additionally, we look forward to a number of outstanding MSTP students joining the program, although final numbers have not yet been determined as of this writing. As always, we are especially grateful to the students, postdocs and faculty who helped us in this year's admissions process!

With the new Graduate School leadership in place, we can expect some Institutional changes in the curriculum going forward. A key focus right now is on shortening the amount of time students spend obtaining their Ph.D. The average time to obtain a Ph.D in Sinai's graduate program is about 5.5 years (across all MTAs); at other major institutions, the time is 4.5 - 5.0 yrs. While details are still being worked out, there are plans being discussed to shorten the number and duration of rotations; to accelerate the timeframe in which students chose a thesis lab and complete their thesis proposal; and to reduce Core and other class requirements. In anticipation of these and other changes, a "task force" of Neuroscience faculty and students is currently exploring how we can best streamline our own program with these broad goals in mind. Stay tuned!!

We are launching a 'big-brother/big-sister' program this fall in which we will pair current Ph.D students with incoming newbies. The goal is to ease the transition to graduate school, help navigate courses, rotations and other bureaucratic hurdles, and to facilitate a sense of cohesion across classes. Students that are interested in participating should contact Steve or George.

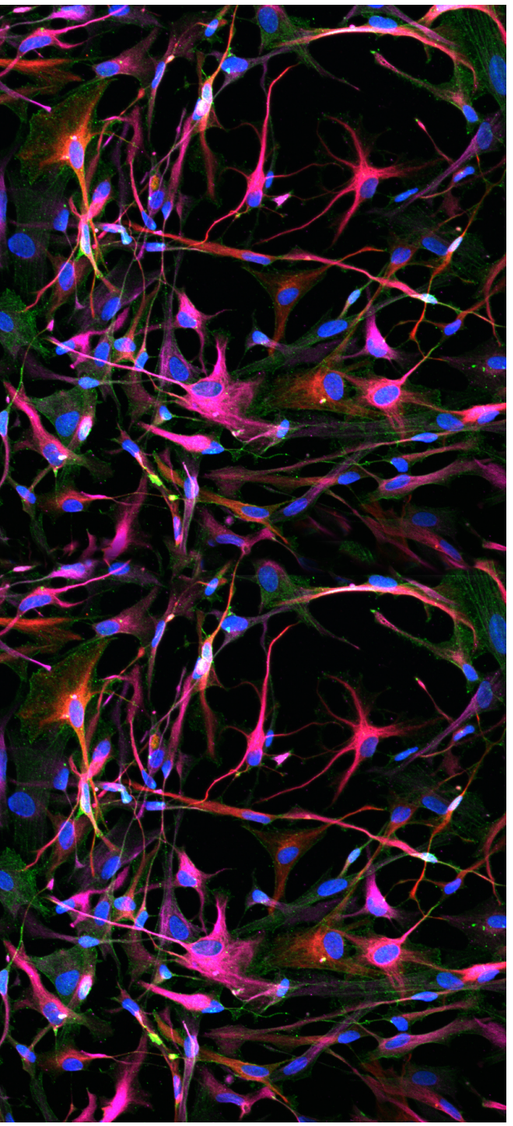
We are also extremely proud of our student- and postdoc-organized (MiNDS) community neuroscience outreach program and Brain Fair, which brings to campus >300 members of the community to explore brain facts and research, and also associated with Brain Awareness Week, our Art of the Brain Exhibition.

Finally, we are particularly proud of our students and postdocs who have successfully obtained their own extramural funding. Additionally, we currently have three T32 training grants (two from the NIMH and one from the NIA), supporting predoctoral and postdoctoral students. As always, in tough financial times, we really need to expand NIH T32 support.

George Huntley and Stephen Salton

Image by Amanda Fakira

2016 UPCOMING EVENTS



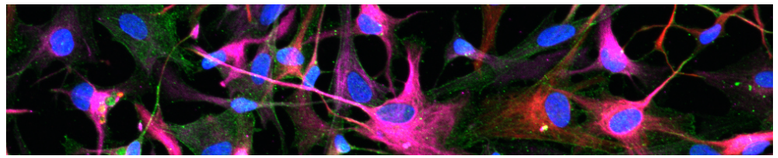


Image by Julia TCW, PhD

AUGUST

Grad School Classes Begin
August 15, 2016 for first year students
August 23, 2016 for returning students

SEPTEMBER

MD/PhD Retreat
September 9-11, 2016

OCTOBER

Society for Neuroscience Meeting
October 2-4, 2016

BIC 3rd Annual Symposium
October 19, 2016

SinaInnovations
October 25-26, 2016 (no classes)

DECEMBER

Grad School Winter Party
December 16, 2016

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

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