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2018 for
the Tenth Annual
Neuroscience
Retreat

The Friedman Brain Institute
and the Neuroscience Training Area

present

the 9th Annual Neuroscience Retreat

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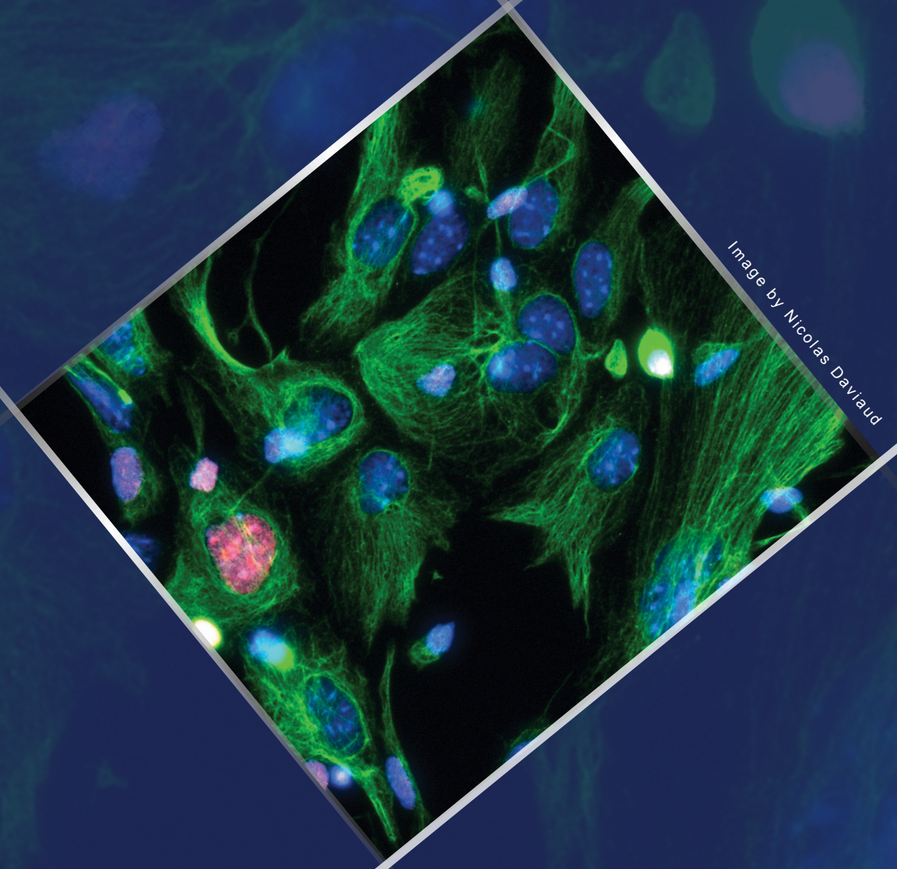

Image by Nicolas Daviaud

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Mount
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THE FRIEDMAN BRAIN INSTITUTE
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9th Annual Neuroscience Retreat Committee

Retreat Organizers:
Panos Roussos, MD, PhD (Genetics and Genomic Sciences and Psychiatry) and **Scott Russo, PhD** (Neuroscience)

Retreat Administrators:
Marie Kopp, Andrea Marie Nievera, Jenny Rivera and Veronica Szarejko

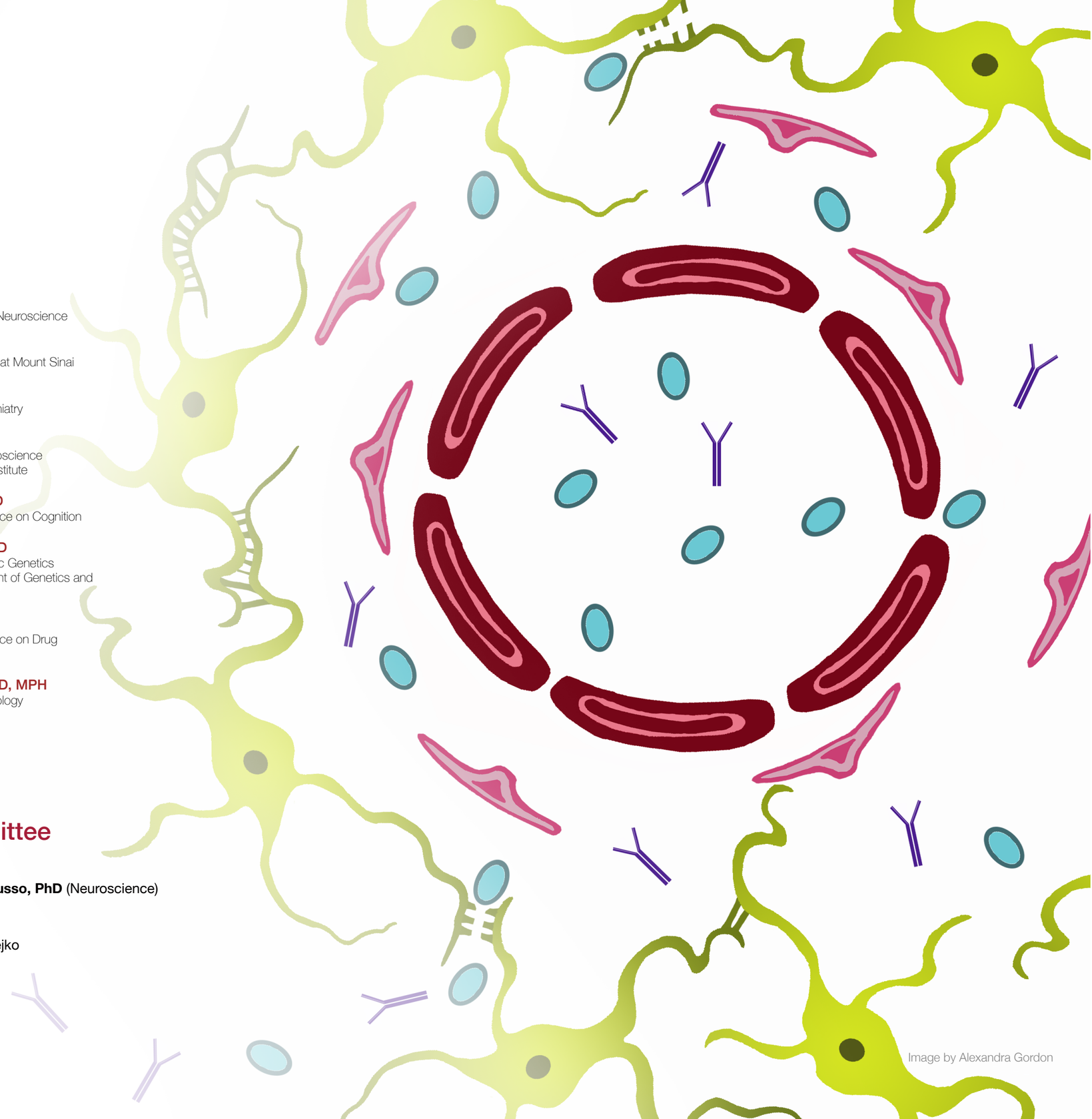

Image by Alexandra Gordon

Image by Mustafa Siddiq

THE FRIEDMAN BRAIN INSTITUTE

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THE FRIEDMAN BRAIN INSTITUTE
AGENDA

REGISTRATION and BREAKFAST

8:45 a.m. — **Sign in and Register** (Lobby)
Breakfast (Room 20, 2nd fl.)

OPENING REMARKS and ANNOUNCEMENTS (Hosack Hall)

9:30 a.m — **Panos Roussos, MD, PhD** (Genetics and Genomic Sciences and Psychiatry)

9:35 a.m — **Eric Nestler, MD, PhD** (Friedman Brain Institute)

10:00 a.m — **George W. Huntley, PhD** (Neuroscience)

10:10 a.m — **Elisa Nabel** (Psychiatry) and **Lucy Bicks** (Neuroscience)
Neuroscience Mentorship Distinction Award (NMDA)

KEYNOTE ADDRESS

10:15 a.m. - 10:50 a.m. — **Paul J. Kenny, PhD** (Chair, Department of Neuroscience)
"Habenula regulation of Nicotine intake:Unexpected links to Diabetes"

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

SESSION ONE

11:10 a.m. — **Moderator- Dani Dumitriu, MD, PhD** (Neuroscience)

11:15a.m. — **Jenny Zou, MD, PhD** (Neuroscience)
"Overcoming intrinsic and extrinsic hurdles of neural repair after injury"

11:30a.m. — **Zachary Lorsch** (Neuroscience)
"CREB-Zfp189 Interactions Regulate a Resilient-Specific Transcriptional Network"

11:45 a.m. — **Josefa Sullivan** (Neuroscience)
"Inhibition of BET-dependent transcription causes an Autism-like disorder in mice."

12:00 a.m. — **Meghan Flanigan** (Neuroscience)
"A lateral habenula microcircuit controlling aggression reward"

12:15 p.m. — **Nick Upright** (Neuroscience)
"Stereological Analysis of DREADD Transduction in Non-Human Primates"

LUNCH

12:30 p.m. - 1:30 p.m. — **Room 20, 2nd floor**

POSTER SET-UP

12:30 p.m. - 2:30 p.m. — **Library, 3rd fl.**

SESSION TWO

1:30 p.m. — **Moderator- Coro Paisan-Ruiz, PhD** (Neurology)

1:35 p.m. — **Emily Stern, PhD** (Psychiatry)
"Measuring and modulating neural mechanisms of sensory phenomena"

1:50 p.m. — **Chloe Solomon** (Translational and Molecular Imaging Institute)
"Taking it to heart: Examining relations between chronic psychological stress, amygdalar activity, and cardiovascular inflammation, using PET/MR imaging

2:05 p.m. — **Anna Zilverstand** (Psychiatry)
"Efficiency in global brain network organization decreases with recency of use incocaine addicted individuals."

2:20 p.m. — **Gabor Egervari** (Psychiatry and Neuroscience)
"Chronic heroin use in humans dysregulates the striatal glutamatergic system and mediates addiction behavior by histone H3 hyperacetylation"

2:35 p.m. — **Garrett Wong** (Neuroscience)
"Genetically regulated transcriptomic study of Parkinson's Disease yields mechanistic insights"

RECEPTION and POSTER SESSION — **Library, 3rd fl.**

3:00 p.m. — **Poster Session and Reception Begin**

3:00 p.m. - 4:30 p.m. — **Poster Session**

4:30 p.m. - 5:20 p.m. — **Music by "The Amygdaloids"**

5:20 p.m. — **Award Ceremony**
Best Poster, Best Oral Presentation, "Call for Images Award" and 2016 BRAIN Award

6:00 p.m. — **Reception Ends**

* NO FOOD OR DRINKS (other than water) ARE ALLOWED IN THE AUDITORIUM

Image from Nicolas Barthelery

Oral Presentations

Zachary Lorsch
Department of Neuroscience

CREB-Zfp189 Interactions Regulate a Resilient-Specific Transcriptional Network

Background: High-throughput RNA sequencing has identified numerous transcriptional alterations in Major Depressive Disorder. However, studies in animals suggest that more changes are required for homeostatic resilience. But how these genes interact to induce resilience is currently unknown.

Methods: We utilized the Chronic Social Defeat Stress (CSDS) model of depression to identify susceptible and resilient mice. For each group, brain tissue was extracted for RNA sequencing. Sequencing data was used to generate differential expression profiles and gene co-expression networks using Weighted Gene Co-Expression Network Analysis (WGCNA). Networks associated with resiliency were then probed bioinformatically to identify putative regulators that were tested in vivo.

Results: Our bioinformatics analysis identified a uniquely resilient transcriptional network regulated by Zfp189, a zinc-finger protein with no currently known function. In accordance with these findings, overexpression of Zfp189 was both pro-resilient and antidepressant. Moreover, RNA sequencing of Zfp189 overexpressing tissue showed preferential changes in the network in which Zfp189 originates, confirming its role as a network driver. Upstream regulator analysis on this network implicated CREB as a modulator of network function, and Zfp189 overexpression was sufficient to prevent the pro-depressant effects of CREB knockout in a model of female stress.

Conclusions: Zfp189 drives a resilient-specific transcriptional network that is regulated by CREB.
Funding: NIH, HDRF

Josefa Sullivan
Department of Neuroscience

Inhibition of BET-dependent transcription causes an Autism-like disorder in mice.

Background: ecent genetic studies of Autism Spectrum Disorder (ASD) patients revealed the importance of transcriptional regulators, especially those controlling elongation, in ASD etiology. This suggests the possibility of a novel, epigenetic mechanism underlying ASD where disruptions in transcriptional elongation lead to abnormal neuronal development and circuit formation. Indeed many ASD risk genes are extremely long, making them particularly vulnerable to impairments in elongation. To address if elongation is causally linked to the development of ASD, we utilized a novel pharmacological approach to inhibit the activity of the bromodomain and extraterminal domain containing (BETs) protein family that facilitates transcriptional elongation via interactions with acetylated histones.

Methods: We developed a novel, brain-permeable BET family inhibitor. Using RNA and Chromatin Immunoprecipitation sequencing, we examine the selective, temporal relationship between impaired BET activity and the development of ASD-like gene expression patterns and behaviors in young mice.

Results: We found that loss of BET-dependent transcription in young mice recapitulates ASD-associated gene expression patterns and leads to anxiety-like behavioral abnormalities. BET inhibition causes highly selective gene expression changes, preferentially suppressing of genes of extended length. Further, these genes have been previously associated with ASD and control neuronal development and activity. We identify the BETs as epigenetic regulators of genes involved in ASD-like behaviors in mice. Our findings indicate the causal role of defective transcriptional elongation in the etiology of Autism.

Funding: NIMH5T32MH096678

Meghan Flanigan
Department of Neuroscience

A lateral habenula microcircuit controlling aggression reward

Elevated interpersonal aggression and violence is a common symptom of multiple psychiatric disorders and represents a significant global health issue that lacks both sufficient therapeutic strategies and satisfactory understanding of relevant neurophathologies. Recent clinical data suggests that aggression is positively reinforcing in some patients and animals, thus implicating classical reward circuitry in aggression. Here, we have characterized a novel orexin circuit between the lateral hypothalamus (LH) and the lateral habenula (LHb) that plays a role in controlling the valence of aggressive social interactions as determined by an adapted model of conditioned-place preference (CPP). Using in-vivo fiber photometry, electrophysiology, viral circuit tracing, histology, and optogenetics, we provide compelling evidence that orexin inputs to the LHb activate a small population of GAD2-expressing interneurons via orexin receptor 2 (OxR2). These LHb GAD2-neurons, in turn, inhibit glutamatergic projection neurons to promote aggression and aggression CPP. The results of this study provide a novel and detailed circuit mechanism by which orexin modulates LHb activity to alter the valence of aggressive social interactions.

Nick Upright
Department of Neuroscience

Stereological Analysis of DREADD Transduction in Non-Human Primates

Background: Non-human primates are advantageous for studying cognitive function due to the similarity of their brains to those of humans, particularly in regards to the prefrontal cortex. Designer receptors exclusively activated by designer drugs (DREADDs) allow for the controlled manipulation of specific cellular signaling and circuitry . We used DREADDs to manipulate dorsolateral prefrontal cortex (dlPFC) function in macaque monkeys.

Methods: An rAAV5/hsyn-hM4Di-mCherry viral vector construct was injected bilaterally into the dlPFC of five monkeys. Monkeys were tested on a spatial delayed response task to assess working memory function after intramuscular injection of either clozapine N-oxide or PBS. We subsequently performed immunohistochemistry for mCherry to quantify DREADD expression in the dlPFC. Neuronal bodies were determined by cresyl violet staining. We used unbiased stereological measures to quantify the level of DREADD transduction and compute the percentage of transduced cells.

Results: We found a greater number of immunolabeled neurons in monkeys that displayed behavioral results compared to those measured from monkeys that showed no behavioral effect after DREADD activation.

Conclusions: This level of detailed histological analysis has two valuable advantages: to facilitate our general understanding of behavioral effects in injected monkeys and to establish a direct relationship between stereological measures and behavioral outcomes.

Funding: FBI and NIH

Chloe Solomon
Translational and Molecular Imaging Institute

Taking it to heart: Examining relations between chronic psychological stress, amygdalar activity, and cardiovascular inflammation, using PET/MR imaging

Background: Chronic psychological stress is associated with increased risk of cardiovascular disease. Innovative PET/MR imaging technology offers the opportunity to examine physiological manifestations of stress in the brain and its effects on arterial inflammation in humans.

Methods: In a cross-sectional pilot study, individuals diagnosed with chronic PTSD were recruited and underwent 18F-fluorodeoxyglucose PET/MRI at Mount Sinai Hospital. We analyzed relationships between perceived stress (Perceived Stress Scale), amygdalar activity, and arterial inflammation.

Results: Data analyzed from 13 subjects (median age 49 years [IQR 45.7-56.7]) diagnosed with chronic PTSD showed amygdalar activity significantly associated with arterial inflammation (r=0.70; p=0.0083). Perceived stress was also associated with amygdalar activity (r=0.56; p=0.0485), arterial inflammation (r=0.59; p=0.0345), and C-reactive protein (r=0.83; p=0.0210).

Conclusions: This pilot study is among the first to link regional brain activity to cardiovascular inflammation. These findings provide novel insights into the mechanism through which chronic psychological stress can lead to cardiovascular disease in humans. PET/MRI could be used to screen for atherosclerosis in severely and chronically stressed individuals, and may help measure treatment response to stress-reduction therapies.

Funding: NIH/NHLBI

Anna Zilverstand
Department of Psychiatry

Efficiency in global brain network organization decreases with recency of use in cocaine addicted individuals

Background: Previous studies in individuals with cocaine use disorder have focused on describing localized changes in resting-state functional connectivity. Here, we used complex network analysis (graph theory) to study how whole-brain network organization is modulated by recency of use.

Method: High-resolution resting-state fMRI scans (10min) were acquired in individuals with recent cocaine use (urine positive, N=26, age 47±8 years), in abstinent cocaine users (urine negative, N=17, age 47±8 years) and in race- and gender-matched controls (N=32; age 40±8 years; co-varying for age). Network structure for each group was visualized using a spring-embedded layout with our 3D-network visualization tool, iCAVE (doi: https://doi.org/10.1101/061374). Global efficiency per brain region was computed to evaluate the functional integration of brain networks (CONN, MIT, Cambridge).

Results: Our resting-state analysis demonstrated linearly decreased global functional integration of frontal and subcortical brain regions as a function of recency of use (recent users<abstinent users<controls). Frontal and subcortical brain regions also showed altered position in the network topography, indicating disintegration.

Conclusions: Beyond localized changes, these results demonstrate whole-brain changes in functional integration in cocaine addiction. Specifically, we observed reduced integration of frontal and subcortical regions involved in executive functioning, reward processing and memory, aggravated by recency of use. Our results suggest that measures of functional integration can be used for identifying intervention targets and developing a novel tool for monitoring disease status.

Funding: NIDA&NWO

Gabor Egervari
Department of Psychiatry and Neuroscience

Chronic heroin use in humans dysregulates the striatal glutamatergic system and mediates addiction behavior by histone H3 hyperacetylation

Background: Despite the current opioid epidemic and significant advances in animal and in vitro models, little knowledge has been directly accrued regarding the neurobiology of the opiate-addicted human brain.

Methods: We used post-mortem human brain specimens from a homogeneous population of heroin users for transcriptional and epigenetic profiling and direct assessment of chromatin accessibility in the striatum. Rat heroin self-administration was used to obtain translational molecular and behavioral insights.

Results: Our transcriptome approach revealed marked impairments related to glutamatergic neurotransmission and chromatin remodeling in the human striatum. In particular, hyperacetylation of lysine 27 (H3K27ac) of histone H3 showed dynamic correlations with heroin use history and acute opiate toxicology. Targeted investigation of GRIA1, a glutamatergic gene implicated in drug-seeking behavior, verified the increased H3K27ac at discrete loci, accompanied by enhanced chromatin accessibility at hyperacetylated regions in the gene body. Analogous epigenetic impairments were detected in the striatum of heroin self-administering rats. Using this translational model, we showed that bromodomain inhibitor JQ1, which blocks the functional read-out of acetylated lysines, reduced heroin self-administration and cue-induced drug-seeking behavior.

Conclusions: Our data suggest that heroin-related histone H3 hyperacetylation contributes to glutamatergic transcriptional changes that underlie addiction behavior and identify JQ1 as a promising candidate for targeted clinical interventions in heroin use disorder.

Funding: NIH

Garrett Wong
Department of Neuroscience

Genetically regulated transcriptomic study of Parkinson's Disease yields mechanistic insights

Background: Genome-wide association studies have identified many loci associated with Parkinson's disease (PD) but elucidating the underlying genes and their mechanisms remains a challenge. Transcriptomic datasets have enabled identification of variants regulating expression in specific tissues. These data can be used to impute expression levels from genotypes in larger samples, which can be tested to identify potentially novel genes.

Methods: We performed a transcriptome-wide association study for PD by jointly analyzing PD GWAS data of 108,990 individuals with gene expression/splicing levels from 7,088 individuals across 61 tissues including 1,028 brains, peripheral blood, immune cells, and 44 tissues from GTEx including 10 brain regions.

Results: We identified 86 significant gene-disease associations ($p<10^{-5}$), of which 26 are in novel PD loci. Majority of the associations (27 genes) stemmed from alternative splicing in brain including well-established MAPT and SNCA but also novel genes including MTOR, CLASP2, CAMLG, GALC and others. Other associations were from innate immune cells. These genes are more likely to interact physically and belong to the same or related pathways.

Conclusions: We identified several PD susceptibility genes in both known and novel loci that are enriched in autophagy-lysosome, synaptic function, mitochondria and immune-related pathways. Our results also suggest that mRNA splicing in the brain is an important source of disease-relevant variation. Overall, this study provides a foundation for further mechanistic studies that will elucidate the molecular drivers of PD.

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: 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

The role of Plexin-B2 in human corticogenesis using cerebral organoids

Chrystian Junqueira Alves1, Nicolas Daviaud[1], Roland H. Friedel[1,2], Hongyan Zou[1,2]

[1] Fishberg Department of Neuroscience and Friedman Brain Institute

[2] Department of Neurosurgery, ISM at Mount Sinai.

The Plexin-Bs are a family of Semaphorin receptors that play important roles in neural development. Previous analyses have shown that neural progenitors in the germinal zones of Plexin-B1/B2 deleted mutant mice exhibited decreased cell numbers and deficient neuronal production, leading to reduced cortical thickness. This phenotype was attributable to impaired progenitor proliferation during the neurogenic period and a change of division mode favoring cell cycle exit. However, the function of Plexins in the developing human cortex is unknown as human corticogensis engage a much complex neural progenitor populations that can not be adequately modeled using mouse mutants.

Cerebral organoids are in vitro grown miniature organs resembling the brain. They develop through intrinsic self-organizing processes upon timely application of specific factors and manipulation of cell culture environment.

To study the role of Plexins during human corticogenesis, we generated cerebral organoids derived from human embryonic stem cells after removal of Plexin-B2 by CRISPR genome editing tool. Preliminary results suggest Plexin-B2 knockout affects embryonic stem cells and the formation of cerebral organoids. The potential mechanisms are compromised progenitor pools, increased cell cycle exit and an imbalance between proliferation and differentiation. Ongoing studies are attempting to elucidate the mechanisms by which Plexin-B2 signaling pathway coordinate proliferation, differentiation and migration of neural progenitors during human forebrain development.

3

A key role of RGS4 in maintenance of chronic pain.

K. Avrampou, S. Gaspari, E. Loh, V. Mitsi, L. Shen, F. Carr, V. Zachariou

Fishberg Department of Neuroscience, Icahn School of Medicine at Mount Sinai

Background: Regulator of G protein signaling 4 (RGS4) is a GPCR modulator expressed in several brain regions associated with pain transmission and perception. RGS4 controls GPCR signaling duration and direction by associating with activated Galpha subunits

Methods: constitutive/conditional knockout mouse models, RNAsequencing, qPCR, Behavioral tests.

Results: Our recent studies reveal that RGS4 is uniquely regulated by long term peripheral inflammation and nerve injury, in the spinal cord and the thalamus. Using the CFA (Complete Freud's adjuvant) murine model of inflammatory pain and the Von Frey, Hargreaves, and cold plate behavioral assays, we report that mice lacking Rgs4 gene recover from allodynia, whereas their wildtype controls show prolonged pain-like behaviors. This phenotype is observed in both male and female mice. RGS4 protein acts in a modality-specificity manner, as prevention of RGS4 action does not affect thermal hypersensitivity. Using viral-mediated gene transfer to conditionally knockdown RGS4, we demonstrate that RGS4 actions in the ventral posteromedial thalamic nuclei modulate mechanical and cold allodynia. RNA Sequencing and biochemical studies on thalamus of RGS4WT and RGS4KO mice revealed several intracellular adaptations that contribute to mechanical hypersensitivity under long-term pain.

Conclusion: Our findings provide new information on the mechanisms underlying long- term pain states and point to RGS4 as a target for the alleviation of chronic pain symptoms.

4

Behavioral and neural mentalization deficits in cocaine use disorder

Bachi, K., Kinreich, S., Kundu, P., Malaker, P., Maloney, T., Parvaz, M., Alia-Klein, N., Goldstein, R.Z., Moeller, S.J.

Icahn School of Medicine at Mount Sinai

Background: Impairments in mentalizing (successful attribution of mental-states to others) characterize multiple psychopathologies and may culminate in profound interpersonal disruptions. Individuals with cocaine use disorder (iCUD) show multiple social cognition deficits and thereby may exhibit alterations in mentalizing behavior and underlying circuitry (prefrontal cortex, superior temporal sulcus, temporoparietal junction, temporal poles; regions similarly implicated in the pathophysiology of drug addiction). We therefore examine the behavioral and neural correlates of mentalizing in iCUD.

Methods: 16 iCUD and 10 controls underwent a 3T multiecho multiband excitation sequence fMRI while performing the Why/How Localizer task, which presents human naturalistic behaviors and asks How versus Why these behaviors are being performed; the task robustly activates the mentalizing network as previously shown in a community sample. Group differences between How and Why are examined for behavior and neural activation (ongoing). Data in iCUD are compared against both the current controls and the mean values of a community sample.

Results: iCUD and current controls did not differ in their mentalizing behavior. Nevertheless, compared to the mean of a community sample of controls, iCUD (but not our sample of controls) were less accurate [one-sample t(15)=2.255, p=.04] and slower [t(15)=2.607, p=.02] in responding to Why questions, consistent with hypotheses.

Conclusions: These preliminary behavioral findings suggest mentalizing deficits in iCUD, with neuroimaging analyses soon to follow.

Funding: NIDA

5

The Role of IL34 in neuron-microglia communication

Ana Badimon, Anne Schaefer

Icahn School of Medicine at Mount Sinai

Background: Microglia are the resident immune cells in the CNS and are the first line of defense and protection from insults in the brain. These cells constantly survey the surrounding environment, secrete neurotrophic factors, and prune inactive synapses in a tightly controlled manner. Dysregulation of these microglial activities have been shown to underlie various neurodevelopmental and neurodegenerative disorders, making it crucial to understand the factors and signals that tightly control microglia function. The neuronal ligand Interleukin 34 (IL34) is a forebrain-specific ligand that regulates microglia survival via signaling through Colony stimulating factor 1 receptor (CSF1R), a receptor located primarily on microglia in the brain. Recent studies have highlighted a more complex, neuroprotective effect of IL34 in maintaining neuron health in models of Alzheimer's Disease. Moreover, we have found an age-dependent decrease in IL34 that correlates with cognitive decline, implying a more elaborate function of IL34 in the brain exceeding cell survival.

Methods: Immunostaining, translating ribosome affinity purification (TRAP), and cell filing

Results: Selective ablation of IL34 in D1 neurons in the striatum leads to changes in D1 neuron morphology and gene expression. These changes are associated with changes in motor activity and exploratory behavior as well.

Conclusions: Neuronal production of IL34 mediates neuron-microglia communication in a cell-specific manner and regulates microglia function in a healthy brain.

Funding: NIMH, NIA

6

MicroRNAs and cocaine addiction: Role for non-proteolytic ubiquitination?

Purva Bali, Alexander Smith and Paul Kenny

Department of Neuroscience, Icahn School of Medicine at Mount Sinai

Background: The negative consequences of cocaine abuse on society are considerable and there are no current FDA-approved treatments for cocaine addiction. MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of protein-coding gene transcripts. Cocaine and other drugs of abuse modulate miRNA expression in addiction-relevant brain regions, including striatum, which in turn influences their motivational properties by controlling expression of targeted genes. We have shown that miR-212, and the closely related miR-132, are upregulated in the striatum of rats with extended access to cocaine. Further, these cocaine-responsive miRNAs influence TNF-α signaling, an important pathway shown to control cocaine-induced striatal neuroplasticity.

Method: We used established cell lines and primary rat striatal cultures and multiple biochemical /molecular approaches to investigate mechanisms by which miR-212/miR-132 may influence addiction-relevant plasticity in striatum

Results?Conclusions: We find that miR-212 and miR-132 exert markedly different effects on TNF-α signaling through a mechanism involving differential effects on the expression of CYLD (cylindromatosis), a key regulator of TNF-α signaling. This K63-deubiquitinase regulates non-proteolytic ubiquitin signaling and is highly enriched in striatum. We find that CYLD plays a critical role in regulating AMPA receptor signaling in primary striatal neuron cultures, providing a potential mechanism by which these miRNAs can influence addiction-relevant neuroplastic responses to cocaine. Currently, we are investigating the role for the miR-212/miR-132-CYLD signaling in striatum in regulating addictive-like responding for cocaine.

Funding: NIH

7

Chromatin accessibility maps of human postmortem brain reveal epigenome brain-region-specific and cell-type-specific signatures

Jaroslav Bendl[1], John Fullard[1], Mads Hauberg[1], Gabor Egervari[2], Yasmin Hurd[1,2], Panos Roussos[1,3]

[1]Department of Psychiatry, [2]Neuroscience, [3]Genetics and Genomic Science, Icahn School of Medicine at Mount Sinai

Background: Mapping of open chromatin regions identifies the location of cis-regulatory elements. Here we present for the first time a multiregion and cell-type-specific map of open chromatin in human brain tissue.

Methods: We have applied ATAC-seq to neuronal and non-neuronal nuclei originating from 14 brain regions of five individuals to generate cell-type-specific maps of open chromatin regions in the human brain. These maps have been utilised to identify robust cell-type-specific and brain-region-specific epigenome signatures by support vector machine approaches.

Results: Our analysis revealed that the majority of open chromatin regions is differentially accessible between neuronal and non-neuronal nuclei, showing enrichment with known cell-type markers and cis-regulatory elements. It is therefore not surprising that the external validation of extracted cell-type-specific signatures yielded perfect prediction accuracy (acc=92%). Large variability among brain regions was observed only for neuronal nuclei (acc=64%) while non-neuronal nuclei seemed to be more difficult to distinguish (acc=75%).

Conclusion: We demonstrated a computational model for identification of epigenome signatures capable of discriminating cell lines and brain regions. This result proves the feasibility of studying the brain chromatin landscape as it provides an insight into the regulation of gene expression in different cells and has identified the potential mechanism of action of numerous disease-associated risk variants.

Funding: NIH/VA

8

Chemogenetic targeting of prefrontal parvalbumin interneurons affects social behavior in mice

Lucy Bicks[1], Beth Lucas, Hiroyuki Koike[1], Michelle Peng1[1], Roger Clem, Schahram Akbarian[1,2], Hirofumi Morishita[1,2]

[1]Icahn School of Medicine at Mount Sinai

[2]Department of Psychiatry

Background: Social processing is a domain that is commonly dysregulated in psychiatric disorders, and is poorly treated by available psychiatric medications. In humans and rodents, portions of the evolutionarily conserved medial prefrontal cortex (mPFC) are part of a network that regulates social behavior. Many disorders with shared social processing deficits show impairments in inhibitory neurotransmission within the brain, particularly in the mPFC, suggesting a role for PFC inhibitory action in regulating social behavior.

Method: We investigated the role of prefrontal parvalbumin (PV) interneurons, a major class of cortical inhibitory neurons, in social behavior of adult mice by leveraging chemogenetic technologies. We selectively expressed hM4Di, an inhibitory DREADD (Designer Receptor Exclusively Activated by Designer Drugs), in PV interneurons in the mPFC.

Results: Acute selective suppression of mPFC PV interneurons decreased sociability in a 3-chamber test and disrupted social recognition in a habituation-dishabituation paradigm. Suppression of PV interneurons did not affect spatial working memory, olfactory discrimination, or anxiety-related behaviors, suggesting a specific effect of PV interneuron suppression on social behavior.

Conclusion: These results demonstrate that PV interneuron activity in the mPFC is necessary for appropriate social behavior in mice.

Funding: NIH

9

Identifying novel MAPT splicing factors and RNA-binding proteins

Kathryn R Bowles, Towfique Raj, Minghui Wang, Bin Zhang & Alison M. Goate

Ronald M. Loeb Center for Alzheimer's Disease, ISMMS, NYC, NY

Background: Correct regulation of splicing is essential for ensuring proteomic diversity by the production of multiple distinct isoforms from a single gene. The MAPT gene consists of 16 exons, many of which are differentially spliced. In human brain, the splicing of Exons 2, 3 and 10 result in the expression of 6 different isoforms, which can be parsed into two groups depending on their inclusion or exclusion of Ex10, although the genetic mechanisms underlying this process have not been thoroughly researched.

Methods: To address this, we have carried out an unbiased genome-wide analysis comparing splicing factor and RNA-binding protein expression with MAPT exons 2, 3 and 10 percent spliced in (PSI) in RNA-seq data from the ROSMAP and MSBB cohorts. We also used recursive partitioning to further refine a panel of novel candidate MAPT splicing regulators, which will be functionally validated in vitro.

Results: Most significantly associated genes were negatively correlated with Ex10 PSI, whereas fewer were positively associated, suggesting that more diverse regulation contributes to Ex10 exclusion compared to inclusion. In contrast, we observed the opposite pattern of association for Ex2 PSI, indicating differential regulation of the splicing of exons 2 and 10.

Conclusion: We identify multiple novel genes associated with MAPT splicing, which may differentially affect inclusion of Exons 2 and 10.

Funding: The Rainwater Foundation

10

mTOR- and Ras-signaling in cord blood correlate with maternal depression and adverse outcomes in early childhood

Michael Breen[1],Aliza Wingo[2],Joseph Buxbaum[1],Dan Stein[3]

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Background: Prenatal exposure to maternal depression can have lasting effects on infant development with risks of psychopathology. Though the impact of prenatal maternal depression has been documented, the potential mechanisms through which maternal psychosocial variables shape development have not been fully elucidated.

Methods: To explore genes and molecular pathways associated with maternal depression and early childhood outcomes, transcriptome-wide umbilical cord blood (UCB) gene expression profiles from mothers diagnosed with maternal depression (N=30) and healthy mothers (N=84) were integrated with a battery of clinical measures from infants since birth to twenty-four months.

Results: A clear pattern of gene expression signatures were identified separating female from male infants with prenatal exposure to maternal depression. Gene co-expression network analyses identified four gene modules associated to maternal depression, including two up-regulated modules implicated in mTOR-signaling and ribosomal pathways and two down-regulated modules implicated in AKT-Ras and p53-signalling. Notably, a strong negative correlation was observed between mTOR and AKT-Ras signaling (r2=-0.75). Infant follow-up measures reported reduced motor-skills, social-communication and height at six and twenty-four months in children with exposure to maternal depression. AKT-Ras and mTOR-signaling in UCB provided a predictor for reduced motor-skills in infants at six and twenty-four months.

Conclusions: This study established clear associations between gene expression changes in UCB, maternal depression and motor-skill development in infants.

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Regional Differences in Gray Matter Volume in Anorexia Nervosa

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Background: Anorexia nervosa (AN) is a severe psychiatric disorder characterized by chronic malnutrition, high rates of mortality and comorbidity, and serious medical complications. Acute AN is associated with reduction in both gray and white matter in the brain, and the extent to which brain volume is fully restored with recovery is unclear. Most studies in AN have focused on global brain volume, with few specifying regions where alterations in gray matter volume (GMV) may be found. The goal of our study was to identify regional differences in GMV in adolescents with AN compared to healthy controls.

Method: We analyzed T1-weighted images of 17 female adolescents using voxel-based morphometry, comparing nine individuals affected with AN to eight healthy controls.

Results: In AN, GMV was reduced in the precuneus, posterior cingulate cortex, and lateral prefrontal cortex ($p < .001$) when compared to controls.

Conclusion: Our preliminary results suggest that regions corresponding to the Default Mode Network may be affected in AN. Future research should seek to link alterations in these brain regions with behavioral, affective, and cognitive symptoms found in AN.

Funding: Data provided from one NIH study and one Le Foundation Grant.

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"TRANSCRIPTOMIC MODELING OF PHELAN-MCDERMID SYNDROME USING NEURONS GENERATED FROM PATIENT IPSCS

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Background: Autism has high heritability and a worldwide prevalence of nearly 1%, but patient heterogeneity has made identifying the underlying etiology difficult. By focusing on monogenic disorders with high penetrance for autism, pathways might be identified that are common to a broader group of autistic patients with related etiology. Phelan-McDermid syndrome (PMS) is one such syndrome and is caused by haploinsufficiency of SHANK3, a gene that encodes for a post-synaptic scaffolding protein at glutamatergic synapses.

Methods: Blood samples from patients with PMS and unaffected siblings are reprogrammed into iPSCs using a modified non-integrating Sendai virus and differentiated into NPCs followed by neurons. RNA is isolated from neural samples and sequenced to identify PMS-associated transcriptomic changes and drugs with anti-correlated expression signatures.

Results: Fourteen pairs of samples have been reprogrammed with half used to generate NPCs and neurons. Initial NPC samples were subjected to RNA sequencing for preliminary investigation into the early developmental transcriptional profile of PMS. PMS patient-derived NPCs showed transcriptional upregulation of components of the Wnt signaling pathway when compared to their healthy siblings.

Conclusions: Identifying gene expression changes in PMS patient iPSC-derived NPCs and neurons will provide a unique perspective that can be used in conjunction with other models of the disease and known drug expression profiles to identify new therapeutics.

Funding: Seaver Autism Center and NIDCR-Interdisciplinary Training in Systems and Developmental Biology and Birth Defects

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ANXIETY, A COMMON TRAIT OF BORDERLINE AND SCHIZOTYPAL PERSONALITY DISORDER.

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Background: The relationship between borderline personality disorders (BPD) and schizotypal personality disorder (SPD) has been debated for years. There are numerous studies that indicate that SPD and BPD frequently co-occur and have similar comorbidities such as mood and anxiety symptoms. In this study, we aimed to compare anxiety symptoms in SPD and BPD patients, compared to patients with other personality disorders and healthy controls. Rather than focusing on categorical anxiety disorders, we assessed anxiety traits using self-reported questionnaires that capture subthreshold anxiety symptoms not fulfilling criteria for overt anxiety disorders.

Methods: Subjects: 854 individuals classified in 5 different groups: healthy controls, BPD, SPD, comorbid BPD and SPD, and other PD (non BPD/SPD). Diagnoses were made using SCID-IV and anxiety was evaluated using the Spielberger State-Trait Anxiety Inventory (STAI).

Results: The BPD, SPD and comorbid BPD/SPD groups scored significantly higher in the STAI trait compared to patients with other personality disorders ($p<0.001$) and healthy controls ($p<0.001$). However, despite slightly higher STAI trait scores among those with comorbid BPD and SPD, there were no significant differences between this group and those with BPD or SPD alone.

CONCLUSION: Patients with BPD and SPD have high levels of anxiety symptoms compared to patients with other personality disorders and healthy controls. High anxiety seems to be a common trait of both SPD and BPD.

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HIF-1α is Upregulated in Human Glioblastoma Populations with Stem Cell Properties

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Background: Glioblastoma (GBM) is a rapidly progressive primary brain tumor, and its malignancy has been attributed in part to the persistent proliferation of a subset of cells known as glioma stem cells (GSC). Increasing evidence shows that the intrinsic properties of GSCs are tightly regulated by specific signals from the microenvironment. Here, we focus on elucidating the molecular mechanisms that govern the stem-like properties previously observed in EGFR+ human glioblastoma populations and on understanding the mechanism of the microenvironmental signals within the tumor mass.

Methods: We prospectively isolated GBM GSCs from fresh tumor samples, based on their ability to bind epidermal growth factor (EGF) ligand and express its cognate receptor (EGFR+), and sequenced their full transcriptome using RNA-seq. To study the role of hypoxia on stem cell properties, immunostaining was performed on GBM tissues and established cell lines, under both normoxic and variably hypoxic conditions.

Results: Differential gene expression analysis revealed distinct upregulation of stem cell pathways in EGFR+ GBM cells, compared to EGFR– counterparts, with overexpression of 45 specific transcription factors. Notably, there was prominent upregulation of the hypoxic inducible factor 1-α transcription factor (HIF1- α), which has been linked to tumor progression in multiple cancers. We confirmed HIF1-α protein expression under hypoxic conditions in human glioblastoma tissues and patient-derived cell lines, as well as the co-expression of EGFR.

Conclusions: Upregulation of HIF-1α expression in EGFR+ GBM stem cell populations suggest its role in the maintenance of tumorigenic glioma properties under hypoxic conditions.

Funding: MSSM

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Targeting Aversion: A Strategy for Alcohol and Nicotine Co-Dependence

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Background: Tobacco and ethanol co-dependence is alarmingly high with alcoholism being 10 times greater in tobacco smokers. An intriguing focus for therapeutic potential is not upon the stimulatory effects of these drugs but rather to target their aversive properties.

Methods: C57BL6 mice were provided ethanol (10, 20, 30, and 40%) or 5% sucrose via the drinking in the dark procedure and self-administration (FR-3). Locomotion was tested using open field.

Results: Self-administration of ethanol induced higher blood alcohol levels (123mmol/L) versus the drinking in the dark procedure (90mmol/L). Aversion to ethanol increased with concentration; microliter intake decreased by ~23% with every 10% increase in concentration. During self-administration of 20% ethanol or 5% sucrose, high doses of nicotine (1.0 mg/kg BW) induced a suppressant effect on rewards earned, ie: a decrease of 39% and 25% in the ethanol and sucrose group, respectively. In the absence of nicotine on the days to follow, both groups exhibited a rise in rewards earned. The sucrose group returned to baseline levels of responding; however, the ethanol group sustained a 30% suppression in responding. Nicotine induced an anxiogenic effect in the ethanol group and an anxiolytic effect in the sucrose group, as evidenced by change in center time legacy.

Conclusion: Nicotine induced a suppressant and durable effect on ethanol intake, thus illustrating a potential targetable neuroplastic adaptation to lower ethanol consumption.

Funding: NIH and CIHR

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An Epigenetic Role for Female Sex Chromosomes in e'XX'aggerating Neuronal Differences

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Background: Major depressive and anxiety disorders demonstrate increased diagnostic prevalence in females. Much work suggests that histone modifications, such as the repressive H3K9me3, influence predisposition to neuropsychiatric disease. Recently, we found that female mice conditionally lacking the H3K9me3 methyltransferase, Setdb1 (Setdb1-cKO), in forebrain neurons postnatally display significant anxiety- and depression-like behaviors, a finding we did not observe in males. Accordingly, we sought to characterize the epigenetic basis of this sex-skewed phenotype.

Methods: Neuronal nuclei were isolated from male and female mouse cerebral cortex using fluorescence-activated nuclei sorting, followed by native chromatin immunoprecipitation with anti-H3K9me3 antibody. After sequencing alignment, bedtools genomeCov was used to quantify total read differences within and across samples to assess absolute H3K9me3 levels.

Results: Intriguingly, female neurons exhibited significantly lower levels of H3K9me3 across the autosomes with reciprocally higher levels across the X chromosomes; this was in contrast to male neurons, wherein the autosomes accounted for the vast density of H3K9me3. Furthermore, Setdb1-cKO female neurons exhibited pervasive H3K9me3 losses across the X chromosomes, with 'reshuttled' coverage onto the autosomes.

Conclusion: This tilted balance of H3K9me3 on the sex chromosomes of female neurons may create a unique point of vulnerability, predisposing these cells to a specific subset of behavioral deficits.

Funding: Supported by the NIH.

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Intracavity Ultrasound (ICUS): A Neuroendoscopic Adaptation of Intravascular Ultrasound (IVUS) for Neuroendoscopic Intracerebral Hemorrhage (ICH) Evacuation

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Introduction: IVUS has been used for many years to visualize atherosclerotic disease. IVUS catheters contain multiple ultrasound emitters and receivers positioned radially to produce a 360-degree circumferential ultrasound image. Due to its slender diameter of 0.035-inches, it has the potential for adaptation in other procedures, including ICH evacuation. The inability to visualize the extent of residual hematoma intraoperatively remains a challenge and an obstacle to maximizing the evacuation efficiency. Here we present ICUS, a novel adaptation of IVUS to meet this need.

Methods: An IVUS catheter is introduced within the endoscope sheath to the distal edge of the hematoma cavity prior to evacuation to obtain a baseline image. The sheath is retracted, leaving the IVUS catheter tip at the distal end. With the ultrasound activated, the IVUS catheter is slowly retracted to scan the entire cavity. This is repeated after clot resection to identify residual hematoma.

Results: A patient with a large parietotemporal ICH underwent evacuation. During the procedure, ICUS was performed using the technique described above. Two residual pockets of hematoma were visualized and subsequently targeted with the endoscope and aspirated. Post-operative CT revealed 95% evacuation.

Conclusion: IVUS was successfully adapted for neuroendoscopic ICH evacuation and identified residual pockets of hematoma. Further investigation of this and other imaging technologies is warranted for improving intraoperative detection of residual hematoma.

Funding: None.

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A neurodegenerative mechanism for nicotine addiction

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Background: Medial habenula(MHb) is bilateral structure located in the epithalamus and serve as a relay station between forebrain and midbrain nuclei. Recently, emerging evidences support that MHb plays an important role in controlling nicotine consumption by mediating the aversive effect of nicotine. Blocking the activity of MHb and its major downstream target interpeduncular Nucleus (IPN) increase nicotine intake due to loss of the controlling signaling. Interestingly, the fiber tract fasciculus retroflexus (FR) connecting MHb and IPN is sensitive to nicotine exposure. Systemic injection with a high dose nicotine causes selective degeneration of this neural circuitry. There is much interest in investigating whether volitional nicotine intake also damage the MHb-IPN. Here we apply multiple approaches to address this question on nicotine self-administrated rats.

Method: MRI, Nicotine self-administration rats model, degeneration sensitive silver staining, iDISCO

Results: Nicotine self-adminstration rats show degeneration of fasciculus retroflexus. The integrity of FR was reduced in the nicotine SA rats. Moreover, they have smaller habenular volume. Interestingly, human smokers also have smaller habenular volume. Strikingly, Rats with selective lesion of MHb-IPN take more nicotine. Finally, we found that there are up-regulation of neurodegeneration protein in the MHb of theses rats.

Conclusion: Our data suggest that neurodegeneration of MHb-IPN may be important for nicotine addiction.

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Cellular and Synaptic Pathology in Intractable Epilepsy

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Background: Nearly one third of epileptic patients develop intractable epilepsy, which does not respond to pharmacological treatment and resection of the epileptogenic brain region remains the best treatment option. Generally, the excitatory/inhibitory imbalance of pyramidal cells in layer III cortical areas plays a role in hyperactive synchrony causing seizures. But, the actual abnormal nature of cell type-specific neurochemical markers, neurotransmitter receptor subunit proteins, and the possible involvement of neuroinflammation and glial cells has not been quantified at synaptic levels in intractable epilepsy.

Methods: Our study has access to materials directly derived from patients allowing us to perform high-resolution quantitative cellular and synaptic analyses in human cerebral cortex using experimental techniques that were previously used in animal models. We have done comprehensive synaptic analyses of unprecedented sophistication in seizure-prone and seizure-free zones of cortical tissue resected from patients within microcircuit-based, integrative, and quantitative frameworks.

Results: Through highly multiplexed immunofluorescence approaches, preliminary evidence indicates significant changes in neurochemical markers like -aminobutyric acid and expression of neurotransmitter receptor activity in seizure-onset zone. Using 3-dimensional reconstruction of LY-loaded neurons, and postembedding immunogold electron microscopy, the dendritic spine analysis predicts decreases in synaptic density lengths in seizure vs. non-seizure zones.

Conclusions: These comprehensive analyses enable direct assessment of altered elements within neural circuits in seizure compared to non-seizure regions.

Funding: N/A

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Neuroimaging of olfactory autobiographical memories cued by personally relevant odors

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Background: Odors serve as unique and potent cues of autobiographical memories. Autobiographical memories evoked by odors have been found to be more emotional, more vivid, less frequently thought of, and older than those evoked by visual, verbal, and auditory cues. In this study, we investigated the relationship between the olfactory system and memories evoked by personally relevant odors. Previous studies have instructed participants to smell a set of odors and describe any autobiographical memories that come to mind. On several occasions, however, participants have failed to retrieve a memory or have retrieved a memory that lacked specific details.

Methods: We employed an alternative approach; we interviewed 10 participants, identified a specific odor that they personally associated with a vivid autobiographical memory, and then acquired that odor. Using functional magnetic resonance imaging, we examined patterns of brain activation following exposure to personally relevant and non-relevant odors.

Results: Preliminary results indicate that relevant and non- relevant odors are associated with different patterns of activation, with greater activation in regions involved in memory retrieval and emotional processing (prefrontal cortex and anterior cingulate cortex) for relevant odors.

Conclusions: Further analysis of the current data set is required to confirm these preliminary results and to expand our understanding of olfactory autobiographical processing.

Funding: Le Foundation

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The role of HDAC1 in the developing human cortical tissue in response to hypoxia injury

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Background: Preterm hypoxia-ischemia is a leading cause of disability and mortality. Histone deactylases (HDACs) play a significant role in brain development and neurodegeneration. Used as a therapeutic strategy, HDAC-inhibitors reduce infarct volume after cerebral ischemic injury and provide neuroprotection in rodents.

Method: I established cerebral organoid (C-organoid) cultures derived from human ESCs to examine the role of HDAC1 in the developing human cortical tissue in response to hypoxia-ischemia. To model ischemia, C-organoids were cultured under low oxygen tension (3%) for 2 weeks.

Results: In normal conditions, HDAC1 is highly expressed in the VZ/SVZ in C-organoids with dynamic levels of acetylated histone H3/H4. When the C-organoids were cultured with a HDAC1-inhibitor, MS275, a severe disruption of the formation of ventricle-like structures or the cortical layers was observed. After hypoxic inujury, analysis highlighted a disorganization of cortex-like structure as well as a reduction of SVZ proliferation and neuronal differentiation, along with a change in levels of acetylated histone H3/H4 in the VZ/SVZ. Remarkably, when C-organoids were culture in low-oxygen tension with the HDAC1-inhibitor, cortical structures were improved, suggesting a protective role of HDAC-inhibitors in the hypoxia injury response of developing cortical tissues.

Conclusion: These results show the potential of this approach to analyze the role of epigenetic regulators during human brain development in response to hypoxia-ischemia insult.

Funding: NIH

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Prenatal Manganese Exposure and Intrinsic Functional Connectivity of Emotional Brain Areas in Children

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Background: Manganese (Mn) is an essential trace metal that is neurotoxic at high levels of exposure. The developing human brain is uniquely vulnerable to exposure to Mn, and prenatal Mn exposure has been associated with changes in brain areas subserving emotion regulation.

Methods: The goal of the present study was to examine whether prenatal Mn exposure is associated with changes in the intrinsic functional connectivity (iFC) of emotional brain areas in childhood. 15 children (aged 6-7 years) were selected from an ongoing longitudinal birth cohort study to participate in a resting state functional magnetic resonance imaging study. Prenatal Mn exposure was determined from maternal blood collected during the 2nd/3rd trimesters of pregnancy.

Results: We found that the bilateral anterior cingulate cortex and right globus pallidus showed reduced iFC with prefrontal areas in children who were exposed to higher prenatal Mn levels, and these children further showed reduced iFC between the bilateral insula and occipito-temporal areas.

Conclusion: These findings indicate that prenatal Mn exposure is associated with reduced iFC of brain areas involved in emotion regulation in children. Future studies should investigate whether this reduced iFC mediates the association between prenatal Mn exposure and emotional dysfunction.

Funding: NIEH

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Characterizing mechanisms of microglial radio-resistance

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Background: Microglia are the resident macrophages of the central nervous system. CSF1 Receptor signaling through its ligands, Interleukin-34 and CSF1, is crucial for microglial survival. The differential expression of these and other ligands allows for a brain-region specific transcriptional profile of microglia, revealing their heterogeneity. Previous studies have shown that microglia locally self-renew and are resistant to replacement from monocyte-derived cells upon exposure to ionizing radiation. The mechanism by which microglia are afforded this radio-resistance is not yet known.

Methods: using flow cytometry, RNA-sequencing, and a combination of in vivo and in vitro irradiation models, we aim to elucidate i) the micro-environmental and cell-intrinsic mechanisms conferring microglial radio-resistance, and ii) the functional consequences of this exposure.

Results: A time course of microglia cell count following 6Gy cranial irradiation shows a decline in forebrain and cerebellar microglia until 5 days post exposure, when they rebound to steady state levels. Compared to peripherally-derived myeloid cells in the brain, we also observe forebrain and cerebellar microglia accumulate less DNA damage as measured by γ-H2AX and DNA single-cell electrophoresis analysis. Lastly, forebrain microglia accumulate less γ-H2AX and proliferate significantly more, 1 week post irradiation, compared to cerebellar microglia.

Conclusions: These preliminary results suggest that microglia are more resistant to genotoxic stress than their peripheral counterparts, and that they have varied sensitivities depending on their location within the brain.

Funding: Immunology Training Grant (4T32AI007605-14).

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Behavior phenotyping of a mouse model of Phelan-McDermid Syndrome with a full deletion of Shank3 gene

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Background: Haploinsufficiency of SHANK3, caused by disruption of one copy of the gene, leads to a neurodevelopmental syndrome called Phelan-McDermid Syndrome (PMS) that can include impaired speech, intellectual disability, neurological changes, and autism spectrum traits. Numerous mouse models have been generated but most target only some isoforms while the vast majority of SHANK3 mutations found in PMS patients are deletions of the entire gene.

Methods: We generated a novel mouse model, in which all Shank3 isoforms are disrupted and carried an extensive behavioral phenotyping of neonates and adults using a battery of test designed to assess the main feature of PMS.

Results. Mice with a full deletion of Shank3 are more severely affected than models with only partial deletions. While social performances were not impaired, the homozygous mice displayed a strong object avoidance and escape behavior in several tests. Additionally, we observed a deficit in both initial training and reversal of Barnes maze. Electrophysiological recording showed that both hippocampal long-term potentiation and long-term depression are impaired in Shank3-deficient animals.

Conclusion. Our new mouse model recapitulates the core symptoms of PMS providing an improvement of both construction and face validity compared to previous model. Ongoing experiments will allow to identify neural mechanisms and brain circuitry involved in PMS and will use this model to screen potential treatments for Shank3-haploinsufficiency.

Funding: Seaver Foundation, NIMH

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Tcf7l2 controls the rewarding and pro-diabetic actions of nicotine through a brain-pancreas signaling axis

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Background: Habitual tobacco smoking dramatically increases the risk of developing type 2 diabetes but underlying mechanisms are unknown. GLP-1 stimulates pancreatic insulin secretion through a mechanism involving transcription factor TCF7L2. Recently, our laboratory identified a key role for Glp-1 signaling in the habenula in regulating the motivational properties of nicotine. Here, we investigated the role for habenular Tcf7l2 signaling in the rewarding and pro-diabetic actions of nicotine.

Methods: Drug self-administration; electrophysiology; oral glucose tolerance test (OGTT)

Results/Conclusions: We found that nAChR function was markedly disrupted in habenula of Tcf7l2 knockout rats. Tcf7l2 knockout and habenula-specific Tcf7l2 knockdown rats consumed more nicotine than wild-type rats. Chemogenetic activation of habenula increased blood glucose levels. Nicotine also increased blood glucose levels and Glp-1r or Tcf7l2 knockdown in habenula blocked this effect. We found that the habenula projects indirectly to the pancreas and other organs involved in glycemic regulation. Rats that self-administered a dose of nicotine that acts on the habenula developed a diabetes-like state, including increased fasting hyperglycemia, increased OGTT and hyperactive sympathetic system. We are currently investigating the role for habenular Glp-1r-Tcf7l2 signaling in nicotine-induced diabetes.

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Fine-mapping of the MS4A locus in myeloid cells

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Background: Genome-wide association studies (GWAS) have identified common variants in the MS4A locus to be associated with Alzheimer's Disease (AD), but the causal variants and genes, and their biological mechanisms, remain unknown. Within the brain, MS4As are selectively expressed in microglia and macrophages. Myeloid cells, which share a similar developmental lineage and gene expression pattern to microglia, also express MS4As at high levels. We use a functional genomics approach to identify the role of relevant MS4As in humans and their dysregulation in AD.

Methods: We performed fine-mapping of the MS4A locus in primary monocytes and macrophages from healthy individuals.

Results: We have identified significant eQTLs for MS4A4A and MS4A6A in myeloid cells that overlap with AD susceptibility variants. Our data does not suggest a single variant driving both effects. Several significant SNPs identified in our analyses are in high LD with AD-associated variants identified in GWAS.

Conclusions: Our results are consistent with other reports exploring the role of innate immune system dysfunction in AD. We have identified two MS4As that link genetic susceptibility to altered myeloid gene expression and are currently setting up experiments to uncover the contribution of these MS4A genes in AD.

Funding: This work is supported by the JPB Foundation.

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A novel compound promotes Aβ clearance and rescues Alzheimer's disease-related cognitive deficits through reduction of brain synaptojanin1 expression

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Background: There is an increasing need to identify more efficacious therapies to slow or stop Alzheimer Disease (AD).We previously characterized a novel mechanism whereby synaptojanin1 reduces amyloid plaque load and attenuates behavioral deficits in AD transgenic animals suggesting a new therapeutic direction for AD.

Methods: A computational screening of putative molecules with Aβ/synaptojanin1-lowering effects led to top-hits among which Nimodipine that decreased synaptojanin1/Aβ levels in cortical cultures derived from wild-type and AD transgenic mouse model (SweAPP/PS1ΔE9).We developed Nimodipine structural analogs and identified a novel compound (SynaptoCpd#9) that exhibits an enhanced potency at lowering synaptojanin1/Aβ levels in vitro with attenuated calcium channel blockade activities.

Results: Consistent with these observations,in vivo test of Nimodipine and SynaptoCpd9 using SweAPP/PS1ΔE9 transgenic mice showed that after three to six months of daily injections at a sub-therapeutic dose, SynaptoCpd#9 exhibited a greater efficacy at reducing brain synaptojanin1/Aβ levels,and rescuing cognitive deficits than its analog Nimodipine.RNA-sequencing analyses of treated mouse brain unveiled several targets for SynaptoCpd#9 that are to be characterized.PK analyses indicated that SynaptoCpd#9 blood-brain barrier penetrability and oral bioavailability were higher than Nimodipine.After three months of oral administration, SynaptoCpd#9 lowered synaptojanin1 level,significantly decreased A β levels, and improved cognitive performance in ApoE4 mice.

Conclusions: Together, our results strongly suggest a role for synaptojanin1 as a drug target in AD and SynaptoCpd#9 as a potential drug candidate for AD clinical trials.

Funding: Alzheimer Association, NIH

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Defining the Transcriptional Drivers Of Proliferation and Migration In Human Glioblastoma

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Molecular advances have revealed global chromatin reorganization in gliomas. However, the ways in which these epigenetic changes affect specific tumorigenic properties is still poorly understood. Our lab has recently shown that EGFR+ glioblastoma (GBM) cells, unlike their EGFR- counterpart, exhibit stem cell properties in-vitro and tumor initiation in-vivo. Knocking out EGFR in GBM patient cell lines attenuates but does not eliminate their proliferative phenotype, suggesting that other oncogenic drivers are also needed to maintain their stem-cell properties.

In order to better define the molecular drivers of tumorigenicity in these EGFR+ GBM populations, we utilized the Assay for Transposase-Accessible Chromatin with High-Throughput sequencing (ATAC-seq) and RNA-seq to characterize the open chromatin regions and activated transcriptomes in EGFR+/EGFR- GBM cells, and in developing neural progenitors cells (NPC) as a comparison, both derived from fresh human tissues in uncultured conditions.

Computational analysis of ATAC-seq data in GBM and NPC populations identified two distinct sets of open chromatin peaks--developmentally-shared peaks were enriched at genes related to stem cell maintenance, while GBM-specific peaks were enriched at genes related to tumor migration. For each set of peaks, we identified the most highly represented transcription factor (TF) binding motifs and confirmed the overexpression of several of these TFs, as well as of their downstream target genes, using parallel RNA-seq data.

This analysis generated a biologically meaningful list of putative TF targets that regulate GBM cell proliferation and migration, the role of which we are currently investigating in-vitro using CRISPR/Cas9.

Funding: Icahn School of Medicine at Mount Sinai

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Cognitive impairment in essential tremor is correlated with temporal lobe tauopathy burden

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Background: Recent evidence suggests that essential tremor (ET), a common age-related movement disorder, has non-motor symptomatology, including cognitive impairment. The neuropathological basis for these changes is unclear, but age-related neurodegenerative changes may play a role.

Methods: A series of clinically diagnosed patients with ET (n=20) were assessed using a battery of neuropsychological scales and systematic post-mortem evaluations were performed. To measure neuropathology, Braak tangle staging, semi-quantitative histopathological assessments, and computer-assisted quantitative morphometrics were used across multiple brain regions.

Results: We found a significant and strong negative correlation (p = .001) between global cognition and pathological tau burden using computer-assisted morphometrics. In contrast, we did not observe a correlation with amyloid burden. Vulnerability across the hippocampal sub-regions was observed and correlated to decreased executive (CA4, CA3, CA2, p = .043, .001,.01) and memory functions (CA4, CA3, CA2, p = .037, .031, .045). We also found that computer-assisted morphometrics provided markedly stronger correlations then qualitative and semi-quantitative approaches.

Conclusion: Our results support the hypothesis that cognitive impairment is correlated to elevated tau burden, not amyloid, in this cohort of ET patients. This highlights the need for future studies addressing the relationship between the pathological drivers of ET and tauopathy.

Funding: NIH

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Histone serotonylation: a novel mechanism of neuroepigenetic plasticity

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Background: Serotonin plays a critical role in neuronal plasticity, with alterations implicated in numerous brain disorders. Recent data have demonstrated the presence of 'reserve' pools of extravesicular serotonin in the nucleus of dorsal raphe neurons; it remains unclear, however, whether nuclear serotonin may plays a role independent of neurotransmission. Serotonin has previously been shown to form covalent bonds with certain proteins via transamidation by the tissue transglutaminase 2 (TGM2) enzyme, a process known as serotonylation.

Methods: We describe histone proteins as novel substrates for serotonylation in vivo utilizing a unique combination of biochemical, genome-wide and functional neurobiological approaches to delineate the molecular functions of these novel modifications in the context of neuronal development and plasticity.

Results: H3 serotonylation acts to facilitate binding of adjacent H3 methylation binding proteins, thereby promoting neuronal genic activation and the facilitation of neural development.

Conclusion: In sum, our data provide the first direct evidence that serotonin in the brain contributes directly to neuronal gene expression via a novel, neurotransmission-independent epigenetic mechanism. Such phenomena will have broad implications within the field of neuroscience and beyond.

Funding: MQ Health, Avenir Award, Sloan Research Fellowship, NARSAD.

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Intranasal Oxytocin Modulates Social Cognitive Errors in Borderline and Schizotypal Personality Disorders

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Background: Borderline (BPD) and schizotypal (SPD) personality disorders are characterized by impaired interpersonal functioning, likely due to abnormal social cognition. Mentalizing is a domain of social cognition. Hypo-mentalizing errors are simplistic interpretations of social cues, likely due to deficits in social information processing. Hyper-mentalizing errors are distorted misinterpretations of social cues, likely due to hypersensitivity to social stimuli. We aimed to characterize mentalizing errors in SPD and BPD patients and test the effects of intranasal oxytocin on mentalizing.

Methods: 45 participants(15 BPD,15 SPD,15 healthy controls[HC])watched theMovie for the Assessment of Social Cognition, a real-life, naturalistic task that measures mentalizing. Multiple-choice questions about movie characters' feelings, thoughts and intentions yield quantitative (mentalizing accuracy) and qualitative measures (hypomentalizing,hypermentalizing errors). Intervention:intranasal oxytocin 24/40IU/placebo. Social cognitive measures were compared across groups (BPD,SPD,HC), and treatments (oxytocin 24IU/40IU vs placebo) using ANOVA.

Results: BPD(p=0.017)and SPD(p=0.004)patients had lower mentalizing accuracy than HCs(F=6.411,df=2,p=0.003). BPD patients made more hypermentalizing errors(F=4.44;df=2;p=0.017)than HCs(p=0.005)and SPD patients (p=0.05). SPD patients made more hypomentalizing errors(F=9.32;df=2;p<0.001)than HCs(p<0.001)and BPD patients(p=0.040). Intranasal oxytocin increased the hyper/hypomentalizing error ratio in both BPD and SPD(F=6.84;df=1;p=0.019).

Conclusions: BPD patients hypermentalize more and SPD patients hypomentalize more. Intranasal oxytocin increased the hyper/hypomentalizing error ratio in both BPD and SPD.

Funding: Internal (University)

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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 deletions in NRXN1 are strongly associated with schizophrenia and autism spectrum disorder. Animal models of homozygous NRXN1 deletions and human induced neurons with engineered heterozygous NRXN1 deletions exhibit deficits in synaptic transmission and neurotransmitter release; however, the molecular mechanisms affecting the penetrance of NRXN1+/- deletions in human neurons and the functional consequences of patient specific NRXN1+/- mutations remain unresolved.

Methods: Using a rare cohort of human induced pluripotent stem cell (hiPSC) derived neurons from four individuals with psychosis and NRXN1+/- deletions and four matched controls, we performed targeted single molecule long read sequencing along with short read sequencing to identify and quantify the complete repertoire of NRXN1α isoforms in this cohort of hiPSC-derived neurons.

Results/Conclusion: hiPSC-derived neurons from NRXN1+/- individuals display differential NRXN1 expression at the gene, transcript and exon level. Preliminary analysis of long read sequencing from hiPSC neurons derived from 5 individuals has identified over 1500 unique NRXN1α isoforms, with many differentially expressed isoforms in NRXN1+/- individuals. Future work will focus on understanding the functional significance of these differentially expressed isoforms using a multi-electrode array. Overall this work may provide insight into how NRXN1 deletions contribute to the genetic risk for neuropsychiatric disorders.

Funding: NIH, NYSCF, NARSAD

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Uncovering the role of long non-coding RNAs (lncRNAs) in autism spectrum disorders (ASD) using integrated transcriptomic approaches

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Background: The contribution of non-coding genomic elements remains largely unexplored in ASD. LncRNAs are increasingly recognized for their role in transcription regulation, and likely contribute to transcriptome dysregulation in ASD.

Methods: We are applying a combination of short-read and long-read RNA-Seq, with and without lncRNA capture to unveil the role of lncRNAs in ASD. We used capture-sequencing (SeqCap) to profile lncRNA expression in postmortem prefrontal cortex (PFC) and cerebellum (CBL) tissue in a cohort of 40 ASD and controls (CTL). We additionally performed full-length isoform sequencing with capture (Capture-IsoSeq) to build a comprehensive map of brain-expressed lncRNAs.

Results: SeqCap enrichment increased the lncRNA fraction of our RNA-Seq datasets from 5% to 57%. We identified 28 differentially expressed (DE; FDR<0.05) lncRNAs and transcripts of unknown coding potential (TUCPs) between ASD and CTL. A “guilt-by-association” analysis further revealed genes under putative cis-regulation of DE-lncRNAs that are implicated in pathways dysregulated in ASD. Finally, Capture-IsoSeq profiling identified ~3,600 novel multiexonic lncRNA/TUCP isoforms expressed in PFC. We have identified many DE lncRNA/TUCP transcripts in a preliminary cohort of 40 ASD and CTL from two different brain regions as a first step towards understanding the role of lncRNAs in ASD etiology.

Conclusions: SeqCap substantially improves our ability to profile lncRNA expression and reconstruct poorly annotated lncRNA isoforms.

Funding: Seaver Foundation, NIH

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Altered neuroticism-associated gene expression in mouse model of cognitive impairment

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Background: Neuroticism is a long-term tendency to experience negative emotions that is also considered to be an underlying vulnerability factor of psychopathology. Neuroticism has been extensively linked to depression, anxiety and sleep disorders, also known as risk factors of Alzheimer’s disease (AD) onset and dementia. To date, the molecular mechanisms of this association are unknown.

Methods: Based on previously published genome wide association studies we specifically focused on 3- identified neuroticism associated Loci. Leveraging this information, we quantified by qPCR hippocampal gene expression in mouse model of acute sleep deprivation (SD) - induced cognitive impairment, assessed by novel object location test for spatial memory.

Results: We found significant diminution of hippocampal gene expression of the glutamate receptor ionotropic kainate 3 (GRIK3) ($p < 0.03$), Kelch-like protein 2 (KLHL2), and actin binding protein involved in hippocampal neuronal cell death ($p < 0.01$), and Protein Tyrosine Phosphatase Receptor Type D (PTPRD) ($p < 0.01$) in response to acute SD relative to control (n=10-13/ group). Altered gene expression was correlated with cognitive impairment.

Conclusions: We present evidence implicating altered expression of neuroticism associated genes as a potential risk factor of cognitive deterioration that may be relevant to preclinical AD and dementia. This work informs new research into neural mechanisms underpinning neuroticism and potential novel intervention in individuals with high risk for AD and dementia.

Funding: P50AT008661-01 Center funded by the NCCIH / ODS and the Altschul Foundation.

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Relationship between pre-lesion connectivity and dynamic plasticity in non-human primates

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Background: The brain displays a remarkable ability to adapt following injury in order to recover function. However, the principles that govern which areas undergo plasticity, and when, are not well known.

Method:Here, we investigated the time-course of plasticity in monkeys after a focal neurotoxic lesion to the hippocampus using multi-modal MRI.

Results: We find widespread functional connectivity alterations throughout the brain, and that the timing of connectivity changes is critically dependent on connectivity with the hippocampus before the lesion. Acutely following the lesion the greatest changes are in areas that are least functionally connected with the hippocampus, but over time this pattern reverses, indicating dynamic reorganisation. This happens despite structural damage being stable, and limited to structures directly connected with the hippocampus.

Conclusion: Our findings shed light on the time-course of functional connectivity changes following damage in the otherwise healthy brain, and may guide studies of adaptive, and maladaptive, plasticity in human patients.

Fundins: Charles H. Revson Foundation, Icahn School of Medicine at Mount Sinai

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Exploring somatic variation in schizophrenia

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Background: Although multiple recent genetic studies have identified numerous schizophrenia (SCZ)-risk loci, these variants account for only a small portion of the disease’s heritability. One potential explanation for this is that not all SCZ risk variants are inherited through the germline, but instead arise as spontaneous mutations during development. We explore the hypothesis that such mutations might contribute to the etiology of SCZ.

Methods: Neuronal and non-neuronal nuclei were isolated from prefrontal cortex (PFC) of 5 SCZ cases and 4 controls using FACS. Genomic DNA was subjected to whole-exome sequencing (WES) and identified variants validated by digital-PCR (dPCR) and sanger sequencing.

Results: We identified 23 and 3 somatic single nucleotide variants (SNVs) in SCZ cases and controls, respectively (Fisher’s exact test: $P = 0.055$). Interestingly, we identified 10 non-synonymous SNVs in SCZ, 80% of which were validated using dPCR and sanger sequencing. Conversely, no non-synonymous SNVs were found in controls.

Conclusions: We identified a trend for somatic SNVs in SCZ, including non-synonymous variants that were validated using two independent experimental approaches. Our preliminary study supports the hypothesis that somatic mosaicism contributes to SCZ.

Funding: NIH/BBRF/VA

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RGSz1: A promising novel target for improving morphine analgesics

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Background: Regulators of G protein signalling z1 (RGSz1) is a member of the RGS family of proteins, known to modulate the amplitude and direction of signal transduction of several G protein coupled receptors (GPCR). RGSz1 is expressed in moderate amounts throughout the brain, and is present in several brain regions expressing mu opioid receptors (MOPR).

Methods: constitutive/conditional knockout mouse models, RNAsequencing, Western blot, Co-Immunoprecipitation, Behavioral test

Results: Using genetic mouse models for global or brain region-targeted manipulations of RGSz1 expression we demonstrate that prevention of RGSz1 action increased the analgesic efficacy of MOPR agonists such as morphine, fentanyl and methadone. In addition, prevention of RGSz1 action delays the development of morphine tolerance, but decreases sensitivity to the rewarding and locomotor activating effects of morphine, and does not affect the development of physical dependence. Using RNA seq analysis we elucidated the pathways affected by RGSz1 activity in the PAG, and identified key adaptations in the Wnt pathway associated with analgesic tolerance to morphine.

Conclusion: These findings reveal novel intracellular molecules that can be targeted to optimize the actions of opioids used for the treatment of chronic pain.

Funding: NINDS

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Gene Regulation as a Function of Epigenetic Marks and Cell Types in Human Brain.

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Background: The goal of our project is to understand the role of regulatory elements of gene as a function of epigenetic marks (H3K4me3, H3K27ac) and cell types (neuronal and non neuronal cells) in human brain.

Methods: We carried out ChIP-seq on human post-mortem frozen brain samples from dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) regions of the brain. We have studied epigenomic profile of 17 individuals from ACC, DLPFC brain regions in neuronal and non-neuronal cell populations for two epigenetic marks (H3K4me3, H3K27ac.)

Results: H3K4me3 and H3k27ac enriched regions were clustered by cell types: neuronal and non-neuronal whereas these regions didn't shown any difference among tissue types: ACC and PFC. The genomic annotation of enriched regions showed varying distribution of promoter regions, exons, introns, 5'UTR, 3' UTR and distal intergenic elements across cell types. We studied statistical analysis of differential histone modification for H3K4me3/H3K27ac enriched regions for different cell types. We investigated the overlap of schizophrenia genes and neuronal, non-neuronal enriched regions for both H3K4me3 and H3k27ac marks.

Conclusions: The chip-seq is done for the first time for H3K4me and H327ac marks for both cell types and is a step towards understanding the molecular etiology of schizophrenia. Our data provides deep insight into the histone enriched regions as a function of cell type: neuronal vs. non-neuronal.

Funding: Psychencode

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Granulocyte-Colony Stimulating Factor (G-CSF) Modulates Behavioral Response to Cocaine

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Background: Addiction to cocaine and other psychostimulants remains a major public health issue, yet pathophysiological mechanisms leading to persistent dysregulated drug use remain incompletely understood. There is growing evidence showing that immune system dysfunction plays a role in the pathophysiology of psychiatric disorders, and evidence has begun to accumulate that cocaine alters immune signaling in ways that may drive pathological use behaviors. From a broad assay of serum cytokines we identified G-CSF as a factor that was upregulated by cocaine, and serum level directly correlated with behavioral response to the drug.

Methods: Using locomotor sensitization, conditioned place preference, and cocaine self-administration techniques we assayed how manipulations of systemic G-CSF affect behavioral response to cocaine.

Results: Pre-treatment with systemic G-CSF resulted in enhanced locomotor sensitization in response to repeated injections of cocaine. Similarly, pre-treatment with G-CSF lead to a left-shift in the dose response curve for cocaine conditioned place preference. In a behavioral economics model that evaluates how animals seek drug in response to increased effort to acquire cocaine, G-CSF treated animals were insensitive to increases in effort and continued to seek cocaine even with low likelihood of reward.

Conclusions: These studies suggest a significant role for G-CSF signaling in the neurological and behavioral response to cocaine, and provide a new target for research into development of therapeutics.

Funding: NIDA, Leon Levy Foundation

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Underlying neuronal circuitry of attention in a rat model of Fragile X Syndrome

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Background: Fragile X Syndrome (FXS) is a neurodevelopmental disorder that is considered to be the most common identified monogenic cause of autism spectrum disorder and intellectual disability. FXS is caused by a reduction in the Fragile X Mental Retardation Protein (FMRP), which is encoded by the FMR1 gene. FXS patients exhibit severe deficits in neural activity of the prefrontal cortex (PFC) and in attention, a PFC-related function. Additionally, prefrontal grey and white matter, as well as regional volumes, are aberrant. These abnormalities have been associated with PFC-dependent cognitive impairments.

Method: To investigate the effects of Fmrp loss on neuronal communication during PFC-dependent behavior, local field potentials will be recorded from prefrontal regions of Fmr1-KO rats during the five-choice serial reaction time task (5-CSRTT), a test of attention. This study will also examine the grey and white matter, as well as volume, of prefrontal regions with magnetic resonance imaging (MRI).

Results: Fmr1-KO rats showed increased omissions on the 5-CSRTT. These deficits suggest that sustained attention is impaired in Fmrp-deficient rats.

Conclusion: This multi-level approach will allow for a better understanding of neural mechanisms affected in FXS-related cognitive impairments.

Funding: NIMH T32, Seaver Autism Center

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Imprinted genes in the brain

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Background: Genomic imprinting is an epigenetic mechanism that regulates imprinted genes' expression by selectively repressing one or the other allele; we call this allelic bias. Besides placental development and growth, neuropsychiatric function has been linked to imprinted genes. In the brain 0.5% of all genes have been repeatedly suggested to be imprinted but one study found 5%. Even less clear is how allelic bias of any given imprinted gene might vary with age, genotype, gender, and psychiatric condition.

Methods: We studied genome-wide allele-specific expression patterns in brain samples from nearly 600 individuals (CommonMind Consortium). We estimated allelic bias with the read count ratio from RNA-seq and genotyping array data. The heterogeneity of individuals in age, gender, ancestry, and diagnosis of schizophrenia provided basis to infer how allelic bias depends on these.

Results: Supporting most previous estimates we found only 30 imprinted genes, eight of which are novel. Exploratory analysis showed that age differentially affects allelic bias of the 30 genes. Unfortunately, the high inherent noise of next-generation sequencing undermines such qualitative results regarding age and other predictors. We are now addressing this with statistical models that account for the complex interdependence of biological predictors and technical noise, and allow differential effects on genes.

Conclusions: Our work helps clarify the number and identity of imprinted genes in the brain. Moreover, subtle patterns of imprinting and allelic bias are emerging as we improve correction for technical noise.

Funding: 02550422

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Alterations of regulatory RNA in the dorsolateral prefrontal cortex contribute to risk for schizophrenia

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Background: We have developed the CommonMind consortium to analyze molecular data from human brain samples in schizophrenia. In this study, we examined changes of the enhancer RNA in schizophrenia.

Method: Enhancer sequences were predicted using cell type-specific (neuronal and non-neuronal) ATAC-seq profiles and FANTOM5 CAGE data. Quantitative trait loci (QTL), differential expression and coexpression network analysis for Ensembl and regulatory transcripts was conducted in 537 human post-mortem samples (258 schizophrenia samples and 279 controls) from the dorsolateral prefrontal cortex (DLPFC). After QC steps, 1,387 regulatory and 21,312 Ensembl transcripts were robustly expressed and subsequently used for downstream analysis.

Results: Differential expression was detected with 118 regulatory and 1,647 Ensembl transcripts in the DLPFC at an FDR of 5%. Gene coexpression analysis identified a subnetwork of 94 regulatory and 1,181 Ensembl transcripts subserving functions related to synaptic transmission that is significantly perturbed in schizophrenia and is highly enriched for schizophrenia genetic signal. Co-localization analysis of expression QTLs linked regulatory and Ensembl transcripts with schizophrenia risk variants.

Conclusion: Our findings point to a functional link between schizophrenia susceptibility loci and regulation of gene expression affecting transcripts clustered in specific subnetworks.

Funding: NIH, VA, FBI

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Deficiency of TYROBP is neuroprotective in a mouse model of early Alzheimer's pathology

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Background: Immune-inflammatory pathways have been identified as key events in the pathogenesis of Alzheimer's disease (AD). TYROBP, a microglial protein, is a direct partner/adapter for several AD related proteins including TREM2, CD33, CR3, and its expression is increased in AD. Moreover, missense mutations in TYROBP have been identified in AD. This evidence points to TYROBP as a potential driver protein in AD.

Method: We crossed the APPKM670/671NL/PSEN1Δexon9 AD mouse model with Tyrobp(-/-) mice. Using a panel of biochemical, physiological, behavioral, and transcriptomic assays, we evaluated the role of TYROBP in AD.

Results: While TYROBP deficiency leads to minor effects on levels of amyloid-β peptides, the morphology of amyloid deposits was modified similar to that reported by others for Trem2(-/-) mice. We identified beneficial modulation of TYROBP deficiency on the phosphorylation of TAU, leading to a reduction in the severity of neuritic dystrophy. TYROBP deficiency altered the expression of several AD related genes, including Cd33. Electrophysiological abnormalities and learning behavior deficits associated with APP/PSEN1 transgenes were greatly attenuated on a Tyrobp-null background.

Conclusion: These results suggest that reduction of TYROBP gene expression and/or protein levels could represent an immune-inflammatory therapeutic opportunity for modulating LOAD at early stages.

Funding: NIH; Foundations: Louis Mayer, Cure Alzheimer's, BrightFocus

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Developmental Changes in Tau Protein Expression and Splicing

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Background: The tau pre-mRNA undergoes alternative splicing to produce multiple protein isoforms. Animal studies have demonstrated a perinatal shift from short to long isoforms, but tau splicing and isoform expression during human brain development have not been well characterized.

Methods: We used multiple large publicly available transcriptomic datasets and RNA in-situ hybridization to map tau regional and temporal variation in tau expression in the developing human brain.

Results: Exons 2 and 10 of the MAPT gene showed a dramatic (>1.5-fold) and statistically significant ($p<0.01$ by glm with time) perinatal increase in splicing index that is unique among the canonical human microtubule associated proteins. This finding was confirmed in two independent data sets. Immature regions (e.g., the ganglionic eminence) showed significantly lower levels of total, 3R and 4R tau expression compared to cortex. RNA in situ hybridization confirmed that 3R tau is the predominant isoform in maturing neurons of the fetal cortex, while adult cases show approximately equal levels of 3R and 4R mRNA.

Conclusions: Immature neuronal precursors express low levels of tau protein, which is a marker of neuronal differentiation. Neurons in the cortical plate show a uniform shift from shorter to longer tau isoforms during the perinatal period with little change before or after.

Funding: Alzheimer's Association, NIH, DOD

Abstracts

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ESTABLISHING A CRISPR-BASED PLATFORM TO STUDY SCHIZOPHRENIA-ASSOCIATED GENES IN HUMAN NEURONS

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Background: Schizophrenia (SZ) is a complex genetic neuropsychiatric disease inherited via both common and rare polygenic risk factors. SZ genome wide association studies (GWAS) have identified many SZ-associated single nucleotide polymorphisms (SNPs) positioned in the putative enhancer regions of neuronal genes, suggesting a link between these SNPs, their respective neighboring gene(s), and SZ risk. Recently, the CommonMind Consortium (CMC) identified five genes with the strongest correlation between genotype and brain expression levels: FURIN, SNAP91, CLCN3, TSNARE1 and CNTN4 (herein referred to as the "CMC genes"); however, the functional role of these five genes in post-mitotic human neurons remains unresolved.

Method: We adapted a CRISPR activation and interference (CRISPRa and CRISPRi, respectively) platform to NGN2-induced excitatory neurons, enabling manipulation of CMC gene expression in human neurons.

Result: we generated CRISPRa (dCas9-VPR) and CRISPRi (dCas9-KRAB) stable NPC lines to achieve consistent expression of dCas9-effectors, and then validated lentiviral-expressed gRNAs for each gene in NGN2-neurons generated from 3 control individuals.

Conclusion: We built up a scalable CRISPRa and CRISPRi platform to manipulate CMC gene expression in human excitatory neurons.

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

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alpha5 nAChR modulation of ventral striatal circuitry controls cocaine reward

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Background: A loss of function SNP in the gene coding for the alpha5 nAChR has been linked to an increased propensity for nicotine addiction. Interestingly, this same SNP appears to be protective against developing cocaine use disorders. Our on-going experiments are aimed at identifying the neural mechanisms underlying the counter-intuitive link between this subunit and the use of different drugs of abuse.

Method: We used a combination of genetically modified mice, behavioral assays of cocaine sensitivity, in vitro electrophysiology, optogenetics, DREADDS, and in vivo calcium imaging.

Results/Conclusion: The rewarding effects of cocaine were found to be diminished in mice lacking the alpha5 nAChR. Loss of alpha5 nAChR modulation also changed the response of cholinergic interneurons (CIN) in the ventral striatum to optogenetic stimulation, and diminished the capacity of cocaine to modulate their activity. Inhibition of alpha5 nAChRs in the major sources of input to CINs, including the parafasicular thalamus and prefrontal cortex, similarly reduced cocaine reward. Our combined data reveal that through its modulation of multiple arms of cortico-mesolimbic reward circuitry, the alpha5 nAChR can play a central role in controlling consumption of multiple drugs of abuse.

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Meta-Analytic Connectivity Modeling Reveals Thalamus Connectivity Dysfunction in Drug Addiction.

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Drug addiction is a complex disorder, characterized by excessive drug use despite adverse consequences. Current models highlight the importance of the midbrain reward system and the prefrontal cortex cognitive control network. The thalamus is thought to link these two networks, however, its involvement in drug addiction is not well understood. Here we examine the network of regions that co-activate with the thalamus in drug addiction using the activation likelihood estimation (ALE) with meta-analytic connectivity modelling (MACM). We identified 17 drug addiction-related papers that showed activation within the thalamus in the BrainMap database. Of these, 6 papers had a Drug Abuse > Healthy Control contrast, resulting in 189 subjects across 10 experiments; 5 papers had a Healthy Control > Drug Abuse contrast resulting in 155 subjects across 9 experiments. We find that in the Drug Abuse > Healthy Control contrast, the thalamus co-activates with a network of frontal, parietal and limbic regions including the dlPFC, ACC, anterior insula, PCC, IPS, and hippocampus. In the Healthy Control > Drug Abuse contrast the thalamus co-activates with temporal and striatal regions. These differential coactivation patterns indicate the potential dysregulation of the thalamus dysregulated in drug addiction, particularly in its connectivity patterns with brain regions in the salience, default and cognitive control networks. Our findings represent the importance of further investigation of the thalamus in drug addiction.

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Transcriptomic Imputation of gene expression across multiple brain regions reveals patterns of Schizophrenia risk throughout development

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Division of Psychiatric Genomics

Background: Transcriptomic Imputation (TI) methods harness powerful machine-learning techniques to quantify complex relationships between genotype and gene expression levels. This allows us to predict and study the transcriptomes of large psychiatric GWAS datasets. Here, we apply these methods to characterize gene expression and molecular pathologies in the largest collection of individuals with schizophrenia to date (SCZ).

Methods: We created gene expression prediction models for the dorso-lateral pre-frontal cortex (DLPFC) across 10,929 genes, using CommonMind Consortium data. We applied these and pre-existing models to predict gene expression and test for disease association in 40,299 SCZ cases and 65,264 controls. We examined enrichment of molecular pathways, and spatio-temporal expression of these genes using publicly available developmental transcriptome data.

Results: We identified 413 genome-wide significant ($p<4x10-7$) genic associations, of which 71 remain significant after conditional analysis. Examining expression patterns of these 71 genes throughout development revealed a set of genes with predominantly pre-natal expression, and a set of exclusively post-natally expressed genes.

Conclusion: We created the first DLPFC TI prediction models, and used these to identify novel genic associations for SCZ. These results help to elucidate developmental trajectories and molecular pathologies of the disease.

Funding: NIH

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Cortical Response during Language Learning in Autism Spectrum Disorder

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Almost 40% of individuals with autism spectrum disorder(ASD) never develop speech, contributing to poorer cognitive and functional outcomes. Understanding the neural basis of language learning in ASD can clarify core deficits and potentially inform effective intervention targets.

Twenty-eight individuals (15ASD; 13typically developing (TD)) heard prerecorded “non-word” stimuli during a passive-listening task. One non-word repeated 50 times; all other words were presented once. Following pre-processing procedures, mean amplitude and latency for the positive-going peak between 250-550ms post-stimulus were extracted over temporal-parietal electrodes.

Both ASD and TD showed significant differentiation of neural response to repeated non-word stimuli: both showed greater amplitude for Repeated versus Novel stimuli (main effect of Condition, $F(1,26)=5.34, p<.05$). However, latency differences were observed between groups. Overall, ASD participants had faster latency, (main effect of Group,$F(1,26)=10.85, p<.01$). However, whereas TD participants responded faster to repeated versus novel non-words, ASD participants showed slower responses to repeated non-words (Group-by-Condition Interaction,$F(1,26)=5.41, p<.05$).

Results demonstrate significant differences in TD and ASD novel language processing. In TD, neural response latency is shorter for repeated stimuli, likely reflecting faster processing when learning new word-like stimuli. In ASD, response latency is faster to novel versus repeated non-word stimuli. Coupled with greater amplitude to repeated stimuli, the ASD latency finding could suggest that language learning occurs in ASD, but is associated with relative slowing of neural processing. This effect may contribute to inefficient language learning in ASD.

Funding: Seaver Foundation

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Investigation of the Cortical Connections of the Macaque Monkey Thalamus Using Diffusion Imaging: Validation of a Key Technique

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Background: Connectivity patterns of the brain determine function. Diffusion weighted imaging (DWI) is a powerful technique for investigating these connectivity patterns in the human brain. However, there is a continued need for studies directly validating DWI, as the gold standard for connectivity is still tract tracing studies in macaque monkeys. We used probabilistic DWI tractography to produce probabilistic maps of the whole-brain connections of the thalamus in monkeys.

Methods: We used high-resolution DWI scans acquired from 19 macaque monkeys on a 3 Tesla MRI scanner and carried out probabilistic tractography from regions of interest in the thalamus to cortical subregions.

Results: We show distinct patterns of connections to thalamic subregions based on the likelihood of anatomical connectivity to each of the cortical subregions. We were able to parcellate the thalamus into subnuclei based on these patterns. Thalamic organization was consistent across individual monkeys.

Conclusions: We found a close correspondence between our probabilistic parcellation of the monkey thalamus and both the results of tract tracing studies in monkeys and previous DWI tractography findings in human subjects. Future work will focus on direct comparisons between the human and monkey thalamus.

Funding: Ichan School of Medicine at Mount Sinai Seed Fund, MRC and Wellcome Trust UK

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Pharmaceutical-Wide Association Study between Maternal Medication during Pregnancy and Neurodevelopmental Disorders in Offspring.

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Maternal medication during pregnancy is a risk factor for neurodevelopmental disorders in offspring (e.g. Wyszynski et al., 2005). Nevertheless, the underlying mechanisms are still poorly understood. Studies provided mixed evidence regarding the role of maternal indication (Croen et al.,2011; Hviid et al.,2013), thus failing to disentangle the effects of the medication from other genetic and environmental factors associated with the disorder. Similarly, although some biological pathways have been shown to be vulnerable to an early pharmaceutical challenge (Hernández-Díaz, 2000), a range of potential biological mechanisms has not been systematically evaluated.

Using two population-based prescription registers, we performed the first pharmaceutical-wide association study to date. Grouping nearly 1000 different medications by their biological target allowed us to collate signals from a range of medications targeting the same pathway. This increased our ability to detect true effects, as well overcome confounding by indication.

Maternal exposure to medication targeting several biological pathways was associated with a significant increase in offspring risk of neurodevelopment disorders, controlling for multiple testing.

Our results uncover novel associations between early interference in particular biological pathways and subsequent neurodevelopmental disorders in offspring.

Magdalena Janecka received Seaver Autism Centre postdoctoral fellowship

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VGF function in depression and antidepressant efficacy

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Background: VGF (non-acronymic) is a secreted protein and neuropeptide precursor that is robustly regulated by BDNF/TrkB signaling in CNS neurons.

Methods: We used viral-mediated VGF knockdown to examine the region-specific roles of VGF in depression. We employed intrahippocampal cannulation and infusion to explore the molecular mechanisms underlying the antidepressant effects of VGF-derived peptide TLQP-62.

Results: VGF is downregulated in dorsal hippocampus (dHc) and upregulated in nucleus accumbens (NAc) in depressed human subjects and in mice susceptible to chronic social defeat stress (CSDS). Viral-mediated Vgf ablation in dHc or NAc led to prodepressive or antidepressant behaviors, respectively. Intrahippocampal TLQP-62 infusion had rapid antidepressant efficacy, which was reduced in dHc BDNF knockdown mice, and in NBQX- and rapamycin-pretreated wild type mice.

Conclusion: In the CNS, VGF expression is regulated by depression in a region-specific manner that parallels BDNF expression. VGF functions in a region-specific manner to regulate depressive behavior. TLQP-62 produces antidepressant effects via mechanisms similar to ketamine.

Funding: NIH (SRS and SJR); Hope for Depression Research Foundation (SRS); Brain and Behavior Research Foundation (SRS)

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Dynamics of spindles across motor learning in mice

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Sleep spindles have been implicated in offline gains during human motor learning with an increase in topographically relevant cortical areas following motor learning and the degree of increase has correlated with the degree of offline gain.

C57/Bl6 mice completed motor learning during 10 trials/day on an accelerating rotarod (4-40 RPM over 5 minutes) on 2 consecutive days. Between days 1 and 2, mice were recorded with video-polysomnography with EEG leads targeted over bilateral primary motor cortex under conditions of ad libitum sleep or 10 hours of sleep disruption.

Offline gain in rotarod performance was observed in normally sleeping animals between days 1 and 2, and such gain was significantly attenuated in animals undergoing sleep disruption. Sleep disruption resulted in reduced total sleep time (both non-REM and REM sleep), increased sleep fragmentation, and reduced spindle count but not spindle density. Sleep following rotarod learning was marked by an increase in both spindle count and density in the first 2 hours, without significant change in spindle duration, coherence, or power in the spindle band (10-16 Hz).

Ad libitum sleep following rotarod motor learning displays an early increase in spindle count and density and results in greater offline gains in motor performance than sleep that is disrupted for the first 10 hours following rotarod learning.

American Sleep Medicine Foundation

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Sex differences in the brain's gray matter in cocaine addiction

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Psychiatry & Neuroscience

Background: Imaging studies published to date in individuals with cocaine use disorder (iCUD) have overlooked sex differences in neuroanatomy. Here we used voxel-based morphometry (VBM) to study the differences in reduction of gray matter (GM) volume between female and male iCUD.

Methid: Brain structure (T1-weighted MRI) was pooled from 6 laboratories including 184 individuals (92 iCUD). The data is part of the multi-site Enigma Consortium, preprocessed similarly at each site by the FreeSurfer pipeline and analyzed using the VBM toolbox. General linear model was applied with contrasts between female control vs. iCUD and male control vs. iCUD. Total intracranial volume, age and laboratories were included in the model as covariates.

Results: Preliminary results revealed significant sex differences in the reduction of GM in two brain regions. Left orbitofrontal cortex GM reduction was found for the male iCUD compared to the male control group while right anterior insula GM reduction was found in the female iCUD compared to the female control group ($P<0.001$, uncorrected).

Conclusion: Findings suggest sex differences in GM reduction in iCUD such that male iCUD showed Left orbitofrontal cortex GM reduction and female iCUD showed right anterior insula GM reduction. These results may help to guide different treatment approaches, for example treatment for females may emphasize self-awareness, while male treatment may emphasize decision making related to reward.

Funding: NIDA

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FACS-RNAseq reveals distinct roles for D1 and D2 medium spiny neurons

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Background: Stress induces pathological changes in the nucleus accumbens (NAc), a largely GABAergic nucleus receiving dopaminergic input from the ventral tegmental area. The NAc contains distinct neuronal populations, the most abundant of which are the dopamine-responsive, GABAergic medium spiny neurons (MSNs). MSNs are subdivided by their response to dopamine, with one class expressing predominantly the dopamine receptor type 1 (D1) and the other expressing type 2 (D2). While these MSNs utilize different G protein signaling cascades and play different – and often opposing – roles in stress responses, few D1- and D2-enriched genes are known. The purpose of the present study was to define transcriptional signatures for D1 and D2 MSNs at baseline and in response to stress.

Method: FACS-RNAseq of neuronal nuclei followed by bioinformatic analysis of upstream regulators was used to assess the unique roles of D1- and D2-MSNs.

Results: At baseline, D2-MSNs show much more transcriptional complexity than do D1-MSNs. With stress, D2-MSNs altering their transcriptional landscape to more closely resemble D1-MSNs, while D1-MSNs adopt a more complex phenotype.

Conclusion:The improved resolution of cell type-specific over whole-tissue RNAseq in NAc uncovered transcriptional effects previously masked by population averaging, and generated novel targets for genetic manipulation to promote stress resilience.

Supported by NIMH

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Ventral Tegmental Area GABAergic Modulation of Dopamine in Social Defeat Stress

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Background: Major depression is a highly prevalent mental disorder with an increasing social burden. Current antidepressants are not efficacious in approximately 30% of depression patients, highlighting a need to develop better treatments. Clinical studies and preclinical models of depression have identified the mesolimbic reward circuitry as a possible mediator of depression symptoms. In particular, our laboratory has identified the ventral tegmental area (VTA) as a key substrate for mediating susceptibility or resilience to chronic social defeat stress (CSDS). VTA dopamine (DA) neurons are functionally heterogeneous; VTA DA neurons projecting to the nucleus accumbens (NAc; VTA-NAc) exhibit a pathological hyperactivity specific to susceptibility and social avoidance behaviors. Although DA neurons are the major cell type in the VTA (~65%), gamma-Aminobutyric acid (GABA) neurons are ~30% of the VTA.

Method: We use the CSDS model for depression with electrophysiological and optogenetic techniques.

Results: Susceptible mice exhibit VTA GABA hypoactivity. We also observe decreased inhibitory tone on VTA-NAc DA neurons after CSDS. The physiological changes within the VTA microcircuitry have behavioral relevance in defeat stress; VTA GABA optogenetic stimulation rescues social interaction in susceptible mice.

Conclusion: Elucidating the contribution of VTA GABA transmission to stress-induced depression may provide novel information for better therapeutic strategies.

Funding: T32MH096678, F31MH108326

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Distribution and Regulation of R-loops in the Brain

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Background: In recent years, our understanding of the myriad functions RNA performs has grown substantially. During transcription, mRNA can reanneal to its template DNA strand to form a structure termed an R-loop. Once considered deleterious transcriptional irregularities, recent research has shown R-loops form over 5% of the mammalian genome and are conserved at specific loci. Importantly, R-loops are now thought to be involved in transcriptional regulation, though this mechanism is poorly understood. Our research is aimed at identifying factors involved in R-loop deposition/turnover, and to characterize R-loop distribution across different cell types.

Methods: The S9.6 antibody recognizes RNA/DNA-hybrids and was validated with dot blots containing synthetic R-loops. DNA/RNA Immunoprecipitation (DRIP) was performed on HEK293T cells and Fluorescence-Activated Cell-sorted neuronal and non-neuronal nuclei from mouse brain. DRIP products were sequenced and aligned, after which peak-calling and region-analyses were performed.

Results: DRIP results in HEK293T cells are consistent with datasets of similar cell-types and S9.6-staining shows expected nucleolar location. However, we have not definitively detected R-loops in mouse brain cells.

Conclusions: R-loops in HEK293T cells cluster around genomic hot-spots (e.g., promoters/terminal regions of highly-transcribed genes) and show highest density in the rDNA-containing nucleolus. Identifying R-loops in mouse neurons requires further research.

Funding: Supported by the NIH

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Sex Differences in Neuropsychiatric Phenotypes: A Rat Longitudinal Study

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Background: Sex differences in mental illnesses have long been acknowledged, but phenotype comparisons between the sexes are often studied at one particular age with limited assessments throughout the course of life. In this study, we considered concepts from the Research Domain Criteria for brain-behavior relationships relevant to psychiatric disorders in males and females during aging.

Methods: We systematically evaluated reward and motivation (palatable food self-administration), hedonia (sucrose preference), depression-like (forced swim test), anxiety (light-dark box), and locomotor (open field) behaviors in male and female rats. Subjects were born and raised in identical conditions and were tested at postnatal days 80, 180 and 300.

Results: Males consistently displayed increased motivation to self-administer palatable rewards compared to females at all three ages, although the level of reward seeking decreased with aging. In contrast to reward, females showed higher locomotor activity. No sex differences were observed in hedonic state in relation to sucrose preference, but higher immobility was apparent in males during forced swim tests, which is considered an indication of depressive symptoms. Females exhibited less anxiety behavior in light-dark box testing. In general, sex differences in specific phenotypes were maintained during aging.

Conclusion: Our results demonstrate persistent behavioral sex differences during aging and provide a framework for future studies on evaluating sex-related vulnerability to psychiatric disorders across life.

Funding: NIH grant DA033660

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Characterizing ΔFosB's transcriptional map in neuropsychiatric disorders using an HA-tagged transgenic mouse

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Neuronal gene expression mediates persistent changes in the function of neural circuits observed in many neuropsychiatric disorders. The progression of addiction, for example, begins with short-term molecular perturbations associated with brief exposure to a drug of abuse. If drug usage persists, these molecular changes initiate longer-term alterations in gene expression that activate states of cellular and circuit activity unique to the addicted brain. One well-characterized regulator of this progression is ΔFosB. ΔFosB, a splice variant of FosB, is lent unusual stability due to the loss of 3' degron domains that allows it to accumulate with continued exposure to a drug or stress. Yet the scope and extent of ΔFosB's transcriptional activity has thus far been elusive due to the lack of antibodies suitable for ChIP-seq. Here, we characterize a transgenic mouse line in which FosB is preceded by a hemagglutinin (HA) tag. As a result, ΔFosB is expressed with an HA tag fused at its N-terminus, allowing for anti-HA targeting of ΔFosB in a number of applications. Specific targeting of ΔFosB in vivo will allow for elucidating its precise genetic targets and their corresponding molecular mechanisms in mediating the onset and persistence of addiction as well as many other neuropsychiatric states.

Funding: NIDA and NIMH

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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 post-translational modifications (PTMs)–e.g., H3 glutamine 5 dopaminylation (H3Q5dop)-in brain, 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 an increase of H3Q5 dopaminylation, thereby indicating a putative role for this novel PTM in drug induced plasticity.

Funding: 1DP1DA042078, Avenir Award, 2016 Sloan Research Fellowship in Neuroscience

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IL-18 signaling in the MHb-IPN control nicotine intake

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Backgrounds: Il-18 is a key pro-inflammatory cytokine acts in the immune system and the central nervous system. Medial habenula (MHb), a bilateral structure located in the epithalamus, is the major brain structure that produce IL-18 in the CNS. Emerging evidences suggest that the activity of MHb and its downstream target Interpeduncular nucleus (IPN) is critical for suppression of nicotine consumption. Here, in this study, we utilize multiple approaches to investigate whether and how IL-18 in the MHb-IPN circuitry affects nicotine intake in rodents model.

Method: Nicotine self-administration rodents, electrophysiology recording, immunostaining

Results: First, we confirmed that IL-18 express in the dorsal part of MHb. Second, we found that local infusion of IL-18 into MHb and IPN suppress nicotine intake in a nicotine self-administration rats and its effect can be blocked by IL-1 receptors in the IPN. c-FOS staining after acute nicotine treatment show that high nicotine actives the IL-18 neurons in the MHb. Electrophysiological recording from IPN brain slice show that IL-18 enhances excitatory synaptic transmission between MHb and IPN. Interestingly, nicotine consumption was also suppressed in the IL-18ko mice and its association with over-activation of IPN by nicotine which revealed by c-fos staining.

Conclusion: We conclude that CNS IL-18 regulates nicotine intake by modulation of MHb-IPN activity through IL-1 receptors.

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Modulation of hippocampus-prefrontal cortex neural oscillations

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Background: Many neuropsychiatric and neurodevelopmental disorders are associated with fronto-temporal dysfunction. To best inform treatment options, understanding the mechanisms supporting normal communication between these distributed networks is important. Currently, synchrony of neural oscillations is thought to represent signaling and communication between brain regions. Conversely, abnormal oscillations and impaired hippocampus-medial PFC (mPFC) interactions have been found in disorders such as schizophrenia and autism spectrum. Previous research shows that modulating local field potentials (LFPs) of the hippocampus using electrical stimulation helps improve cognition and performance can be predicted based on comodulation of hippocampal LFPs in different frequency bands. However, the mechanisms by which deep brain stimulation modulates brain function are largely unknown.

Methods: We hypothesize that specific stimulation parameters (e.g. theta pulse/burst) alter oscillation patterns across structures and determine their functional effects. We tested this hypothesis by varying the magnitude and temporal patterning of fimbria fornix (FFx) electrical stimulation in behaving rats.

Results: Preliminary results show that FFx stimulation modulated the amplitude and phase relationship of theta LFPs (4-12 Hz) in CA1 and mPFC, and that they varied with stimulus type and magnitude. Theta burst stimulation increased synchrony and reduced the phase differences between mPFC and hippocampal theta LFPs.

Conclusions: Future experiments will vary patterned stimulation to determine how different stimulation parameters alter cognitive performance in memory tasks.

Funding: NIH, Seaver Autism Center

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The Roles of the OFC and mPFC in Certain vs Uncertain Environments

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Background: Behavioral flexibility is the ability to adapt to a changing environment (Kolb, 1990). The orbitofrontal cortex (OFC) is critical for guiding behavior in the face of changing stimulus-outcome associations (Schoenbaum et al., 2009b). If associations vary in a predictable way, their common features blur together to form 'learning sets', i.e. abstract rules (Harlow, 1949), which depends on an intact medial prefrontal cortex (mPFC; Fuster, 2001). How the OFC and mPFC interact to form predictions that integrate the inherent variability of change in the environment remains unknown.

Methods: We will use spatial reversals and reinforce a choice deterministically (always/never) or probabilistically (often/rarely), and assess performance after local inactivation of OFC and mPFC. Our hypothesis is that if contingencies change reliably (deterministically), mPFC-dependent abstract rules guide behavior; if contingencies change unreliably (probabilistically), then the broader reward history is tracked through OFC-dependent outcome expectancies.

Results: Preliminary results show the mPFC is needed when contingencies are reliable, and the OFC is not.

Conclusions: Future experiments will do the same under uncertain contingencies.

Funding: NIH

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Episodic emotional memories can be updated with neutral information when reactivated

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Background: Previous findings suggest that neutral episodic memories (EM) can be updated with new neutral information when they are reactivated and subsequently undergo a process called "reconsolidation". Here, we test (A) whether emotional EM can likewise be updated upon reactivation with new neutral information, and (B) whether the updating of (A) might be due to reconsolidation.

Method: Participants were enrolled in a three-day experiment. On session 1, they learned emotional items. On session 2, half of the group was reminded of session 1 and then learned new neutral items, while the half of the group was not reminded. Participants were asked to recall emotional items learned on Session 1, on (A) Session 3 or on (B) Session 2.

Result: On session 3, (A) the reminder group versus no-reminder group reported more neutral intrusions, when they recalled the emotional items. Finally, for (B), when memory for emotional items learnt on session 1 was tested right after learning neutral items on session 2, reminder vs. no-reminder group showed a similar level of neutral intrusions.

Conclusion: We show that neutral EM can be incorporated into an originally emotional memory at a later point by reactivating the emotional memory through the process of reconsolidation.

Funding: Swiss National Science Foundation and University of Geneva

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Memory allocation is disrupted in conditional WT1 KO mice

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Background: Little is known about memory allocation, the process that determines which neurons in a neural network will store a specific memory. Contextual memories are encoded in sparse populations of neurons in the hippocampus. Recent findings showed that shared neuronal populations may link distinct memories close in time, and increasing neuronal excitability affects the probability of a neuron to participate in a memory trace or engram.

Methods: WT1flox/flox mice were injected with AAV8-Cre virus into the Dentate Gyrus (DG) in order to generate animals that express a non functional WT1 protein specifically in that region. A separate group of animals was injected with both AAV8-Cre virus and AAV8-hM4D(Gi) virus. Both groups were challenged in a sequence of different contexts where only one context was paired with two foot shocks.

Results: Mice lacking functional WT1 protein showed increased neuronal excitability, as indicated by enhanced LTP, and formed false memories, as measured by higher freezing time in the neutral context A (never shocked). We blocked the behavior finding by injecting CNO in animals expressing the hM4D(Gi) receptor.

Conclusion: These findings suggest that the increase in excitability caused by knocking down WT1 in DG cells interferes with memory allocation leading to formation of false memory.

Work supported by NIH grant.

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Adolescent maturation of frontal top-down cortical circuits to establish visual attention

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Background: Cortico-cortical connections rewire postnatally when structural and functional underpinnings for adult cognition are established. A long-range top-down projection from the anterior cingulate cortex (ACC) to the visual cortex modulates visual processing, a hallmark component of visual attention. Dysregulated top-down functional connectivity is observed in several neurodevelopmental disorders during attention tasks, however, pathophysiologic insight is limited. Here we identify contributions of adolescent top-down development to adult attentional behaviors.

Methods: Developmental changes in top-down connectivity were detected by circuit-specific rabies-mediated input-mapping in adolescents and adults. Changes occurring on post-synaptic top-down neurons were identified by dendritic spine analysis. Functional impact of adolescent neuronal activity for adult attention was assessed by chemogenetic silencing of top-down neurons during adolescence and subsequent five choice serial reaction time task (5CSRTT).

Results: More “local” inputs onto top-down neurons from the ACC and secondary motor area were observed in adolescents compared to adults. This developmental input pruning was coupled to a loss of spines on proximal apical dendrites. Adolescent silencing of top-down neurons led to specific deficit in attentional behavior in adulthood.

Conclusions: Our study demonstrated adolescence as a key window for the maturing top-down cortical circuit to establish proper visual attention processing in adulthood by engaging longer, more distal connections through loss of local excitatory input.

Funding: R21MH106919-01A , 1F30MH111143-01A, Seaver Foundation

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Integrated analysis of rare variation in schizophrenia and other neurodevelopmental disorders

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Background: Family and case-control sequencing studies have implicated large gene sets in schizophrenia (SCZ); however, very few individual risk genes have been identified.

Method: We developed hierarchical Bayesian models to infer rare-variant genetic parameters for SCZ and four neurodevelopmental disorders (NDs). The predicted parameters were used to identify risk genes/gene sets for these disorders.

Results: For SCZ, two risk genes (FDR<0.05) were identified, and top risk genes were enriched in both known gene sets and novel gene sets. For NDs, we identified 164 and 58 genes (FDR<0.05) for developmental disorders (DD) and intellectual disability (ID), respectively, including 101 novel DD genes and 15 novel ID genes.

Conclusions: Our results in schizophrenia replicate those of previous studies for known gene sets as well as for the single known genes, confirming the robustness of the approach. Furthermore, we achieve greater power in DD and ID by virtue of disease-specific genetic architecture inference.

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Delta-9-THC treatment alters glutamate receptor gene expression in human stem cell-derived neurons

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Background: Considering the recent trend towards cannabis legalization in the US, and that its use is self-reported by over 25% of pregnant women in spite of cognitive and behavioral deficits associated with prenatal Δ9-tetrahydrocannabinol (THC) exposure, it is imperative to understand the consequences of THC exposure on developing human neurons. Studying the consequences of in utero exposure on human fetal brain development is convoluted by confounding factors such as variable dose, timing and duration of exposures between pregnancies, multiple illicit drug use and genotype-dependent effects. Neural cells derived from human induced pluripotent stem cells (hIPSCs) most resemble fetal brain tissue, and present an unprecedented platform for studying THC effects on neural cells. We hypothesize that THC treatment of hIPSC-derived neurons would recapitulate several known molecular deficits of THC exposure.

Methods: Starting with hIPSCs derived from healthy individuals, we generated neurons by NGN2 overexpression and by directed differentiation, which recapitulates in vivo development, and quantified gene expression by qPCR.

Results/Conclusion: We demonstrate that THC treatment of hIPSC-neurons derived from healthy individuals – generated by NGN2 induction from hIPSCs or hIPSC-derived neural progenitor cells or by directed differentiation from NPCs – recapitulated known molecular outcomes of THC exposure, such as reduced glutamate receptor subunit expression.

Funding: NIDA T32DA007135

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Critical period for social dominance plasticity in mice:
A novel animal model for adolescent social behavior development

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Introduction: Many neurodevelopmental disorders such as Autism and Schizophrenia are characterized by disruptions in social cognition. However, modeling complex social behavior development in rodents is challenging. Here, we investigated social dominance hierarchies, known to be plastic to manipulations of synaptic efficacy in PFC, in group-housed male mice as a model of complex social behavior development.

Methods: Dominance rank was assessed using the tube test, a well-validated assay to assess dominance ranks between pairs of mice. Baseline hierarchies were assessed weekly from P21 to P70. We induced social disruption by switching the dominant mice across cages at different time points.

Results: We found that baseline hierarchies among group-housed mice were more flexible during adolescent periods and stabilized into adulthood. Social disruption specifically destabilized hierarchy during adolescence, but not in adulthood, implicating a specific critical period of heightened plasticity in social dominance during adolescence. In an animal model of open-ended cortical plasticity, we found heighted plasticity within mouse hierarchies, suggesting some mechanisms regulating hierarchy plasticity are shared with other forms of cortical plasticity, such as plasticity in V1.

Conclusions: These results suggest that social dominance development provides a novel animal model to assess adolescent plasticity, and underlying neural correlates of social behavior maturation.

Funding: NIH, Friedman Brain Institute, Mindich Child Health and Development Institute

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PU.1 affects microglial function relevant to Alzheimer's disease

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Background: More than 20 genetic loci associated with risk for Alzheimer's disease (AD) were identified in GWAS, but only a few genes have been validated for their contribution to the pathology. We have reported rs1057233, a variant located in the 3'UTR of SPI1 that is associated with lower levels of SPI1 expression and protection against AD. SPI1/PU.1 is a myeloid specific transcription factor, and is expressed in microglia.

Methods: For our functional study we mimicked changes in SPI1 levels with transient overexpression and knock-down of PU.1 in BV2 mouse microglial cell line. We performed RNA sequencing and treated these cells with bioparticles, e.g. myelin, zymosan, early/late apoptotic Jurkat and N2A cells, to analyze phagocytic activity.

Results: Increase in PU.1 levels resulted in a significant upregulation of phagocytic activity, while down-regulation of PU.1 led to a reduction in uptake. Several AD risk genes – APOE, CLU, CD33, TYROBP, MS4A4A and MS4A6D were regulated by SPI1 and, therefore, may contribute to the effect of SPI1 on microglial function. Our data from the RNA sequencing of BV2 cells with differential SPI1 expression suggest that genes modulating cell chemotaxis, proliferation and response to stress are also affected and will be further investigated in cell and mouse models.

Conclusion: Changes in expression levels of PU.1 regulate microglial function and may contribute to AD risk.

Funding: NIH, JPB

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Age-dependent 'haploinsufficiency' of SYNJ1 in PIP2 regulation contributes to dopamine neuron vulnerability

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Backgrounds: Parkinson's disease (PD) is the most common movement disorder with a high incidence in aged people and it is known to be caused by selective loss of Substantia Nigra dopamine neurons. While majority of the clinical cases are sporadic, over 20 genetic variants and many environmental factors have been reported to associate with disease risk, among which, aging is considered the greatest contributor. Identifying genetic changes for disease-vulnerable dopamine neurons in the context of aging is therefore crucial for understanding PD etiology.

Methods: We used a combination of biochemical, immunohistochemistry, live cell imaging as well as behavioral assessment on WT and transgenic mice to understand how aging influences PD risk via down-regulating SYNJ1/PARK20 gene.

Results: We found midbrain dopamine neuron-specific reduction of synaptojanin1 (encoded by SYNJ1 gene) expression due to aging. Aging-related decrease in synaptojanin1 results in 2-fold elevation of PIP2 levels in the midbrain compared to the cortex in 1-year old mice. The impaired PIP2 metabolism sensitizes dopamine neurons to pathological synj1 deficiency. Primary cultured midbrain neurons display a reverse gene dose-dependent increase in calcium entry along the axon during synaptic activity. Aged SYNJ1+/- mice exhibit reduced dopamine levels in the striatum accompanied by behavioral deficits and loss of dopaminergic nerve terminals.

Conclusions: Synj1 down-regulation predisposes aged individuals to PD pathogenesis.

Funding: NINDS, PDF

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3D genome mapping of the human brain and its implications for schizophrenia

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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, including schizophrenia (SZ).

Methods: in situ Hi-C is performed on isogenic human induced pluripotent stem cell-derived neural progenitor cells, glutamatergic neurons, and astrocytes from two control cell lines. 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. The data are processed bioinformatically to arrive at contact maps.

Results/Conclusion: Having established that all libraries met quality control standards, we probed the enrichment in the three cell types for significant interactions with SZ risk haplotypes, uncovering a potential neuron-specific burden. There is early evidence that some genes interacting with SZ noncoding variants are involved in neurodevelopment and may point to a risk architecture for the disease.

Funding: NIMH

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MicroRNA 219 mediated neurodegeneration in Alzheimer's disease.

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Background: Alzheimer's disease is a neurodegenerative disorder and one of the most common forms of dementia in the world. Neuropathologically, AD is characterized by extracellular amyloid-β deposition and intracellular formation of neurofibrillary tangles (NFT) composed of abnormal hyperphosphorylated forms of Tau. MicroRNAs (MiRNAs) are small non coding RNAs which bind recognition motifs in multiple mRNA targets and silence expression through posttranscriptional mechanisms, such as translational repression or target mRNA degradation. Additionally some microRNAs play a key role in gene activation. Expression-profiling studies indicate that alterations in miRNAs occur in the brains of AD patients, but the extent to which these changes influence the accumulation of tau remains unclear. MicroRNA profiling of CSF has revealed Mir-219 as one of the potential biomarkers for AD detection. MiR-219 is downregulated in brain parenchyma from AD patients, modulates tau toxicity invivo and regulates tau expression at the post-transcriptional level.

Methods: We have employed computational tools to classify the MiR-219 targets as modulators of Tau toxicity, validated our hits in clinical AD cohort datasets and transgenic Drosophila models.

Results: Our results implicate a set of MiR-219-targeting genes that may modulate phosphorylation and toxicity of Tau.

Conclusions: These findings provide a novel molecular mechanism that may underlie MiR-219 mediated changes in the gene regulatory network of Tau.

Funding: Tau Consortium

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Nicotinic Activation of Somatostatin Inhibitory Neurons Restores Cortical Plasticity in Adulthood

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Background: A network of inhibition is critical for experience-dependent cortical plasticity, yet contributions of interneurons other than Parvalbumin (PV) interneurons have largely been unexplored. Here we aimed to identify Lypd6, an endogenous positive modulator of nicotinic acetylcholine receptors (nAChR), as a molecular target in Somatostatin (SST) interneurons for regulating cortical plasticity in adulthood, and tested the role of Lypd6 specifically in V1 SST-cells on reactivating V1 plasticity.

Methods: Cell-type specific viral manipulations of Lypd6 gene expression and modulation of neuronal activity by chemogenetic approach were coupled with in vivo extracellular electrophysiological recordings to assess V1 plasticity.

Results: Lypd6 expression in SST-cells declines dramatically after V1 critical period. Viral overexpression of Lypd6 specifically in adult SST-cells reactivated V1 plasticity through the α2 nAChR by increasing SST-cell activity and in turn inhibiting PV-cells. Chemogenetic activation of SST-cells alone confirmed the causal role of SST-cell activity in reactivating V1 plasticity. Furthermore, Lypd6-overexpression-based plasticity was normalized by chemogenetic activation of PV-cells. Together this highlights a key role of a2-containing-nAChR signaling through SST->PV disynaptic inhibitory circuits in plasticity regulation.

Conclusions: Our 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 deficits in SST-cells.

Funding: T32MH096678 (MS), T32DA007135 (MD), MCHDI, MOD, KTEF (HM)

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Characterizing clinical profiles in borderline personality disorder based on symptom dimensions

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Background: Impulsive aggression (IA) is a core dimension of BPD. However, different measures of IA (clinical/behavioral vs. self-report measures) are only modestly intercorrelated in patients. We aimed to examine which measures better discriminate between BPD patients and healthy controls (HCs), and compare clinical/symptom profiles across high vs. low IA groups.

Methods: 664 BPD subjects diagnosed using the SIDP-IV structured interview and 222 HCs with no Axis I/II disorders were assessed through self-report questionnaires (STAXI,BIS,BDHI) and clinician-administered ratings (SIDP-IV BPD criterion 4&5,SCID eating disorder diagnosis). Logistic regressions were conducted with BPD diagnosis as the dependent variable and self-report and/or clinical variables as independent. K-cluster analyses divided subjects into high and low impulsivity groups, with clinical/self-report variables compared across clusters.

Results: Logistic regression for self-report variables showed Sensitivity=0.95 and Specificity=0.83. Self-report clusterss:The high impulsivity group had significantly more BPD criteria (t(244)=2.21,p=0.03) and higher rates of comorbid paranoid personality disorder (X2(1,264)=7.98,p=0.005). Clinical measure clusters:The high impulsivity group had higher STAXI Trait Anger Scores (t(349)=3.06,p=0.002) and rates of comorbid ASPD (X2(1,481)=7.40,p=0.007)

Conclusion: There is not strong agreement among measures used to evaluate IA in BPD. Different clinical and symptom profiles are associated with high vs. low IA in patients. Classifying a BPD patient as impulsive/aggressive depends on the chosen measures.

Funding: Internal (University)

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Effects of Ondansetron on Brain Functioning

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Ondansetron, medicine to treat nausea and vomiting, has been shown to reduce symptom severity in patients with obsessive-compulsive (OCD) and tic disorders. However, the neural mechanisms underlying this effect remain unknown. This study investigated the effects of ondansetron on resting-state functional connectivity in healthy controls, and determined how dosage affects modulation of sensorimotor regions associated with OCD and tics.

Resting-state fMRI data was acquired from 53 subjects during a placebo-controlled, double-blinded, single-dose challenge of ondansetron. Each subject was randomized to receive either 8 mg (n=18), 16 mg (n=18) or 24 mg (n=17) of ondansetron. Voxel-to-voxel analyses were conducted to compute global correlation using the conn toolbox.

A dose-dependent change in global connectivity was found in the sensorimotor cortex encompassing precentral and postcentral gyrus (whole-brain corrected, FDR-p=0.01), such that greater reductions in this area for ondansetron compared to placebo were found as dosage increased. This finding was driven by reduced global connectivity for ondansetron compared to placebo in the 24 mg group but no difference or increased global connectivity for ondansetron compared to placebo in the 16 and 8 mg groups.

High-dose ondansetron reduced the global connectivity of sensorimotor cortex, an area associated with OCD and tics. The results suggest that high dose ondansetron could be used to target abnormal functioning of sensorimotor brain regions in patients with these disorders.

NIH

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Cannabinoid 1 and delta opioid receptor heteromers in chemotherapy-induced peripheral neuropathy

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Background: Delta opioid receptor (DOR) and cannabinoid 1 receptor (CB1R) associate to form heteromers and exhibit distinct pharmacological properties and disease-specific dysregulation including neuropathic pain. Here we focus on the specific location and in vivo consequences of CB1R-DOR heteromer signaling in an animal model and postmortem sections obtained from patients suffering neuropathic pain secondary to chemotherapy (i.e.paclitaxel).

Method: Thirty C57BL/6J mice were treated with vehicle or paclitaxel on alternate days and mechanical allodynia was assessed on days 0, 4, 7 and 15. On day 16, 14 mice were sacrificed and tissues were collected and levels of CB1R and DOR and the heteromer in spinal cord were assessed. In addition, signaling and pharmacological studies were performed in vitro and in vivo respectively.

Results: We find a significant increase in the abundance of CB1R-DOR heteromers in a pre-,postsynaptic location and astrocytes at the dorsal region of the spinal cord of animals with allodynia and postmortem human spinal cord sections. Signaling studies in murine spinal cord membranes showed increased activation and synergistic analgesic effect when concurrent treatment with low doses of SNC80, a DOR agonist, and a CB1R ligand (HU210 or PF514273) were added together compared to each alone.

Conclusion: These results suggest a specific regulation of CB1-DOR heteromer levels, signaling and analgesic properties in the spinal cord during pain.

Funding: NIH and Foundation Alfonso Martin Escudero

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A new longitudinal clinical, genetic and neuropathological study of movement disorders

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Background: Emerging evidence indicates that degenerative movement disorders have distinct and overlapping genetic and environmental risk factors. Studies have uncovered unique, but also overlapping neuropathological signatures of these diseases. We are systematically developing a large cohort of movement disorders subjects at the Robert and John M. Bendheim (RJB) Parkinson and Movement Disorders Center for collaborative translational research projects.

Methods: Subjects have been recruited from RJB center since June 2016. At the time of enrollment, subjects are asked to provide blood and access their clinical records. Blood is subsequently fractionated for further genetic and biomarker analysis. We have developed protocols for brain donation to generate neuropathological data.

Results: We have recruited 154 individuals. The median age in the collection is 65 years (range=17-86) with gender ratio roughly 2:1 towards men. Among the cohort, there are 30 controls and 110 with Parkinsonism. Other diagnoses include progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, ataxia, dystonia, essential tremor, myoclonus, and others. Genotyping is ongoing on the Illumina Global Screening Array, including ClinVar and NeuroX common risk variants.

Conclusions: Our goal is to develop a longitudinal cohort of extensively phenotyped patients with movement disorders. This resource will be critical for advancing our understanding these diseases and stratify risk.

Funding: NIH R01 and departmental

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Structural changes in the primate brain following cognitive training

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Background: Cognitive training therapy has been used to assist recovery after loss-of-function. However, how long these interventions last and underlying neuronal dynamics remain unknown. We investigated this using MRI measures of structural change and microstructural measures of neuron morphology. We hypothesized training monkeys on an object-recognition memory task that depends on the ventrolateral prefrontal cortex (VLPFC) would lead to grey matter volumetric (GMV) increases with specific microstructural correlates.

Methods: We injected layers 2/3 pyramidal neurons of the VLPFC and control region, perirhinal cortex (PRh), via electric current with Lucifer Yellow dye. We traced neurons then performed Sholl analysis of traced neurons. We also analyzed high resolution z-stack images of dendritic segments for spine characteristics.

Results: Monkeys learning VLPFC-dependent task showed increases GMV selectively in VLPFC compared with control monkeys. Sholl analysis revealed increased basal dendritic branching complexity in VLPFC. This finding was reversed in PRh, which displayed increased basal dendritic branching complexity in the control monkeys. There was also a group difference for spine density, apical head diameter and spine volume.

Conclusions: Cognitive training resulted in dynamic long-lasting changes that can be measured with both MRI and microstructural measures of dendritic arborization and spine growth. This is the first study of this relationship in non-human primates.

Funding: NIGMS Icahn School of Medicine at Mount Sinai

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Optogenetic analysis of polyphenol-mediated resilience against sleep deprivation-induced cognitive deficits

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Background: Sleep deprivation (SD), a common problem in our society, is linked to a number of co-morbidities including memory impairment. Recent publications suggest that SD disrupts memory consolidation through impairments in CREB and mTOR signaling, and downregulation of plasticity-related genes. Treatment with a Bioactive Dietary Polyphenol Preparation (BDPP) and microbiota-derived phenolic metabolites confers resilience against SD through diverse mechanisms, including upregulation of CREB and c-fos. However, the mechanisms through which BDPP confers resilience in memory-bearing neurons are unclear.

Method: We utilized c-fos-tTA transgenic mice to label neurons with ChR2-mCherry in the contextual fear conditioning paradigm. Mice were injected with AAV9-TRE-ChR2-mCherry and recovered while on Dox. Mice were habituated to Context A, then fear conditioned in Context B while off Dox to label a subpopulation of neurons with ChR2-mCherry. Mice were reintroduced to Context A under optogenetic stimulation to record ChR2-mCherry-related fear recall.

Results: Mice expressing ChR2-mCherry exhibited a higher level of freezing in Context A under optogenetic stimulation than during habituation, or those expressing mCherry. Fluorescent imaging shows that ChR2-mCherry is expressed once Dox is withdrawn. Only neurons expressing ChR2-mCherry show a response to optogenetic stimulation.

Conclusion: Having validated our optogenetics system, studies to investigate mechanisms through which BDPP confers resilience will follow.

Funding: NCCIH Center Grant P50 AT008661-01 to GMP

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Brain habit center regulates new learning: Role for D1 and D2-MSNs

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Background: Learning new actions that result in successful outcomes (instrumental conditioning), and storing this information for future use, is critical for survival. Surprisingly little is known about the mechanisms underlying this type of learning. Information flows through the basal ganglia as part of two pathways; a 'direct' striatonigral pathway comprised of medium spiny neurons (MSNs) that express D1 receptors (D1Rs) and an 'indirect' striatopallidal pathway comprised of D2R-expressing MSNs. These pathways exert opposite effects on motor behavior, but their roles in new instrumental learning is unknown. Here, we targeted inhibitory M4-Gi-DREADD to discrete regions of the striatum, and D1 or D2 MSNs contained therein, to investigate the mechanisms of new instrumental conditioning.

Methods: Chemogenetics, operant conditioning, in-vivo Ca2+ imaging.

Results/Conclusions: We show that inhibition of D1-MSNs in the anterior dorsolateral striatum (aDLS), a region heavily implicated in habitual behaviors, immediately after learning a new instrumental response completely ablated the new memory. Contrarily, D2-MSN inhibition greatly enhanced memory consolidation. In well-trained mice responding in a habitual manner, D2-MSN inhibition in this same site blocked habit-like behavior, reflected by the restoration of satiety-induced devaluation, whereas D1-MSN inhibition has no effects in this task. These data indicate that D1-MSNs in the aDLS regulate new instrumental learning whereas D2-MSNs in this site suppress new learning and drive habitual responding.

Funding: NIH

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Integrative bioinformatics approach to systematically identify environmental chemicals that disrupt critical periods of plasticity

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Background: Given the thousands of chemicals released into the environment there is an urgent need for high-throughput approaches to identify chemicals impacting neurodevelopment. Central to childhood neurodevelopment are critical periods of plasticity wherein neural circuitry is optimized by the environment. If chemicals perturb these periods, development of normal function can be permanently disrupted.

Methods: To identify anti-plastic chemicals, we computationally matched transcriptional signatures of critical period plasticity to 1742 chemical gene sets from the Comparative Toxicogenomics Database. To gain insight into biology, we applied Chemogenomics Enrichment Analysis (CGEA) to the chemicals across 5191 GO Biological Processes and 96 LINCS ligands. We tested CGEA convergent pathways using qPCR and immunohistochemistry.

Results: We identified 50 anti-plastic chemicals, including antimicrobials, metals, and pesticides. CGEA identified 33 GO Biological Processes and multiple cytokines (FDR < 0.05) enriched among the 50 chemicals, which converged on pathways related to response to pathogen, immune cell chemotaxis, and inflammation via IL1 and TNF . These pathways mimic a host inflammatory response to infection, including microglia activation. Using the LPS model of inflammation, we found that LPS at a dose that disrupts critical period plasticity activates cortical microglia (>Iba1, p = 0.02; >CD68, p = 0.03) and decreases the P2y12 purinergic receptor required for critical period plasticity (p = 0.01).

Conclusions: Anti-plastic chemicals may induce an inflammatory response, activating microglia to disrupt critical period plasticity. Next steps include directly testing the capacity of anti-plastic chemicals to induce an inflammatory response to disrupt plasticity.

Traineeship, NICHD-Interdisciplinary Training in Systems and Developmental Biology and Birth Defects T32HD075735 (M.R.S) and P30 NIEHS Grant P30ES023515 (J.T.D and H.M.)

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Amygdala lesions alter local field responses related to reward-based decisions 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 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: Visual stimuli associated with different reward amounts evoke strong LFP responses in both OFC and MFC. OFC responses were strongly modulated by the reward values whilst MFC responses best represented which stimulus was later selected. Bilateral lesions of the amygdala strongly altered both reward values and choice encoding in the OFC and MFC.

Conclusion: These data suggest that LFP responses in the OFC and MFC represent the relevant information to make adaptive and optimal decisions, and that amygdala inputs are required to properly represent these information.

Funding: NIMH BRAINS R01, NARSAD, Philippe Foundation & Icahn seed funds

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Dendritic Spine Development of Long-range Frontal Cortex Neurons Projecting to Visual Cortex

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Background: Top-down cortical neurons projecting from the anterior cingulate cortex (ACC) to visual cortex (VC) are involved in visual processing, a hallmark of visual attention. We previously found that adolescent chemogenetic silencing of top-down neurons produces an adult attention deficit. Rabies-mediated input mapping revealed developmental pruning of local input neurons, however, correlated changed on the post-synaptic side remain unknown. We thus sought to examine excitatory post-synaptic developmental changes of the top-down neurons by dendritic spine analysis.

Methods: We visualized spines selectively in ACC top-down neurons in adolescents and adults by injecting an AAV5 virus expressing eGFP in VC into p12 and >p60 mice. Retrogradely labelled ipsilateral and contralateral neurons were analyzed. Dendrites were characterized by their distance from the soma as well as apical vs basal location. Spine volume and type were analyzed in Neuron-Studio.

Results: Ipsilateral top-down neurons displayed a developmental increase in spine volume with loss of spines on proximal apical dendrites. Developmental spine volume changes did not occur on contralateral neurons. Distal dendrites showed an increase in spines density.

Conclusions: Proximal apical dendrites undergo developmental pruning consistent with previous input map findings. Discrepant trajectories of ipsilateral and contralateral top-down dendritic spine development suggest distinct involvement in separate circuits. Future research will examine inhibitory synapses, and if developmental excitatory spine pruning is activity-dependent.

Funding: NIMH

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Establishing a platform for functional characterization of astrocytes differentiated from human induced pluripotent stem cells

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Apolipoprotein E (APOE) is a risk factor for late-onset Alzheimer's disease (AD). APOE ε4/ε4 ncreases AD risk by >10-fold. We hypothesized that astrocyte differentiation and co-culture with microglia or neurons offer a platform to study cell autonomous and/or non-cell autonomous mechanisms of APOE genotype.

We have developed protocols to efficiently and reproducibly generate pure populations of astrocytes (that secrete APOE) from human induced pluripotent stem cell (hiPSC)-derived neural progenitor cells (NPCs). To study APOE genotype effects on cellular phenotypes, APOE ε4/ε4 hiPSCs were engineered to generate isogenic APOE ε3/ε3 lines using CRISPR/Cas9 genome-editing.

Our RNAseq comparisons show that hiPSC-astrocytes cluster with human astrocytes. hiPSC-astrocytes resemble a quiescent state of astrocytes, capable of secretion of inflammatory cytokines upon stimulus. hiPSC-astrocytes phagocytose myelin and show activated calcium signals in response to glutamate in a manner similar to primary astrocytes. When hiPSC-astrocytes were co-cultured with microglia or neurons, they promote microglia phagocytosis and neuron firing, respectively. We are currently investigating the impact of APOE genotype on transcriptional changes and functions of isogenic neurons and astrocytes.

This established platform will allow us to determine whether differences in neuronal and astrocyte functions are intrinsic to the cell or induced by APOE4 secreted by other cells.

JPB Foundation

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PROLIFERATIVE GLIAL PATHOLOGY IN DRUG RESISTANT HUMAN EPILEPSY

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Background: Temporal lobe epilepsy (TLE), the most common type of epilepsy, normally shows pathological neuronal hyperexcitability, glia scar formation and myelin dysregulation. However, the functional and molecular contributions of each specific neural cell type to epileptic maintenance remains undefined.

Methods: Immunofluorescence and cell culture were used to functionally characterize glial cells from primary drug-resistant TLE epileptic tissues and normal postmortem temporal cortex as control. In parallel, we developed fluorescence-activated-nuclei-sorting (FANS) strategy to isolate neurons (NeuN+), oligodendroglial progenitors (OPCs) (highOlig2+), and astrocytes (PAX6+) from both tissues types. RT-qPCR was used as quality control for the validation of cell-type specific gene expression.

Results: In-vivo characterization of glial pathology in human TLE by immunofluorescence shows proliferative Ki67+ glia, colocalizing with either GFAP or Olig2, in contrast to the largely quiescent glia in normal adult cortex, suggesting the reversion to more immature astrocytic and oligodendroglial phenotypes. In addition, EGFR+ astrocytic (GFAP+) cells, freshly isolated from lesional TLE, showed ability to form proliferating neurospheres in-vitro. RT-qPCR analysis confirmed enrichment of neuronal, OPC, and astrocytic markers in each FANS-isolated nuclei population.

Conclusions: We demonstrate the successful isolation of neuronal, OPC, and astrocytic nuclei from human brain tissue, and implicate an immature aberrant phenotypic remodeling in both OPCs and astrocytes within the epileptic scar. Ongoing analysis of gene expression (RNA-seq) and open chromatin states (ATAC-seq) will help us to decipher the specific transcriptional and epigenetic pathways maintaining this aberrant glial phenotype in epilepsy, allowing us to define better therapies in this debilitating disease.

Funding: NIH, Icahn School of Medicine at Mount Sinai

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The role of miR-128 in neuronal regulation of epileptic seizures

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Background: Recent studies have identified the neuron enriched microRNA-128 (miR-128) as a key regulator of neuronal activity. Our lab demonstrated that reduction in miR-128 levels in postnatal forebrain excitatory neurons causes fatal seizures in mice, while its overexpression attenuates chemically-induced seizures of different origins.

Methods: To reveal a therapeutic role for miR-128 in regulating seizures, we use a genetic mouse model and an AAV viral approach to over express miR-128 in a mouse model for a severe form of epilepsy named Dravet syndrome. This syndrome carries mutation in the sodium channel alpha subunit SCN1A gene. SCN1A-deficient mice suffer from fatal epilepsy and reproduce many features of the human Dravet syndrome.

Results: Our preliminary results suggest that miR-128 has the ability to reduce the number of seizures in SCN1A-deficient mice and by doing so rescuing the lethality of the Dravet disease.

Conclusions: Our study will advance our understanding of the mechanisms controlling neuron activity and facilitate the development of novel therapeutic approaches for treatment of epilepsy and other disorders associated with abnormal neuronal activation.

Funding: NINDS

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HDAC3 inhibition ameliorates spinal cord injury by immunomodulation.

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Following Spinal Cord Injury (SCI), the innate immune response of microglia and infiltrating macrophages clears up cellular debris and promotes tissue repair, but it also inflicts secondary injury from inflammatory responses.

Microglia and macrophages respond to CNS insult within minutes and may exhibit a pro-repair or pro-inflammatory phenotype. Immunomodulation aimed at maximizing the beneficial effects while minimizing the detrimental roles of cells of the innate immune response may aid functional recovery after SCI. However intracellular drivers of global reprogramming of the inflammatory gene networks are poorly understood. We show that SCI resulted in a robust upregulation of Histone Deacetylase 3 (HDAC3) in microglia and macrophages at the injury site. Remarkably, blocking HDAC3 with a selective small molecule inhibitor shifted microglia/macrophage responses towards a broad inflammatory suppression, resulting in neuroprotective phenotypes and improved functional recovery in our mouse model of SCI.

Mechanistically, HDAC3 activity is largely responsible for histone deacetylation and inflammatory responses of primary microglia to classis inflammatory stimuli. Our results reveal a novel HDAC3-mediated epigenetic regulation of the innate immune response after CNS injury, thus pointing towards new directions of immunomodulation for SCI repair.

Funding: NIH

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ELK1 is a Key Regulator of Synaptic Plasticity and Heroin Addiction

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Background: Chronic heroin use alters synaptic plasticity in brain regions relevant to addiction that can contribute to heroin-seeking behaviors. We have shown that levels of phosphorylated ELK1 (pELK1), a transcription factor downstream of μ-opioid receptor signaling, are reduced in the striatum of human heroin abusers. Additionally, pELK1 levels negatively correlate with history of heroin intake in heroin self-administering rats. The mechanism by which ELK1 contributes to heroin addiction is unknown. The cytoplasmic localization of ELK1 attenuates dendritic branching. We hypothesize that cytoplasmic unphosphorylated ELK1 (unpELK1) impairs synaptic function and increases heroin-seeking.

Methods: Rat striatal-cortical neurons were cultured and treated with morphine (DIV8-14, every other day) or transfected with ELK1 vectors (DIV7). Spine density was measured using confocal microscopy and NeuronStudio. To determine in vivo function, a peptide inhibiting ELK1 nuclear import, thereby increasing unphosphorylated cytoplasmic levels, was infused into the accumbens of rats prior to a cue-induced relapse heroin self-administration session.

Results: Consistent with the literature, we show that chronic morphine exposure reduces striatal spine density (ANOVA, $p<0.001$). Overexpression of unpELK1 reduces spine density (t-test, $p<0.05$), recapitulating the chronic heroin phenotype. Furthermore, infusion of the inhibitory ELK1 peptide increases heroin-associated lever pressing (t-test, $p<0.05$).

Conclusion: Our data suggests that cytoplasmic unpELK1 alters synaptic plasticity and increases heroin-seeking behavior. These findings provide neurobiological insights suggesting an important link of ELK1 cellular localization to heroin addiction vulnerability.

Funding: NIH

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Development of surface EMG-triggered closed loop stimulation for individuals with spinal cord injury.

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[1] Rehabilitation Medicine; [2] Neurology

Background: Past studies have shown that synapses between nerve circuits in the spinal cord can be strengthened temporarily after a short period of paired stimulation between motor cortex and peripheral nerves. We hypothesize that spinal synapses may further potentiate by involving subjects' active movement, using internal electromyographic (EMG) signals to trigger external paired stimulation – a form of closed-loop stimulation. We seek to develop a non-invasive EMG-triggered closed loop stimulation system for spinal cord injured individuals.

Methods: The system includes an EMG acquisition device, force dynamometer, microcontroller, transcranial magnetic stimulator (TMS), and peripheral nerve stimulator (PNS). A data acquisition (DAQ) board integrates the devices. Our self-developed LabVIEW program synchronously records thumb EMG and pinch force signals with 1000Hz sampling rate. Once the signal detection, either from subjects' EMG or pinch force, exceeds a target threshold, the DAQ board generates digital output to the microcontroller to trigger TMS, PNS, or both with specific stimulation intervals.

Results: The system reliably delivers stimuli with 20-25 milliseconds latency when triggered by EMG/pinch force between the range of 5 and 80 percent of maximal voluntary contraction. The algorithm includes a background noise detection to calibrate baseline EMG signals.

Conclusion: This working prototype system will be applied on our upcoming human study to test different combinations of TMS and PNS triggered by EMG signals to improve hand function after spinal injury.

Funding Pending: NYSCIRB DOH01-FLLOW2-2016-00011

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An integrative genomics approach to infer underlying statistical causal network among gene expressions

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Background: Although enormous effort in understanding the role of genetic variants has identified hundreds of genetic loci associated with diseases, systematic understanding continues to lag behind the pace of gene discovery. While biological systems constructed from hierarchies of organization, the relationships between components can be represented as a complex network.

Methods: Here, we detailed a procedure for identifying potential key drivers of complex traits that integrates DNA-variation and RNA-seq gene expression using Bayesian probabilistic model. We systematically assessed if variations in DNA lead to variations in relative traits and support statistical causative or independent function to the complex traits in the study.

Results: Using the DNA-variation as instrumental variables, we elucidated gene regularity network over 23,208 transcripts generated from the CommonMind Consortium in the dorsolateral prefrontal cortex of 209 cases with schizophrenia and 206 controls. We calculated the effects of actual or hypothetical manipulations of the genes in the system and explored the role of gene-gene interactions.

Conclusions: An essential attribute for increasing confidence in potential clinical validity of gene variation with risk factors and disease end points will be the elucidation of the complex network of gene interactions underlying complex human diseases.

Funding: NIH, VA, FBI

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Neural correlates of reward in anterior cingulate, ventral striatum, and amygdala

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Background: Anhedonia, a loss of positive affect from rewarding events, encompasses two distinct affective deficits: a hedonic deficit manifesting as loss of pleasure from reward receipt, and an anticipatory deficit that reduces work toward rewards. Lesions of subcallosal anterior cingulate cortex (ACC) reduce maintenance of arousal in anticipation, but not receipt, of reward. However, a mechanistic understanding of how the subcallosal ACC influences reward anticipation in interconnected structures such as the ventral striatum (VS) and amygdala is lacking. We hypothesize subcallosal ACC modulates reward-related neural activity in VS and amygdala during reward anticipation.

Methods: Two rhesus macaques performed Pavlovian and instrumental trace conditioning tasks while neuronal activity was recorded in in subcallosal ACC, VS, and basolateral amygdala. Autonomic measures and task-related behavioral responses were continuously collected.

Results: Monkeys showed elevated behavioral (anticipatory licking) and autonomic (pupil size) responses in anticipation of rewards, which were modulated by each animal's individual reward preferences. Neuronal activity in subcallosal ACC, VS, and amygdala was similarly modulated by preference, but the timing of these responses differed between areas. Unexpectedly, more neurons in amygdala than subcallosal ACC or VS encoded future rewards during trace intervals.

Conclusions: Neuronal activityin subcallosal ACC, VS, and amygdala correlates with sustained behavioral and autonomic responses in anticipation of rewards, a key component of motivated behavior.

Funding: NIMH BRAINS R01, NARSAD, ISMMS seed funds

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Elucidating the effects of Thap1 mutations on gene transcription signatures in neonatal mice by RNAseq

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Background: THAP1 [Thanatos-associated protein] domain containing, apoptosis associated protein 1] is a ubiquitously expressed transcription factor with DNA binding and protein-interaction regions. However, THAP1 downstream targets and the mechanism via which it causes dystonia are largely unknown.

Methods: We previously created two lines of mice with physiologic mutations, a Thap1C54Y knockin (KI) mouse and a mouse with a null allele. The C54Y mutation prevents binding of Thap1 to DNA in vitro. We also examined mouse ES cells harboring the mutations for their ability to differentiate into neurons. In vivo, we sought to determine the role of Thap1C54Y and null alleles on the gene transcription signatures at postnatal day 1 (P1) in the mouse striatum and cerebellum in order to correlate with specific genes and /or pathways with potential points of convergence on the pathogenesis of DYT6 dystonia. We quantitative and functionally validated our findings.

Results: IPA pathway analyses of the Thap1 mutants revealed convergence of multiple signaling pathways involved in neuronal plasticity, axonal guidance, and oxidative stress response, which are also present in other forms of dystonia.

Conclusions: Our findings may help to elucidate key pathways involved in the pathogenesis of DYT6 dystonia.

Funding: NIH and NYSTEM

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

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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 α1 and β3 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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MiNDS: Mentoring in Neuroscience Discovery at Sinai

Ana Badimon, Carla Golden, Casey Lardner, and Josefa Sullivan

The Friedman Brain Institute, Icahn School of Medicine at Mount Sinai

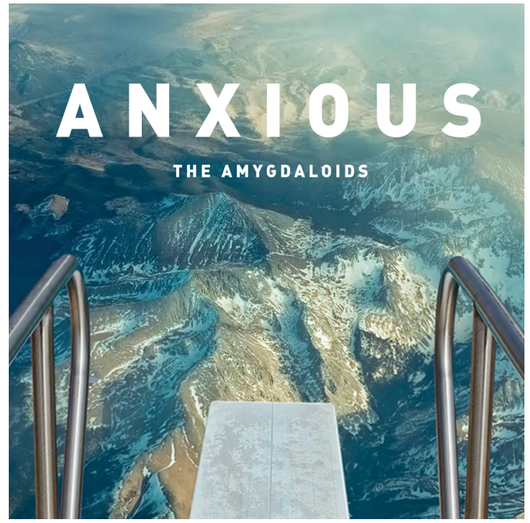
MiNDS, Mentoring in Neuroscience Discovery at Sinai, is a student- and volunteer-run community outreach initiative based out of the Icahn School of Medicine at Mount Sinai. Our program strives to make neuroscience education more engaging, accessible, and fun to empower and inspire students and the general public. By extending our resources to local East Harlem schools and community centers as well as schools and communities in the rest of New York City, MiNDS provides a bridge between the scientific and medical endeavors accomplished here at Mount Sinai and the people that are truly affected by them. Any Mount Sinai affiliate interested in teaching or outreach can get involved. We have something for everyone!

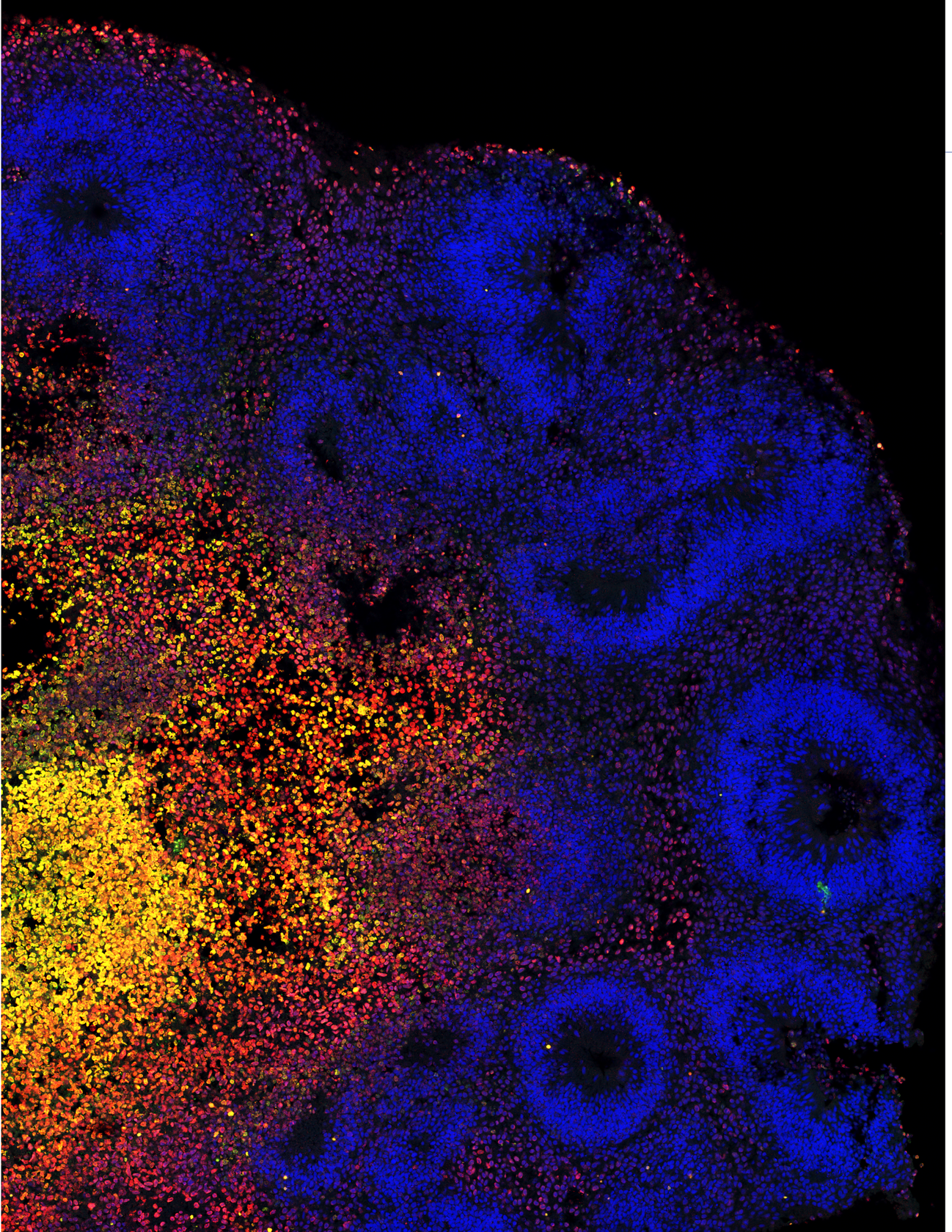
MiNDS promotes interactive and educational neuroscience experiences through on-site and off-site lessons. Our outreach programs include one-time lessons, longer partnerships with individual schools, collaborations with the New York Academy of Sciences, the Art of the Brain Exhibit, storytelling, and of course, our annual Brain Awareness Fair.

Contact MiNDatSinai@gmail.com to get involved!

Post Poster Reception

Featuring music by The Amygdaloids





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 at least 8 outstanding Ph.D. students for Fall 2017, representing a variety of backgrounds and interests, and additionally, a number of outstanding MSTP students, 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, efforts have been initiated to shorten the amount of time students spend obtaining their Ph.D. at Mount Sinai, which is about 5.5 years (across all MTAs); at other major institutions, the time is 4.5 - 5.0 yrs. The number and duration of rotations has been shortened, to accelerate the timeframe in which students chose a thesis lab and complete their thesis proposal. In addition, the Year 1 Core curriculum is now completed by mid-April, facilitating an early transition into the laboratory.

A 'big-brother/big-sister' program was successfully launched Fall 2016, in which current Ph.D. students were paired 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 >500 members of the community to explore brain facts and research, and also the associated Brain Awareness Week, and our Art of the Brain Exhibition.

Finally, we are particularly proud of our students and postdocs who continue to successfully obtain 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, it is imperative to maintain and continue to expand NIH T32 support.

George Huntley and Stephen Salton

Image by Chrystian Alves

2016 UPCOMING EVENTS

MAY

Studying the Brain
May 2, 2017

Brain Fair
May 5, 2017

AUGUST

Grad School Classes Begin
August 14, 2017

SEPTEMBER

Annual Postdoc Day
Sept. 15, 2017

MD/PhD Retreat
September 8-10, 2017

White Coat Ceremony
September 18, 2017

OCTOBER

BIC 4th Annual Symposium
October 19, 2017

SinaInnovations
October 17-18, 2017

NOVEMEBER

Society for Neuroscience Meeting
November 11-15, 2017

DECEMBER

Grad School Winter Party
December 15, 2017

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

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