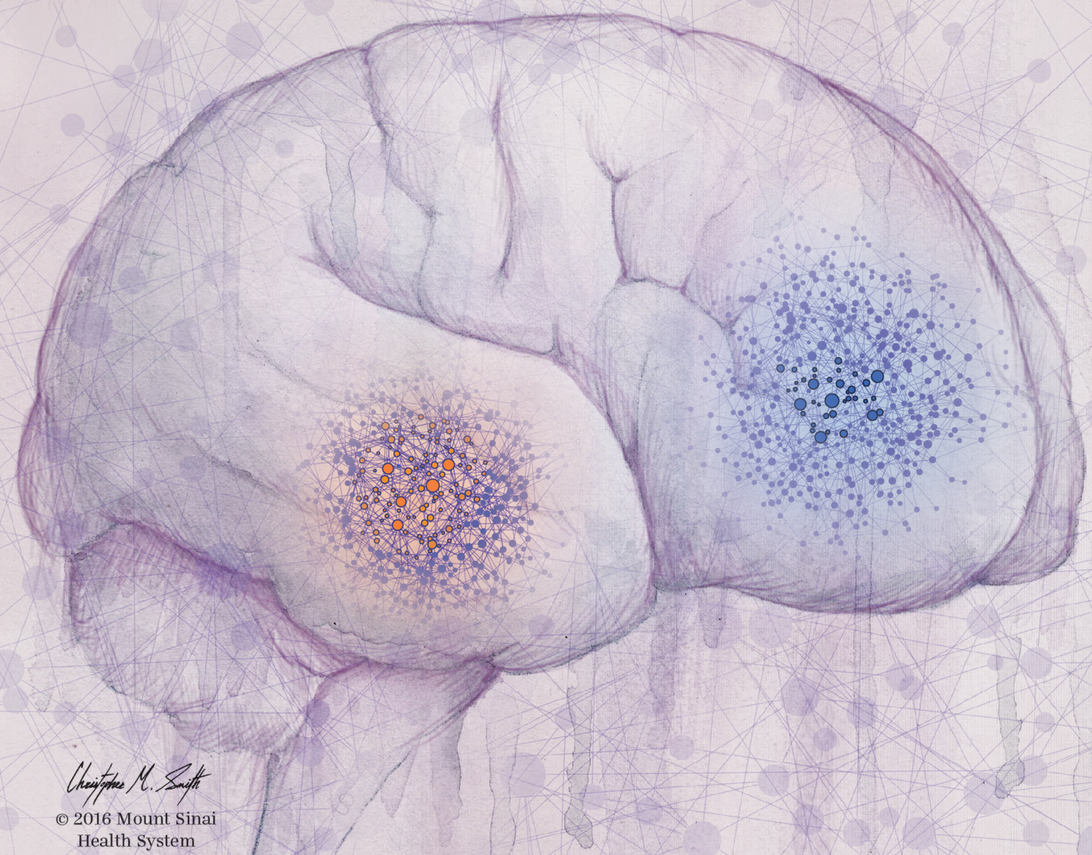
We hope you will join us in **2019** for the Eleventh Annual Neuroscience Retreat

THE FRIEDMAN BRAIN INSTITUTE and
NEUROSCIENCE GRADUATE PROGRAM

April 27, 2018

10TH ANNUAL
NEUROSCIENCE RETREAT



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THE NEW YORK ACADEMY OF MEDICINE
1216 FIFTH AVENUE

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Image by Chrystian Alves

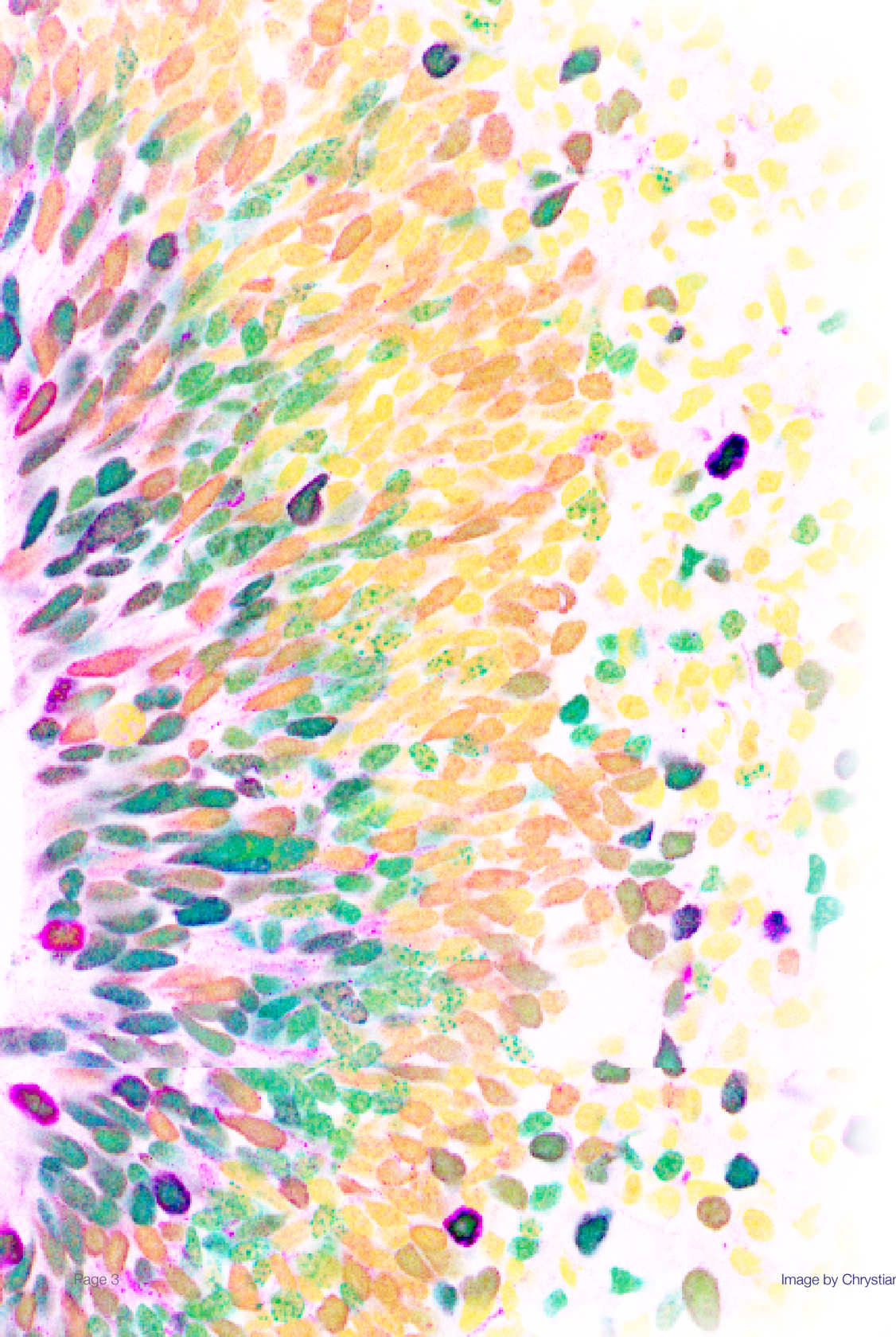


Image by Chrystian Alves

THE FRIEDMAN BRAIN INSTITUTE

CONTENTS

THE FRIEDMAN BRAIN INSTITUTE
AGENDA

REGISTRATION & BREAKFAST

8:30 AM • **Sign in, Register (lobby) and Poster Set-up** (Library, 3rd Floor)
Breakfast (Gallery) - NO FOOD/DRINKS IN HOSACK HALL

OPENING REMARKS & ANNOUNCEMENTS (Hosack Hall)

9:00 AM • **Anne Schaefer, MD, PhD**
(Associate Professor, Neuroscience and Psychiatry)

9:20 AM • **Eric Nestler, MD, PhD** (Director, Friedman Brain Institute)

9:20 AM • **Paul Kenny, PhD** (Chairman, Department of Neuroscience)

9:45 AM • **George W Huntley, PhD** (Co-Director, Neuroscience Graduate Program)

KEYNOTE ADDRESS

9:55 AM - 10:30 AM • **Alison M Goate, DPhil** (Director, Ronald M. Loeb Center for Alzheimer's, Professor, Neuroscience, Neurology and Genetics and Genomic Sciences)

10:30 AM - 10:50 AM • **BREAK**

SESSION ONE

Moderators - Denise Cai, PhD (Neuroscience) **& Tim Ahfeldt, PhD**
(Neuroscience and Neurology)

10:55 AM • **Kristen Brennand, PhD**
(Associate Professor, Genetics and Genomic Sciences, Neuroscience and Psychiatry)

11:15 AM • **Véronik Lachance, PhD** (Neurology)
Investigation of NRBF2-mediated autophagy in the pathogenesis of Alzheimer's disease

11:30 AM • **Anna Zilverstand, PhD** (Psychiatry)
Resting-State Connectivity Defines Neurobiological Subtypes Underlying Different Cognitive-Emotional Profiles in Cocaine Addiction

11:45 AM • **Ashley Lepack** (Neuroscience)
Roles for histone dopaminylation in cocaine-induced plasticity

12:00 PM - 1:00 PM • **LUNCH - Room 20, 2nd Floor**

12:30 PM - 2:30 PM • **POSTER SET-UP - Library, 3rd Floor**

SESSION TWO • **Moderators - Denise Cai, PhD** (Neuroscience) **& Tim Ahfeldt, PhD**
(Neuroscience and Neurology)

KEYNOTE ADDRESS

1:05 PM - 1:40 PM • **Winrich Freiwald, Ph.D**
(Associate Professor, Neurosciences and Behavior, The Rockefeller University)

1:40 PM • **Joseph M Castellano, PhD** (Assistant Professor, Neuroscience and Neurology)

1:55 PM • **Masato Sadahiro** (Psychiatry)
Nicotinic Activation of Somatostatin Inhibitory Neurons Restores Cortical Plasticity in Adulthood

2:10 PM • **Molly Heyer, PhD** (Neuroscience)
The parvalbumin interneuron-enriched microRNA-206 regulates fear- and schizophrenia-related behaviors in mice

2:25 PM • **Kirstie Cummings, PhD** (Neuroscience)
Prefrontal somatostatin-expressing interneurons promote fear memory expression

RECEPTION & POSTER SESSION • **Library, 3rd Floor**

2:40 PM - 6:00 PM • **Mardi Gras Celebration begins**

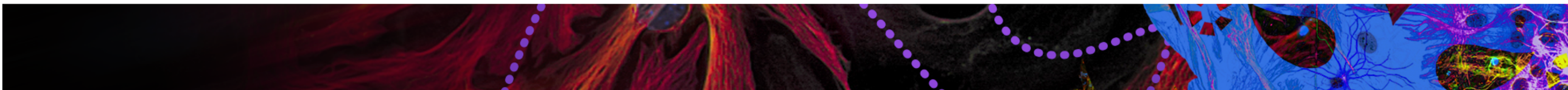
2:40 PM - 4:10 PM • **Poster Session**

5:20 PM • **Award Ceremony**
Best Poster, Best Oral Presentation, Call for Images Award, 2018 BRAIN Award, Neuroscience Mentorship Distinction Award (NMDA), PostDoc Award

6:00 PM • **Reception Ends**

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

Image by Patrick R. Hof and Dan Meyer



Véronik Lachance, PhD
Department of Neurology

Investigation of NRBF2-mediated autophagy in the pathogenesis of Alzheimer's disease

While it is known that autophagic activity declines over aging, enhanced or decreased expression of autophagy genes has been shown in Alzheimer's Disease (AD) patients, confounding the role of autophagy in the pathogenesis of AD.

Herein, we analyzed multiple transcriptomics dataset to assess the expression of 130 autophagy related genes from different brain regions from control and AD subjects.

We found that members of the Beclin1-NRBF2-ATG14L-PIK3C3 complex are all downregulated in AD. Given that deletion of NRBF2 in mice displays no lethality, that NRBF2 regulates APP processing, stabilizes and promotes PIK3C3 kinase complex activity, we employed that unique autophagy model to evaluate if NRBF2 depletion can phenocopy AD pathology. We report that loss of NRBF2 impairs long-term potentiation and causes memory deficits in mice. In fact, NRBF2-KO mice showed several AD-like characteristics.

Taken together, our data suggest that dysfunctional NRBF2-PIK3C3 autophagy complex predisposes the pathogenic process relevant to AD.

NIH and CIHR

Anna Zilverstand, PhD
Department of Psychiatry

Resting-State Connectivity Defines Neurobiological Subtypes Underlying Different Cognitive-Emotional Profiles in Cocaine Addiction

Resting-State Connectivity Defines Neurobiological Subtypes Underlying Different Cognitive-Emotional Profiles in Cocaine Addiction Zilverstand, Curtin, Parvaz, Alia-Klein, Goldstein (ISMMS) We applied data-driven methods to discover neurobiological subtypes of cocaine addiction based on individuals' resting-state brain function alone. We hypothesized that different neurobiological subtypes may be characterized by different cognitive-emotional functioning linked to different neurobiological mechanisms. We acquired a resting-state scan from 42 individuals with Cocaine Addiction and 32 healthy controls, using Graph theory methods to extract functional connectivity (Global Efficiency). Average Global Efficiency (per 16 brain networks) was input into an unsupervised classifier (SOM = self-organizing map), which generated a similarity map of all participants based on their brain connectivity. K-centroid clustering was applied to detect subgroups within this map. We characterized the discovered subtypes on clinical characteristics and cognitive-emotional functioning using the Multidimensional Personality Questionnaire (MPQ-BF). We identified four neurobiological subtypes, which separated cocaine users from healthy controls with 92% accuracy. Within cocaine users, the discovered subtypes differed on capability for self-constraint and reward sensitivity. In 50% of cocaine users we found low constraint, whereas the other half demonstrated high reward sensitivity ($p<0.01$, MPQ-BF). Cocaine users with low constraint showed increased motor network connectivity, whereas cocaine users with high reward sensitivity demonstrated increased connectivity of the salience network. Both cocaine user subtypes had equally severe, recent and chronic cocaine use. The discovered cocaine user subtypes differed in regards to the underlying neurobiological mechanisms, but not in terms of addiction severity. Results may therefore have important implications for developing targeted treatments.

Ashley Lepack
Department of Neuroscience

Roles for histone dopaminylation in cocaine-induced plasticity

Background: Drug addiction is a debilitating disease that is characterized by loss of control over drug intake. While drug addiction remains a devastating health and societal issue, few advances have been made in the treatment of this disorder. Although the molecular mechanisms mediating addiction remain unclear, there is now emerging evidence that drugs of abuse promote alterations in cell-type specific gene expression patterns in brain, thereby 'high jacking' normal cellular functions to promote aberrant forms of behavioral plasticity. We have recently identified a novel set of histone posttranslational modifications (PTMs)-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: We employ a wide array of biochemical, biophysical, molecular and behavioral approaches in a well-established rat model of cocaine self-administration.

Results: Our results indicate that chronic withdrawal from volitional administration of extended access to cocaine in rodents results in high levels of dopamine accumulation in the nucleus of dopamine producing neurons in VTA, as well as a robust increase in H3Q5dop. Furthermore, we have demonstrated that inhibiting dopaminylation in VTA is sufficient to block cocaine-seeking behaviors following extended withdrawal periods. Taken together, these studies will aid in our understanding as to how monoamines, specifically dopamine, function in brain to regulate neurotransmission independent neuronal plasticity and cocaine-mediated behaviors.

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

Masato Sadahiro
Department of Psychiatry

Nicotinic Activation of Somatostatin Inhibitory Neurons Restores Cortical Plasticity in Adulthood

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 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 a2-subunit-containing-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 nAChRa2 signaling through SST->PV disynaptic inhibitory circuits in plasticity regulation.

Conclusions: Our identification of the first SST- and nAChRa2-specific plasticity regulator provides novel therapeutic targets for disorders with limited recovery due to diminished plasticity, and psychiatric disorders with known deficits in SST-cells or associations with Chrna2 expression.

Funding: F31EY028829 (MS), R01EY024918 (HM)

***Equal contribution**

Molly Heyer, PhD
Department of Neuroscience

The parvalbumin interneuron-enriched microRNA-206 regulates fear- and schizophrenia-related behaviors in mice

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

Methods: miR-206 conditional knockout (KO) mice were created by homologous recombination in embryonic stem cells. Behavioral tests included open field, a cognitive operant task, prepulse inhibition, predation, and fear conditioning. Miniature IPSCs (mIPSCs) were recorded from PFC pyramidal neurons.

Results: miR-206 KO mice have reduced mIPSC frequency in mPFC, impaired prepulse inhibition, cognitive deficits, and enhanced acute fear/anxiety-related behaviors. KO mice also reduced activation of the lateral periaqueductal grey. The sensorimotor gating deficit was recapitulated in mice with selective deletion of miR-206 in parvalbumin-e
xpressing neurons.

Conclusions: Loss of miR-206 causes SZ-relevant behavioral deficits, including sensorimotor gating impairment, cognitive dysfunction and anxiety-like behaviors. Thus, miR-206 may be a candidate for the development of novel therapeutics relevant to SZ.

Funding: Seaver Postdoctoral Fellowship (M.P.H.); N.I.H. and BBRF (P.J.K.)

Kirstie Cummings, PhD
Department of Neuroscience

Prefrontal somatostatin-expressing interneurons promote fear memory expression

In addition to excitatory projection neurons, prefrontal cortex harbors a network of local inhibitory neurons composed mainly of parvalbumin- (PV-INs) and somatostatin-expressing (SST-INs) interneurons. Intriguingly, in vivo electrophysiological recordings have indicated that in contrast to conditioned stimulus (CS)-evoked spiking of projection neurons, fear memory expression is associated with suppression of activity in prelimbic PV-INs. However, it remains unclear how fear conditioning might drive these dynamic changes in prefrontal population activity. We performed immunohistochemical c-Fos staining and observed that a large majority of PL layer 2/3 SST-INs are activated in response to both fear memory acquisition and retrieval. Correspondingly, whole-cell recordings from acute brain slices indicate that fear conditioning leads to a lamina-specific increase excitatory synaptic transmission in excitatory projection cells as well as SST-INs, but not PV-INs. These data suggest that SST-INs may be important for fear learning and/or memory expression. In support of this idea, in vivo optogenetic activation or silencing of SST-INs promoted or suppressed fear memory expression, respectively. Optogenetics-assisted electrophysiological recordings in PL revealed that SST-INs provide monosynaptic input onto PV-INs, indicating a potential role for SST-INs in disinhibition of fear-related excitatory projection neurons. Overall, our results suggest that SST-INs may play a key role in gating fear-related prelimbic circuitry and their expression of synaptic plasticity after fear conditioning could constitute a mechanism for memory storage.

Funding: NIMH RO1 to RLC and NIMH F32 to KAC

1

Dissecting the role of MEF2C, MS4A4A and MS4A6A in calcium signaling and interferon response in the context of the DAM response to brain tissue damage in aging and disease

Franco Abbate, Anastasia Efthymiou, Edoardo Marcora, Alison Goate

Icahn School of Medicine. Department of Neuroscience

Recently, genome-wide association studies have identified a number of genetic loci associated with late-onset Alzheimer's disease (AD) and highlighted a number of genes that play key roles in myeloid cells, including microglia.

Along with well established AD genes such as APOE and TREM2, a number of new candidates such as MEF2C and the MS4A locus genes have recently been the subject of our studies in microglial cells. We hypothesize that these four genes, along with others previously reported, may be components of a calcium signal transduction pathway that modulates the response of microglia to tissue damage that occurs in the brain during aging and disease. Our work aims to uncover the biological functions of MEF2C, MS4A4A, and MS4A6A in microglia with a particular focus on their interactions in the molecular pathway mentioned above. At the same time, eQTL data analysis performed in our department along with other scientific evidence suggests an important role for MEF2C, MS4A4A, and MS4A6A in the interferon response, which has also been implicated in brain aging and disease. In this regard, we are exploring the biological impact of knocking-down these three genes in the response of microglial cells to interferon and other signals associated with tissue damage in the brain.

Funds: NDC-MS4A

2

Brain Volume Differences between Binge and non-Binge Eaters

Nadia Abdo, Shaunte Baboumian, Spiro Pantazatos, Allan Geliebter

Mt. Sinai St. Luke's, Department of Psychiatry, Icahn School of Medicine at Mount Sinai,
Institute of Human Nutrition, Department of Psychiatry, Columbia University

Background: Binge eating has gained increased attention, and the DSM-5 (2013) includes revised criteria for binge eating disorder (BED). Brain imaging may provide further insights to distinguish disordered eating phenotypes, as brain volume differences in binge eating disorder are not well studied.

Method: We compared volumetric differences in 330 adults (124 m, 206 f; age 18-59; BMI 27.56±9.36 SD), using structural MRI scans from the Nathan Kline Institute Rockland Sample (Nooner, 2012). Binge eating behavior, using the Eating Disorders Examination Questionnaire, was based on reported eating at least one unusually large meal with a loss of control during a 28-day period. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, controlling for sex and total brain volume.

Results: Preliminary findings show an increased volume in binge eaters versus non-binge eaters in the insula, right caudate, putamen, accumbens, and increased cortical thickness in supramarginal gyrus, left cuneus, precentral gyrus, insula, pars opercularis, and pars triangularis (all p's < 0.05 uncorrected) after analyzing 113 brain regions.

Conclusion: Consistent with fMRI findings, binge eating adults showed increases in limbic region volume, including areas implicated in reward processing, motor control, and positive reinforcement of "liking" suggesting a binge eating neural phenotype.

Funding: Nathan Kline Institute; R01 DK080153 (AG)

3

Fyn Kinase Linked to Glutamatergic Related Synaptic Alterations and Tau Pathology in the Striatum of Human Heroin Abusers

Diana Akpoyibo, Gabor Egervari, Joseph Landry, James Callens, Noel Warren, Panos Russos, and Yasmin Hurd

Icahn School of Medicine at Mount Sinai

Background: Attempts to develop new medications to combat the existing opioid epidemic is critically dependent on improving our understanding of the neurobiology underlying the addicted human brain.

Methods: A cell-type specific direct assessment of chromatin state using ATAC-sequencing was performed in the dorsal striatum, a brain region implicated in addiction, on postmortem human brain specimens of heroin users. A rat heroin self-administration model and in-vitro chronic morphine treatment of primary cortical-striatal neuronal cells were used to obtain behavioral and translational molecular insights of candidate genes.

Results: FYN, an Src tyrosine kinase, was revealed as the gene with the most epigenetic alterations in neurons of heroin abusers. Increased FYN mRNA and protein levels were observed following opiate exposure. Administration of Saracatinib, an Src inhibitor, reduced heroin self-administration and cue-induced drug-seeking behavior in the rat model. FYN levels correlated with glutamate and synaptic plasticity-related genes. Additionally, levels of pTau-Y18, a target of FYN, were elevated in the striatum of human heroin users and in the preclinical models following opiate exposure.

Conclusions: Overall, our data demonstrates that opiate related epigenetic increases of Fyn contribute to glutamatergic related synaptic disturbances and neurodegenerative pathology and suggests Saracatinib as a promising candidate for targeted clinical interventions in opiate use disorder.

Funding: NIH/ NIDA

4

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

Al-Kachak, A., Russo, S.J., David, Y., Maze, I.

ISMMS, MSKCC

The field of neuroepigenetics has grown rapidly over the past few decades and has recently implicated chromatin phenomena in the etiology of several psychiatric disorders including major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field still has only a limited understanding of the underlying mechanisms contributing to this disorder. New data from our laboratory suggest potential alternative mechanisms of action for monoamines–so-called histone monoaminylations–whereby, for example, the presence of serotonin in the nucleus of dorsal raphe (DRN) neurons may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood.

Male C-57 mice were virally injected with either empty vector, wild-type H3.3, or modified H3.3Q5A, blocking any serotonylation. Mice were then repeatedly subjected to bouts of chronic social defeat stress by a larger CD-1 mouse screened for aggressive behavior and behavioral response was analyzed via social interaction testing.

H3.3 Q5A injected animals (both control and defeated) had a significantly greater SI ratio than empty vector and H3.3 wild-type injected animals.

Globally blocking serotonylation in DRN promotes a pro-adaptive resilient response in face of CSDS, which will be further explored in a more targeted, cell-type specific manner.

Source: MQ Mental Health Research Charity and the National Institutes of Health

5

Microglial TYROBP deficiency modulates brain C1q phenotype in mouse models of Alzheimer's amyloidosis and tauopathy

Mickael Audrain[1,*], Jean-Vianney Haure-Mirande[1,*], Minghui Wang[1], Soong Ho Kim[1], Tomas Fanutza[1], Robert D. Blitzer[1], Eric E. Schadt[1], Bin Zhang[1], Michelle E. Ehrlich1[1,†] and Sam Gandy1,[†]

[1]Icahn School of Medicine at Mount Sinai

Microglial cells are the resident phagocytes of the central nervous system (CNS) and represent a key cell type implicated in the CNS inflammatory response. Mutations and/or differential expression of microglial cell surface molecules such as TREM2, CD33 and CR3 have been associated with altered relative risk(s) for developing Alzheimer's disease (AD). TYROBP (aka DAP12) is a microglial adaptor protein that acts as a key driver of a microglial activation network underlying AD. TYROBP binds TREM2, CD33, and/or CR3 and is increased in the brains of humans and mouse models of AD.

We crossed Tyrobp-deficient mice with either APP/PSEN1 or MAPT P301S mouse models in order to determine the effect of loss of TYROBP function on amyloid and/or tauopathy features of these mice. We will present the effects of Tyrobp deficiency on the microglial inflammatory response and AD pathology, and, in turn, on the behavior and electrophysiology. One unexpected feature of Tyrobp-/- x APP/PSEN1 or MAPT P301S mice was a reduction in levels of complement initiating protein C1q, a molecule known to modulate synaptic sculpting.

Thus, one potential consequence of the excess TYROBP observed in the AD brain might be to play a role in complement-related synaptic pruning by microglia.

NIH, ADRC, BrightFocus foundation

6

A key role of RGS4 in the maintenance of chronic pain.

K. Avrampou, V Mitsi, S. Gaspari, A. Ramakrishnan, E. Loh, Li Shen, F. Carr, V. Zachariou

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

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 the duration and direction of GPCR signal transduction 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 murine models of inflammatory and neuropathic pain we demonstrate that male and female mice lacking the Rgs4 gene recover from tactile and cold allodynia, whereas their wildtype controls show prolonged pain-like behaviors. This phenotype is mainly mediated by actions of RGS4 on the thalamus, as conditional knockdown of RGS4 in the ventral posterolateral thalamus leads to recovery from mechanical allodynia. RNA Sequencing studies on ventralposterior thalamus of RGS4WT and RGS4KO mice demonstrate that prevention of RGS4 action affects several intracellular pathways and molecules that promote the maintenance of chronic 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.

Funding: NINDS

Abstracts

7

Epigenetic control of brain region-specific microglia clearance activity by PRC2

Pinar Ayata[1,2], Ana Badimon[1], Hayley J. Strasburger[1], Mary K. Duff[1], Sarah Montgomery[1], Yong-Hwee E. Loh[1], Anja Ebert[3], Anna A. Pimenova[1,2], Brianna R. Ramirez[1], Andrew T. Chan[1], Josefa M. Sullivan[1], Immanuel Purushothaman[1], Joseph R. Scarpa[4], Alison M. Goate[1,2,4], Meinrad Busslinger[1], Li Shen[1], Bojan Losic[4], and Anne Schaefer[1,2*]

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The integrity of the brain depends on the robustness of neuronal survival as well as on the rapid elimination of dying neurons and non-functional synapses. The latter function is carried out by microglia, the resident myeloid cells of the brain. Here we show that microglia clearance activity in the adult brain is regionally restricted and tightly regulated in accordance with the rate of neuronal attrition. We found that cerebellar, but not striatal or cortical, microglia exhibit high levels of basal clearance activity, which correlates with an elevated degree of cerebellar neuronal attrition. Moreover, we found that exposing forebrain microglia to apoptotic cells activates gene expression programs supporting clearance activity. We provide evidence that the Polycomb repressive complex 2 (PRC2) epigenetically restricts genes that support clearance activity in striatal and cortical microglia. Loss of PRC2 leads to the aberrant activation of a microglia clearance phenotype. Our findings suggest the induction of microglial clearance activity outside the context of dying neurons causes pathological changes in neuronal morphology and associated behaviors. Our data highlight a key role of epigenetic mechanisms in preventing microglia-induced neuronal alterations associated with neurodegenerative and psychiatric diseases.

8

Reduced prefrontal cortical structural integrity as a marker of premorbid childhood trauma in cocaine addiction.

Bachi K., Parvaz M.A., Moeller S.J., Gan G., Zilverstand A., Goldstein R.Z., Alia-Klein N.

Childhood trauma affects neurodevelopment and promotes vulnerability to impaired constraint, depression, and addiction. We hypothesized that childhood trauma contributes to reduced structural integrity of the prefrontal cortex in individuals with cocaine use disorders (iCUD). Using the Childhood Trauma Questionnaire we formed 3 groups (low [L] versus high [H] childhood trauma among iCUD; CON, N=29; CUD-L, N=23; CUD-H, N=24), and regional gray matter concentration (GMC) was obtained using voxel-based morphometry on T1-weighted MRI scans. Whole-brain group comparisons showed reduced GMC in the right lateral orbitofrontal cortex (OFC) in CUD-H as compared with controls (cluster-level pFWE-corr < 0.001) and CUD-L (cluster-level pFWE-corr = 0.035); there were no significant differences between CUD-L and controls. A hierarchical regression analysis across both CUD groups revealed that childhood trauma, but not demographics and drug use, and beyond constraint and depression, accounted for 37.7% of the variance in the GMC in the right lateral OFC (p < 0.001). Beyond other contributing factors, childhood trauma predicted GMC reductions in the OFC in individuals with cocaine use disorder. These findings underscore a link between premorbid environmental stress and morphological integrity of a brain region central for behaviors underlying drug addiction. These results further highlight the importance of accounting for childhood trauma, potentially as a factor predisposing to addiction, when examining and interpreting neural alterations in cocaine addicted individuals.

9

Children with Autism Spectrum Disorder and Phelan-McDermid Syndrome Show Impaired Attention to Social Stimuli

Victoria Baskett[1,2], Sylvia Guillory[2], Emily Isenstein[2], Ting Wang[2], Jennifer Foss-Feig[2]

[1]Columbia University, [2]Seaver Autism Center

Phelan-McDermid Syndrome (PMS) is caused by a mutation/deletion in the Shank3 gene; roughly 75% of PMS individuals are diagnosed with Autism Spectrum Disorder (ASD). ASD is characterized by impairment in social interactions, notably impaired attention to faces, and repetitive behaviors. PMS is typified by intellectual impairments, coupled with ASD symptomology. This study examined visual attention in children with ASD and PMS.

Eye-tracking during a visual paired comparison (VPC) paradigm was completed for 50 participants (25 ASD, 17 PMS, 8 typically-developing (TD)). Participants viewed two identical images side-by-side during the familiarization phase. In the test phase, familiar images were again shown alongside novel images. Attention and novelty preference were measured by percent looking time.

TD participants showed novelty preference for social and nonsocial stimuli ($p<0.05$). Participants with ASD showed no preference for social stimuli, but intact novelty preference for nonsocial stimuli ($p<0.05$). Participants with PMS showed no preference for either novel images. Looking time during familiarization was similar for TD, ASD, and PMS individuals, indicating adequate task engagement across groups.

Results indicate that ASD individuals show impaired novelty preference and attention to social, but not nonsocial, images, despite attending similarly to all images during familiarization. Despite high rates of ASD in individuals with PMS, there appear to be additional differences in attention and novelty preference in this population.

Funding: Seaver Foundation

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Role of brain H3Q5 histaminylation in circadian rhythmicity

Bastle, R.[1], Rahman, T.[1], Al-Kachak, A.[1], Fulton, S.[1], Lepack, A.[1], Farrelly, L.[1], Lyu, Y.[1], Maze, I.[1,2]

[1]Department of Neuroscience, [2]Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029

Background: We have previously uncovered roles for H3Q5 serotonylation and dopaminylation in depression- and drug-related behavior; however, histaminylation remains to be explored. Given that brain histamine levels are largely rhythmic across circadian cycles, we sought to explore the role of H3Q5 histaminylation in regulating circadian behavior.

Methods: We used specific antibodies to detect H3Q5 histaminylation (i.e., H3Q5his) at several time points across 24 h in mouse tuberomammillary nucleus (TMN), the source of brain histamine, using Western blot. We then reduced levels of H3Q5his in the mouse TMN using a lentivirus that mutates the Q5 into an alanine (i.e., LV-H3Q5A) and tested circadian and anxiety-related behavior.

Results: Across the 24-h zeitgeber, TMN H3Q5his expression exhibited a rhythmic pattern, where levels appear to rise and fall during the transitions into subjective night and day, respectively. Upon H3Q5his knockdown in the mouse TMN, circadian locomotor was altered compared to controls and the LV-H3Q5A group exhibited slightly reduced anxiety-like behavior.

Conclusions: H3Q5 histaminylation appears to be regulated differentially across circadian periods and itself regulate circadian and anxiety-like behavior in mice. Future studies will utilize ChIP-seq to identify enriched loci for the modification across 24 h in the TMN, coupled with transcriptional profiling using RNA-seq.

Funding: NIDA

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Synapse Composition in a mouse model of CYFIP1 haploinsufficiency

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Neurodevelopmental disorders such as Autism Spectrum Disorder (ASD) and schizophrenia affect millions of individuals worldwide. Unfortunately, treatments for these disorders remain ineffective, leaving many with a sense of mental fragmentation. It is imperative to understand the mechanisms facilitating these disorders in order to create novel therapeutic treatments. CYFIP1 is a gene which has been implicated in ASD and schizophrenia. This project focuses on the postsynaptic neuron and in particular on key synaptic proteins in the postsynaptic density. Through a series of sequential immunohistochemistry procedures, imaging, and analysis in MetaMorph, my data shows that a key scaffolding protein, SynGAP, is displaced when Cyfip1 levels are reduced. There is a decrease in localization of SynGAP puncta at the PSD in mice characterized by CYFIP1 haploinsufficiency. This has important implications because synaptic SynGAP levels are regulated locally to support learning and decreased levels of SynGAP can cause intellectual disability. Taken together with data reported from other labs, decreased levels of SynGAP caused by reduced levels of Cyfip1 likely cause a major change in synapse composition. These data also suggest that the intellectual disability seen in humans with reduced SynGAP may share features of disabilities observed in humans with reduced Cyfip1 levels. By studying the molecular underpinnings of these shared features, future studies may be able to identify targets for new pharmacological agents that could be used as treatments.

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Emotion Processing Abnormalities in Bipolar Disorder; an fMRI study using an emotional Go/Nogo task

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Background: Bipolar disorder (BD) is characterized by emotion processing deficits; however, their neural underpinnings are still poorly understood. We previously identified an emotion processing bias, measured by an affective go/nogo (AGNG) task, as a potential neurocognitive endophenotype in BD. Stable BD and their siblings had a response bias toward negative emotional stimuli compared with healthy controls (HC). We aimed to expand our prior finding by examining the neural underpinnings of this negative emotional bias. Specifically, we aimed to compare fMRI activity in frontolimbic areas during an AGNG task in BD and HC.

Methods: Subjects: 10 euthymic BD patients and 15HC. Participants were scanned while performing an AGNG paradigm. They were asked to respond to or inhibit a response to happy, sad or neutral faces. fMRI data was analyzed using SPM. First-level individual analyses were conducted, applying the general linear model to assess the effects of inhibition and valence of the stimuli for each participant. In the second-level group analyses, voxel-wise statistical maps were used to examine effects across groups.

Results: BD patients had higher prefrontal activation ($p<0.05$) when inhibiting responses to happy (as opposed to sad) stimuli, compared to HC. Prefrontal cortex, cerebellum and limbic areas where less activated ($p<0.05$) in BD compared to HC during inhibition of negative distractors. Conversely, during inhibition of positive distractors BD patients showed higher prefrontal activation than HC.

Conclusions: Our preliminary, unpublished results are consistent with previous findings suggesting abnormalities in frontolimbic regions during tasks requiring inhibitory control of emotional stimuli in BD.

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Profiling of chromatin accessibility and gene expression in stimulated neuronal cells of childhood-onset schizophrenia patients

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Background: Childhood-onset schizophrenia (COS) is a rare complex disorder characterized by impaired neuronal functioning. Although family studies indicate high heritability, the precise underlying biological mechanism remains to be explored. In pursuit of finding “missing heritability” of the disorder, we profiled epigenomics and transcriptomics responses to neuronal activation.

Methods: hiPSC-derived neurons were isolated from six COS cases and six controls. To measure the change after neuronal activation, we harvested these cells one and six hours after stimulation with 50mM KCl and under non-stimulating conditions, followed by RNA-seq and ATAC-seq profiling.

Results: After one hour of KCl activation, neurons invoked substantial expression changes in genes that regulate activity dependent neuronal processes. These changes are driven by differentially opened chromatin regions but do not remain persistent: six hours after stimulation, epigenomics and transcriptomic profiles are almost identical with their non-stimulated counterparts. Moreover, our data suggest that a subset of these dynamically regulated genes is case/control-specific, potentially implying disrupted neuronal responses in COS.

Conclusions: Our systematic experimental framework offers an alternative approach to study the mechanisms of neuropsychiatric diseases. Here we identified gene expression and epigenome signatures that are disrupted in COS.

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Cell-type specific increase of deltaFosB in response to aggressive behavior in mice

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Aggression is an adaptive social behavior that provides evolutionary advantage. However, excessive aggression can have negative consequences for both aggressive individual and the society. Not many studies have been conducted that examine the molecular characterization of aggression motivation. Our previous results indicate a positive correlation between the level of deltaFosB in the nucleus accumbens (NAc) and intensity of aggression. Using a transgenic mouse line (D1-tdTomato), we observed that the level of deltaFosB in dopamine receptor D1 medium spiny neurons (D1-MSNs) is highly correlated to the intensity of aggression. To directly address the issue of the role of deltaFosB in D2-MSNs, we study the level of deltaFosB, in D2-MSNs by using a D2-eGFP transgenic mouse line.

Funding: This research was supported by US National Institute of Mental Health grants

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Functional consequences of NSUN2-mediated RNA methylation in the adult mouse prefrontal cortex

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The RNA methylome, in contrast to the DNA methylome, has barely been explored in the context of the normal and diseased brain. RNA cytosine methylation (m5C), characterized by the addition of a methyl group on the 5' position of a cytosine in RNA, is a novel modification only recently characterized in mammalian tissue and most abundant in tRNAs. NSUN2, a tRNA methyltransferase, is expressed at high levels in the central nervous system and has been linked to neurodevelopmental defects in humans and mice. NSUN2 knockout mice exhibit deficits in cognitive and emotional behavior, a phenotype that may be related to altered methylation at distinct tRNA cytosines. However, it is still unknown whether tRNA methylation patterns regulate brain function or behavioral outcomes outside the realm of development. Here, we characterized NSUN2 expression in the adult prefrontal cortex and then used viral overexpression of NSUN2 in the male and female adult mouse PFC to elucidate the effect of altered NSUN2 expression on tRNA methylation and cognitive and emotional behavior. Results indicate that NSUN2 is abundant in the adult PFC and only present in neurons, which may explain its role in downstream molecular and behavioral consequences, including increased depressive-like behavior. Understanding the role of tRNA methylation in the adult brain may elucidate mechanisms underlying aberrant brain function during adulthood.

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Identifying novel MAPT 17q21.31 sub-haplotypes associated with Tauopathy

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The 1.5Mb inversion region at the 17q21.31 locus confers two distinct haplotypes. The major H1 haplotype is associated with increased risk for Tauopathies, as well as with Parkinson's disease. Given this association, we sought to determine whether different, specific sub-haplotypes within the major H1 haplotype underlie risk for developing different Tauopathies.

We compared case-control genotype data from AD APOE4-/- and PD cohorts, and identified separate haplotype blocks within the 17q21.31 locus that were associated with disease. We identified sub-haplotypes conferring either protection or risk for PD with odds ratios ranging from 0.15-2. In contrast, AD-associated blocks had modest ORs ~1.1-1.6.

Next, we identified PD and AD sub-haplotypes in individuals within an independent RNA-seq dataset and found no effect of sub-haplotype on MAPT expression or splicing. However, protective H2 and H1 sub-haplotypes were significantly associated with increased LRRC37A expression.

The association between both H1H1 sub-haplotype and major H1/H2 haplotype groups with increased LRRC37A expression is suggests protection against disease. LRRC37A is within a region of copy number variation, therefore its increased expression could be due to structural variation. We will investigate this possibility with long-read sequencing and ddPCR, and by replicating these data in independent genotype and expression datasets.

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Brain Volume Differences in Restraint Eating: Data from the Nathan Kline Institute

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Background: Eating disorders are prevalent among young women. One aspect of disordered eating is "Cognitive Restraint". This eating behavior refers to a desire to purposefully restrict food consumption, without considering normal physiological cues of hunger and satiety. Cognitive restraint should be distinguished from dieting; those who restrict their food intake eat less than they would like to consume, but the amount is not less than what is required to maintain energy homeostasis. Cognitive restraint mirrors the behaviors of Anorexia Nervosa. Brain imaging is an efficient tool to measure disordered eating. Previous studies have found increased fMRI activation of the medial OFC, prefrontal regions, and frontal motor area.

Methods: We used preliminary data from NKI and compared volumetric differences in 165 structural MRI scans, using restraint type eating behavior as classified by the Three Factor Eating Questionnaire. Cortical reconstruction and volumetric segmentation were performed on the 165 scans with the Freesurfer image analysis suite.

Results: Structural MRI scans revealed significantly reduced brain volumes in restraint type versus non-restraint type in the nucleus accumbens, putamen, caudate, left hippocampus, left amygdala, and left thalamus (all p-values < 0.05).

Conclusion: Restraint eating shows significantly reduced brain volume in the executive function and motor function.

Funding: Nathan Kline Institute; Allan Geliebter, PhD

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Dynamic landscape and genetic regulation of RNA-editing in schizophrenia

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Background: RNA-editing is increasingly recognized as a molecular mechanism that plays roles in neurodevelopment and maintenance of normal neuronal function. Aberrant editing has been linked with schizophrenia, but is rarely studied on a genome-wide level using large patient cohorts and multiple implicated brain regions.

Method: We surveyed the global landscape and genetic regulation of RNA-editing in two brain regions (DLPFC and ACC) across hundreds of schizophrenia cases and controls using data from the CommonMind Consortium. All results were validated using a large independent DLPFC dataset from the Human Brain Collection core (HBCC).

Results: A high degree of altered RNA-editing patterns in schizophrenia were shared across both brain regions. Sites encoding AMPA glutamate receptor activity were edited to a lesser extent, while sites encoding translational initiation were edited to a greater extent in schizophrenia compared to controls. These sites predominately impact 3'UTR regions and interfere with binding of RNA-binding-proteins and RNA-secondary structures. All results were validated in non-overlapping HBCC samples. Additionally, ~25% of RNA-editing sites were associated with nearby cis genetic polymorphisms, including 3 sites with evidence for co-localization with schizophrenia GWAS signals.

Conclusion: Our findings show altered and widespread cis variation on RNA-editing implicated in schizophrenia neuropathology.

Source: U01-MH103392

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Using induced pluripotent stem cells derived from patient blood for transcriptional modeling in Phelan-McDermid Syndrome

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Background: Monogenic syndromes with high penetrance for Autism may provide insight into the genes and pathways that underlie deficits in the non-syndromic patient population. Phelan-McDermid syndrome (PMS) is one such syndrome that is caused by haploinsufficiency of SHANK3, a post-synaptic glutamatergic scaffolding protein. While human postmortem samples are limited, especially from the brain, iPSCs generated from patients offer a nearly limitless pool of human-derived cells for disease modeling and drug discovery. By differentiating iPSCs from PMS patients into neural progenitor cells (NPCs) and neurons, they can be used to illuminate distinct points in the neurodevelopmental trajectory of PMS.

Methods: IPSC lines were derived from patient blood samples and used for NPC generation, followed by 6 weeks of differentiation into neurons. RNA sequencing was performed on NPC and neuron samples, and a transcriptional signature for PMS was identified through differential expression and network analyses.

Results: Gene ontology enrichment analysis of differentially expressed genes in PMS samples revealed a dysregulation of neurodevelopmental genes associated with neurogenesis and organization of the postsynaptic density.

Conclusions: Characterization of the transcriptional profile of neural cells derived from PMS patient iPSCs offers valuable insight into the early neurodevelopmental changes associated with PMS.

Funding: NIH and Seaver Center

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The α5 Nicotinic Acetylcholine Receptor Subunit May Mediate Anxiety and Alcohol Reinforcement through Progesterone Signaling in the Interpeduncular Nucleus in a Sex Specific Manner

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Background: Single nucleotide polymorphisms for the α5 nicotinic acetylcholine receptor (nAchR) subunit increase the risk for tobacco and alcohol co-dependence. To enhance our understanding of this subunit in alcohol reinforcement, we utilized α5*nAchR knockout models in a sex and brain region specific manner.

Methods and Results: Female WT mice earned significantly more self-administered ethanol rewards, exhibited higher blood alcohol levels, and greater indices of anxiety versus global α5*nAchR KOs. In contrast, WT and KO males were indistinguishable (n=100). The mechanism for the sex-specific phenotype may be due to progesterone, as it is a negative allosteric modulator of α4β2nAchRs but a positive transcription factor for α5*nAchRs. Pre-treatment with a progesterone receptor antagonist significantly reduced ethanol reinforcement in female KO mice, and vice versa, progesterone pre-treatment significantly increased ethanol reinforcement. CRISPR technology was developed to locally KO α5*nAChRs in the interpeduncular nucleus (IPN) with a 15% in vivo mutation rate. Behavioral analysis is underway to confirm the role of progesterone-α5*nAChR signalling in the IPN.

Conclusion: Female binge drinking is an arising issue that can further perpetuate life stressors and end organ damage. We identified that progesterone may act on α5*nAchRs, perhaps in the IPN, in order to increase anxiety levels and alcohol abuse in female rodents.

Funding: NIH and CIHR

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Murine leukemia virus expressing HIV-Tat (MLV-Tat) transactivates HIV-LTR in vitro and induces neurocognitive impairment in MLV-Tat infected mice

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HIV infects CNS early after primary infection and HIV-infected individuals are at high risk of cognitive and motor diseases known as HIV-associated neurocognitive disorders (HAND), despite successful antiretroviral therapy (cART). cART suppresses HIV replication but HIV can persist at low-levels in cellular reservoirs, as infected T cells and macrophages. These cells can produce viral and cellular proteins that contribute to the diseases. We have shown that EcoHIV, chimeric HIV that expresses MLV-envelope protein in place of gp120, can infect mice, causes cognitive impairment. EcoHIV carries all HIV genes except gp120, and it is not clear which of EcoHIV functions may be responsible for the cognitive disease observed in infected mice. Here we describe MLV-Tat expresses HIV-Tat and infect mouse cells in vitro and transactivate HIV-LTR, demonstrating that MLV-expressed Tat is biologically active. MLV-Tat was infectious in three mouse strains as indicated by expression of MLV-envelope and tat message. Most intriguingly, MLV-Tat but not MLV-infected mice showed cognitive impairment in radial arm water maze 30 days but not ten days after infection and we showed these mice developed peripheral infection tested in thymus. Our data show that HIV-Tat is a sole contributor to cognitive impairment observed in MLV-Tat infected mice and suggest critical role of this protein in pathogenesis of HAND in people.

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The Effects of Paternal Seizure Disorders and Anti-Epileptic Drug Use on Offspring Neurodevelopmental Outcomes

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Objective: To study the effects of men with epilepsy taking anti-epileptic drugs (AEDs) at the time of conception on neurodevelopmental outcomes of their offspring.

Background: Teratogenicity and neurodevelopmental outcomes in the children of epileptic women using AEDs during pregnancy have been studied. Scarce data exist in men. However, AEDs reduce sperm motility, alter morphology, and decrease overall sperm count. This raises the concern that AEDs may influence fertility. It is unknown if AED use in epileptic men effects conception and neurodevelopment in children.

Design/Methods: This is a retrospective, questionnaire-based study involving males over eighteen obtaining care at the Mount Sinai Neurology Clinic. The experimental group contains patients previously diagnosed with epilepsy and on AEDs during conception. The control group contains patients receiving care for other neurological conditions. Descriptive data analyses were completed.

Results: To date, data has been collected for 14 babies born to fathers taking AEDs during conception versus 128 controls. Currently, no statistically significant differences have been observed between experimental and control groups regarding birth weight, conception time, premature birth rates, or incidence of Autism Spectrum Disorders and other neurological conditions.

Conclusions: Initial data does not indicate an association between paternal AED use during conception and negative neurodevelopmental outcomes. Data is still being collected.

Funding: None.

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Microglia at the crossroads of CNS-peripheral immune communication

Andrew Chan, Carles Martinez-Romero, Adolfo García-Sastre, Anne Schaefer

The primary function of the central nervous system (CNS) in vertebrate systems is to integrate sensory information and control an individual's behaviors to detect potential dangers and to maximize survival by adjusting behavioral responses. In addition to processing external sensory information, an organism must also be able to sense internal dangers including the presence of infections. In the periphery, innate immune cells respond rapidly to pathogenic insults by releasing sickness-inducing proinflammatory cytokines such as IL-1B, TNF-a, and Type I Interferons. Yet, the mechanisms by which immune mediators communicate with the CNS and induce behavioral changes are less clear. We propose that microglia, the tissue-resident macrophages of the CNS, mediate a critical role in sensing peripheral infection and shaping the sickness behavior response. To address the specific role of microglia during this process, we employ a well-established mouse model of Influenza A virus with a predictable course of infection and timing of sickness behavior onset. Using immunofluo-rescence staining for microglia activation markers in combination with interferon-activation reporter mice, we identified specific brain regions that show selective and early microglia activation in response to flu infection that precede symptoms of sickness behavior. These data raise exciting questions regarding the mechanisms of region-specific microglia activation in response to peripheral organ inflammation and the specific contribution of microglia in regulating specific neurons and neuronal circuits controlling sickness behavior.

Funding for this project provided by NIH and NIA.

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Functional Implications of a Neuron-Specific Heterochromatic Lattice Involved in Retrotransposon Silencing

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BACKGROUND: An increasing number of studies have been exploring the developmental regulation of the spatial (3D) arrangement of chromatin and chromosomal conformations in the nucleus. However, few have dissected the relevance of this type of epigenomic organization in the adult brain.

METHOD: We intersected a combination of chromatin immunoprecipitation, transcriptomic, and chromosome conformation capture (in situ Hi-C) data to explore the aforementioned issue.

RESULTS: Surveying chromosomal contacts in adult mouse cortical neuronal and non-neuronal cells unexpectedly revealed a select number of loci participating in a genome-wide chromatin lattice specific to neurons. Overlaying chromatin immunoprecipitation data profiling the repressive, constitutive heterochromatin-associated histone modification H3K9me3 in neurons suggests that the observed lattice, which includes heterochromatic portions of the sex chromosomes, is likely to be important for repeat DNA silencing. This includes a class of endogenous retroviruses (ERVs), intracisternal A particles (IAPs) which could serve as a source of double-stranded RNA (dsRNA) upon aberrant transcription, potentially inciting pervasive inflammatory responses. Transcriptome profiling of mice with mutations in repressive chromatin regulators showed increased expression of IAPs with accompanying reactive gliosis.

CONCLUSION: Our ongoing experiments will further explore the role of the neuronal 3D genome in the context of repeat DNA silencing.

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A neurodegenerative mechanism for nicotine addiction

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BACKGROUND: Medial habenula (MHb) is bilateral structure in the epithalamus and serve as a relay station between forebrain and midbrain nuclei. It has been shown that MHb plays an important role in controlling nicotine consumption by mediating the aversive effect of nicotine. Interestingly, the MHb-IPN neural circuitry is sensitive to nicotine exposure.

METHOD: nicotine self-administration, rodents and human MRI, two-photon microscopy, nicotine –uncaging, electron microscopy, iDISCO , GcAMP6s, western blot, DTA

RESULTS: Degeneration sensitive silver staining showed degeneration in the fasciculus retroflexus (FR) of nicotine SA rats. The integrity of FR in the nicotine SA rats was reduced. Moreover, nicotine SA rats have overall smaller habenular volume. Strikingly, human smokers also have smaller habenular volume compared to non-smokers. Interestingly, rats with selective lesion of their MHb-IPN have more nicotine intake. The nicotine-induced degeneration may be caused by excitotoxicity mechanism because we found that nicotine-induced a large calcium influx in the MHb-IPN. Indeed, we found that the calcium-activated cysteine proteases Calpain II, an important player in excitotoxicity, was up-regulated in nicotine SA rats.

CONCLUSION: Our data suggest volitional nicotine intake causes degeneration of the MHb-IPN and the integrity of the MHb-IPN is important to control nicotine intake. Thus, nicotine-degeneration positive feedback mechanism may play important role in nicotine addiction.

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Prefrontal tuning on mnemonic chunking in a spatial self-ordered search task.

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The capacity of working memory (WM) is limited to no more than four items, but we rarely notice this constraint because we are able to implement mnemonic strategies, such as chunking, that can overcome this limitation. Prefrontal neurons encode information in WM, but it is unclear how this changes with mnemonic chunking. To assess this, we trained two monkeys to perform a spatial self-ordered search task with six identical targets. The subjects were required to saccade to each target one at a time, returning to fixation after each target, thereby requiring him to use WM to keep track of which targets have been visited. Strengths of mnemonic chunking were quantified by using the graph theory concept of "modularity index" (MI), which computes a normalized measure of transition probabilities within chunks to across chunks. Preliminary data indicate that blocks with higher MIs also have fewer errors, consistent with the notion that stronger chunking improves WM performance. Further, we were able to decode two-dimensional target spatial information from lateral prefrontal cortex neurons using ridge regression, and categorize target selections using linear discriminant analysis. We will use these two decoding results to show how prefrontal neurons predict strengths of mnemonic chunking in a spatial self-ordered search task.

Funding: FBI Seed Funds.

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Nr4a1 promotes the maturation of the striatal patch neurons and regulates the dopamine D1 receptor signaling pathway

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Background: The GABAergic medium-sized spiny neuron (MSN) is the output neuron of the striatum. MSNs may be classified into striosome, aka patch, and matrix, according to neurochemical differences between the two compartments. The patches comprise ~15% of the striatal volume, have a preponderance of D1R+MSNs, and express the transcription factor Nr4a1 and the μ opioid receptor. Imbalances between striosomes and matrix are hypothesized to contribute to several movement disorders, including dystonia and levodopa-induced dyskinesias. We sought to determine the role of Nr4a1 in striosome development and in striatal function in response to cocaine.

Method: We used the GENSAT Nr4a1-EGFP mouse and the Nr4a1-null mouse, to examine striosome neuronal development and components of the D1R signal transduction system in vivo and in vitro. In addition, we examined the induction of pERK after cocaine administration (20mg/kg) and the locomotor response to acute cocaine and sensitization to chronic cocaine.

Results: Nr4a1 overexpression, as occurs in the Nr4a1-EGFP mouse, is sufficient but not necessary to promote striosome development. Moreover, Nr4a1 overexpression reduces long-term potentiation (LTP) and the expression of DrD1 signaling pathway components leading to a diminished molecular response to acute cocaine and decreased sensitization to chronic cocaine.

Conclusion: Nr4a1 promotes the maturation of the striatal patch medium spiny neurons and negatively controls the dopamine receptor D1 signaling pathway

Funding: CCXDP, NINDS

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Neural mapping of odor-triggered autobiographical memories.

Denise Croote, Daniela Schiller, PhD

Background: Odor-cued memory is widely acclaimed for its perceptual and emotional nature, representing a unique form of memory that differs significantly from visually and verbally-cued memory. Olfactory memories can range from pleasant recollections of holidays past, triggered by the smell of pine, to extremely unpleasant flashbacks of time spent in combat, triggered by the smell of diesel. The ability to induce these vivid emotional states is likely due to the intimate anatomical connection between the primary olfactory cortex and the limbic system. Despite their established emotional nature, a mechanistic understanding of the neural underpinnings of these memories is lacking.

Methods: To address this gap, we presented subjects with odors that triggered memories, in addition to control odors, during fMRI and examined representations of individual olfactory memories. We assessed the temporal and spatial stability of individual memories by identifying regions where the BOLD signal and spatial pattern of activation were highly stable over multiple retrievals of the memory using intra-subject correlation.

Results: We found that repeated memory retrievals produced strong temporal correlations in the visual cortex, paracingulate gyrus, hippocampus, amygdala, and insula, and strong spatial correlations in the visual cortex.

Conclusions: The strong correlations observed in the visual cortex point to the presence of substantial sensory reinstatement, a testament to the transformative nature of these memories. Altogether, these findings suggest that individual olfactory memories produce highly reliable neural activity across a range of networks.

Source: Le Foundation

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Development and characterization of an innovative model of preterm hypoxic injury using Cerebral organoids

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Preterm hypoxia-ischemia (HI) is a leading cause of disability and mortality with limited treatment options. We established cerebral organoid (c-organoid) cultures derived from human ESC to model HI in the developing human cortical tissue.

C-organoids contain cortical structures mimicking early to mid-gestation developing human brain. To study short and long-term impact of non-lethal hypoxia, we developed a transient HI model, whereby c-organoids are subjected to low oxygen tension for 24 hours during maturation.

Immediately after HI, an increased level of HIF-1α and DNA damage marker was observed in C-organoids. An increase of cell death marker AC3 was also detected 7 and 14 days after HI. Interestingly, after one week of recovery in normoxia condition, neural progenitor cells, as well as outer radial glia, continue to exhibit decreased proliferation and increased apoptosis, indicating long-term effects of transient HI. A further characterization of different isochronic progenitor cohorts was performed highlighting the fact that differentiating and migrating cells seems to be more sensitive to HI than proliferating stem cells.

In conclusion, cerebral organoids represent an ideal model to understand the impact of hypoxic injury in the developing human cortex, thus shedding light into the underlying mechanisms of HI-induced developmental defects and neurological diseases later in life.

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CSF1 Shapes Both Microglia and Cerebellum Development and Function

Veronika Kana, **Fiona A. Desland**, Samuel A. Rose, Christie Chang, Pinar Ayata, Ana Badimon, Andrew Leader, Meghan E. Flanigan, Scott J. Russo, Brian D. Brown, Anne Schaefer, Miriam Merad

Microglia are the tissue resident macrophages of the central nervous system (CNS). They maintain CNS homeostasis by phagocytizing pathogens, clearing neuronal apoptotic debris, and developing proper neural networks through synaptic pruning. Microglia development and survival is tightly regulated by factors released from its environment. Colony Stimulating Factor-1 (CSF1) Receptor signaling through its two ligands, Interleukin-34 and CSF1, is crucial for microglial survival. The differential expression of these and other ligands allows for a unique brain-region specific transcriptional profile of microglia, revealing the heterogeneity within this population of cells. Much of the work exploring the roles of microglia in the CNS centers mainly on functions specific to regions within the forebrain. There is a significant gap in our understanding of the particular ways in which microglia help to shape the cerebellar niche. To help with this understanding, we have generated unique mice that are deficient in either or both CSF1R ligand. Here, we explore the distinct ways in which cerebellar microglia develop, and shed light on how disrupting this important CSF1-CSF1R axis may alter cerebellar homeostasis, resulting in defective motor and social behavior.

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MicroRNA-128 attenuates spontaneous seizures and lethality in a mouse model of Dravet Syndrome.

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Dravet Syndrome (DS) is a devastating juvenile epilepsy disorder primarily caused by de novo mutations in Scn1a, which codes for the voltage-gated sodium channel NaV1.1. The severity of this particular seizure disorder corresponds to a high rate of Sudden Unexplained Death in Epilepsy (SUDEP), which makes the need for viable treatment options all the more urgent. microRNA-128 is a forebrain-enriched microRNA that we have previously shown plays a pivotal role in governing neuronal excitability. Here we used both a genetic and a viral approach to overexpress miR-128 either systemically or more specifically in the forebrain of a mouse model of DS. We found that overexpression of miR-128 leads to a near complete rescue of both the lethality and spontaneous seizures typically seen in these mice. Moreover, we used the Axion microelectrode array (MEA) system to demonstrate that overexpression of miR-128 in primary cortical cultures leads to a decrease in neuronal activity, including decreases in both mean firing rate and number of bursts. Thus, miR-128 may serve as a powerful therapeutic tool not only in DS but in other disease states of the brain that are perpetuated by hyperexcitation, as well.

Source: NIH, CURE Foundation, Pfizer

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Investigating the effect of the MS4A locus on Alzheimer's disease risk

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The MS4A locus on chromosome 11 contains variants that are associated with protection from Alzheimer's disease (AD) risk and delayed age-at-onset. Within the brain, MS4A genes are preferentially expressed by microglia and macrophages, suggesting that myeloid cells are mediating the association between these genes and AD. Little is known about the normal function of these transmembrane proteins, although recent literature has shown that they may act as chemoreceptors. We have shown this region of the MS4A gene cluster is also an expression quantitative trait locus (eQTL) and that protective alleles of the AD-associated variants are associated with decreased expression of two MS4A genes, MS4A4A and MS4A6A, in peripheral myeloid cells. Conditional analysis on these variants suggests that both the disease and gene expression associations in this locus are being driven by a single common haplotype. Stimulation of human monocytes with interferon gamma (IFNγ) is associated with decreased expression of MS4A4A, and ablates the cis-eQTL effect of the disease-associated variant for MS4A4A and MS4A6A. This suggests that IFNγ and MS4A signaling may be related and presents a new avenue to study the function of this gene family.

Source: This work is supported by the JPB Foundation, the NIH NIA T32 Training Grant, and the Neurodegeneration Consortium.

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Defining the Habenula in fMRI Studies

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Background: The habenula (Hb) plays an important role in reward processing through inhibition of ventral tegmental area (VTA) dopamine release and has been implicated in depression. However, the small size of the Hb (~30mm^3 per hemisphere) presents challenges to accurately defining Hb regions of interest (ROIs) in low-resolution fMRI space. Building on our recent finding of strong Hb-VTA connectivity using high-resolution 3T data (Ely 2016), independently corroborated at 3T (Hesu 2016) and 7T (Torrisi 2016), we evaluated strategies for optimizing Hb ROIs using anatomical MRI and resting-state fMRI data.

Methods: We performed automated Hb segmentation (Kim 2016) on 68 anatomical datasets from the Human Connectome Project. We then compared six methods of generating Hb ROIs in fMRI space, using functional connectivity with the VTA across 1 hour of resting-state data as our primary metric. We also examined whole-brain connectivity for each Hb ROI (p_{TFCE}<0.05).

Results: Anatomical, but not functional, Hb ROI optimization significantly increased connectivity with the VTA. Whole-brain analyses revealed Hb connectivity with anterior cingulate, insula, and primary sensory cortices, as well as serotonergic raphe nuclei.

Conclusions: Incorporating information from individuals' anatomy (e.g. volume constraints), but not resting-state timeseries, significantly improved Hb-VTA connectivity and increased specificity and sensitivity across the brain. Interestingly, Hb connectivity with cortical regions was restricted to task-positive brain parcels, terminating abruptly near boundaries with task-negative areas.

Funding: NIH

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Quantitative assessments of pathology in primary age-related tauopathy

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Background: A new category of Alzheimer disease (AD) neuropathologic changes termed primary age-related tauopathy (PART) was described. Subjects with PART have no or sparse amyloid-beta peptide containing-plaques,yet develop AD-type neurofibrillary tangles in the medical temporal lobe. Subjects with PART may have normal cognition, mild cognitive impairment, or dementia.

Methods: Hippocampal sections from subjects were stained using immunohistochemistry for abnormal tau and amyloid. Subjects were categorized as possible or definite PART (n=933). Then, neurofibrillary tangle burden was measured using semi-quantitative and computer-assisted morphometrics. The resulting data was then correlated with pre-mortem clinical symptomatology and genetic data using R.

Results: Semi-quantitative Braak tangle staging was strongly correlated with age (r=0.38, p<0.001) but not cognitive impairment (p=0.15). In contrast, quantitative morphometric measures of tau burden were correlated with both age (r=0.34, p<0.001) and cognitive impairment (r=0.18, p=0.002). Pure PART subjects had significantly less tau pathology when compared to those with mixed pathology (p<0.001) and were significantly less impaired cognitively (p=0.02).

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Histone serotonylation: a novel mechanism of epigenetic plasticity

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We provide evidence for a new class of histone posttranslational modifications, serotonylation of glutamine, which occurs at position 5 (Q5ser) on histone H3. We demonstrate that the tissue Transglutaminase 2 (TGM2) enzyme, preferentially serotonylates H3 tri-methylated on lysine 4 resulting in the presence of combinatorial H3K4me3Q5ser in vivo. H3K4me3Q5ser displays its strongest enrichment in brain and gut, two organ systems responsible for the bulk of 5-HT production. Genome-wide analyses of H3K4me3Q5ser enrichment in both cultured serotonergic cells and in brain, indicate that the mark is highly sensitive to cellular differentiation and correlates with permissive, TAF3 (transcription initiation factor TFIID subunit 3) associated gene expression. Cells ectopically expressing an H3 mutant that cannot be serotonylated display significantly reduced expression of H3K4me3Q5ser target loci. These data identify a direct role for 5-HT, independent from its contributions to neurotransmission, in the mediation of permissive gene expression in mammalian cells, and as a putative co-regulator of TAF3/TFIID recruitment to H3K4me3- marked chromatin.

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Long-Term Neurobiological Effects of Multiple Early-Life Anesthesia Exposures

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Background: Several human studies have explored the effects of multiple general anesthesia exposures in early life (before the age of 4). These studies use a population-based cohort approach to show that anesthesia increased the risk for learning disabilities, socioemotional changes, and attention deficit/hyperactivity disorder. Animal studies of early-life anesthesia indicate widespread neural and glial apoptosis from anesthetic exposure, including hippocampal damage. In addition, anesthetics are linked to synapse loss and mitochondria damage. However, whether negative neurobiological effects persist through development has not been thoroughly studied. The present project continues a longitudinal study in nonhuman primates, and investigates the long-term neurobiological effects of multiple neonatal exposures to the inhalant anesthetic sevoflurane.

Methods: Rhesus macaques received four-hour exposures to sevoflurane, or brief maternal separation as a control, at postnatal days 7, 21, and 35. Monkeys were subsequently subjected to socioemotional and cognitive testing from 6-48 months of age. Monkeys exposed to sevoflurane exhibited persistent increases in anxiety and deficits in visual recognition memory. I performed electron microscopy targeted in CA1 of the hippocampus in a blinded subset of sevoflurane and control monkeys (n=3/group), focusing on alterations to synapse size and number as well as mitochondrial morphology, number, and synaptic distribution.

Results: I report inter-individual variability for mitochondrial density and synapse size that may indicate underlying group differences, to be confirmed following the unmasking of group identity following whole-group data collection.

Funding: NIH

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A preclinical assessment of the impact of adolescent THC exposure on adult reward processing and emotional reactivity

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Background: Cannabis is one of the most widely used illicit substances worldwide, particularly amongst adolescents. Studies have shown that adolescent 9-tetrahydrocannabinol (THC) experience is associated with potentiated risk to develop psychiatric illness. This is particularly concerning given the increasing THC concentration being consumed by teens today. Determining how various doses of THC impacts emotional reactivity and reward sensitivity would significantly improve our understanding as to how periadolescent cannabis use may precipitate adult psychopathologies.

Methods: To address this question, we exposed male adolescent rats to a “recreational” dosing regimen of 1.5, 3, or 5 mg/kg of THC or vehicle. In adulthood, animals were put through a series of behavioral assays to test reward responsivity and emotional reactivity.

Results: Animals exposed to 1.5 mg/kg dose of THC showed enhanced reward devaluation and reduced risky decision making. However, THC experience dose-dependently increased food self-administration and reduced social interaction after an acute social isolation stressor.

Conclusions: These results further suggest adolescent THC exposure impacts on adult behavior related to reward, providing more insights regarding the dose relationship to reward value itself and responsivity to social stress. Molecular studies are underway to identify mechanisms underlying the protracted effects of adolescent THC on adult behavioral phenotypes relevant to psychiatric vulnerability.

Funding: NIH

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

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Neurexin-1 (NRXN1) is a highly alternatively spliced presynaptic cell-adhesion protein essential for synaptic function. Heterozygous intragenic deletions in NRXN1 are strongly associated with schizophrenia and autism spectrum disorder. Animal models of NRXN1 deletions and engineered NRXN1+/- human induced neurons exhibit deficits in synaptic transmission; however, the molecular mechanisms affecting the penetrance of NRXN1 deletions and the functional consequences of patient specific NRXN1 mutations remain unresolved.
Using a rare cohort of human induced pluripotent stem cell (hiPSC) neurons from four individuals with heterozygous NRXN1 deletions, we examined population-wide neuronal activity using a multi electrode array. A hybrid sequencing approach including targeted single molecule long read sequencing and targeted short read sequencing was developed to identify and quantify the complete repertoire of NRXN1α isoforms in our hiPSC cohort.
NRXN1+/- hiPSC neurons display deficits in neuronal activity and dendritic arborization. Hybrid sequencing of fetal PFC identified ~100 NRXN1α isoforms, which exhibit significant overlap with control hiPSC neurons. However, there were many differentially expressed isoforms in hiPSC neurons from NRXN1+/- individuals. Expression of a single NRXN1α isoform was able to increase the neuronal activity in NRXN1+/- hiPSC neurons. Future work will investigate the impact of NRXN1+/- specific isoform expression on neuronal activity, which may provide insight into how NRXN1 deletions contribute to the genetic risk for neuropsychiatric disorders.

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Intranasal Oxytocin Modulates Social Cognitive Errors in the Psychosis Spectrum

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Deficits in social cognition, particularly in mentalization, or the ability to understand mental states of others, is characteristic of schizotypal personality disorder (SPD). Oxytocin has been proposed as a modulator of social cognition.

15 SPD, 15 HC, and 15 psychiatric controls received intranasal oxytocin 24/40IU/placebo. Mentalizing was assessed with the MASC, psychosis symptoms with the PANSS, and schizotypal traits with the SPQ. ANOVA and Pearson correlations were used to compare mentalizing scores across groups and treatments, and to symptom measures.

SPD showed greater “hypomentalizing” errors (F=12.92,p=0.001) and lower hyper-hypomentalizing ratios (F=2.84,p=0.099) than HCs. In a subset (8 SPD), oxytocin increased the hyper-hypomentalizing ratio (F=6.84,p=0.019). “No mentalizing” and “hypomentalizing” was correlated with the PANSS negative symptoms subscale (r=0.25,p=0.013; r=0.37,p<0.001). “Hyper-mentalizing” was correlated with the PANSS positive symptoms subscale (r=0.20,p=0.044), and “ideas of reference” (r=0.37,p=0.033) and “suspiciousness” SPQ subscales (r=0.41,p=0.017). MASC accuracy was inversely correlated with the PANSS positive and negative symptom subscales (r=-0.30,p=0.003; r=-0.48,p<0.001) and “ideas of reference” SPQ subscale (r=0.39,p=0.024).

As hypothesized, SPD made greater “no mentalizing” and “hypomentalizing” errors; correlated with negative symptoms. Conversely, “hypermentalizing” was correlated with positive symptoms and delusional and paranoid traits. Oxytocin increased the tendency to hypermentalize, normalizing the low hyper/hypomentalizing ratio in SPD, supporting the role of social cognitive impairments in psychosis and the use of oxytocin as a modulator of this.

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Study of stress inducing neuroinflammation, and consequences on the expression of cell adhesion molecules in mice brain.

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Background: Neurexins (NRXNs) are Synaptic cell adhesion molecules(CAMs) described in the formation and function of excitatory and inhibitory synapses. CAMs are described to be highly affected by neural activity and environmental stimuli. Thus, changes on gene expression patterns or alternative RNA splicing of these key proteins allow for the regulation of the specificity of neuronal wiring in an activity-dependent manner. Using several models of stress induction in mice, we aim to further explore first, how stress might trigger neuroinflammatory pathways in the brain, and second, how these processes influence NRXNs at synapses.

Methods: We use different groups of male C57BL/6 mice and submitted them to different stress-induction paradigms. We quantified the differences in gene expression using qRT-PCR. We analyzed the induction of neuroinflammatory pathways in brain tissue, using immunohistochemistry (IHQ) for brain markers and the enzymatic assay of caspase-1 activity.

Results: Differential gene expression patterns were found across the groups of animals submitted to different stress condition. In addition, we found an increase on caspase-1 activity on brain lysates and a remarkable positive staining for inflammatory markers in the immunohistochemistry experiments.

Conclusion: We analyzed experience-dependent changes on NRXN 1 and 3 after stress induction in mice. In addition , we found signs of neuroinflammation in the brain that might affect synaptic function. Current experiments aim the study of how these stress-induced might affect cognitive behaviors.

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Dietary polyphenols promote resilience against sleep deprivation-induced cognitive impairment through activating protein translation.

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Background: Sleep deprivation (SD) is associated with memory impairment. SD impairs mTORC1-dependent protein translation, thus disrupting memory consolidation in the hippocampus. Previous evidence suggests supplementation with a bioactive dietary polyphenol preparation (BDPP) rescues SD-induced impairment of hippocampus-dependent memory. However, the mechanism through which polyphenols confers benefits in memory function is not yet clearly understood

Method: C57BL/6J mice, pretreated with BDPP, were sleep deprived immediately following training in the object location paradigm. Brains were collected at the end of SD. Memory performance was examined the next day. Primary corticohippo-campal neuronal cultures treated with brain bioavailable phenolic metabolites were used to identify the BDPP-derive phenolic compounds, responsible for the rescue of SD-mediated memory impairment.

Results: Mice pretreated with BDPP prior to training exhibited cognitive resilience to SD in addition to an increase in phosphorylation of mTOR and its direct downstream targets, eIF4E, 4E-BP1 and p70S6K in the hippocampus. Select polyphenol metabolites, e.g. cyanidin-3’-O-glucoside and 3-(3´-hydroxyphenyl) propionic acid, rescued mTOR and p70S6K phosphorylation in primary corticohippocampal neuronal cultures, as well as rescue 4E-BP1 phosphorylation in response to treatment with 4EGI-1, a specific inhibitor of eIF4E-eIF4G interaction.

Conclusions: Dietary polyphenols rescue SD-mediated memory impairments through mechanisms involving activation of mTORC1-dependent protein translation.
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Cell type and brain region-specific differential chromatin accessibility analysis in Alzheimer’s Disease.

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Background: Regions of open chromatin house regulatory elements required to mediate cell-type and tissue specific gene expression. Studies of human brain have shown that dysregulation of these regulatory mechanisms is associated with Alzheimer’s Disease (AD). The majority of previous studies, however, has been conducted using homogenate tissue derived from a single brain region and have included small numbers of AD cases and controls. Here, we present the largest cell type and brain region-specific study of differential chromatin accessibility in AD.

Methods: Using frozen posrtmortem tissue from 209 cases with AD and controls, we used ATAC-seq to profile chromatin accessibility in 2 distinct populations of cells (neuronal and non-neuronal), isolated by FACS from two different brain regions (parahippocampal gyrus and superior temporal cortex).

Results: We performed cell type and brain region differential analysis of chromatin accessibility among cases and controls. We identified more robust changes of the neuroepigenome in parahippocampal gyrus, which is the most vulnerable brain region in AD.

Conclusions: Our analysis uncovers some of the molecular mechanisms underpinning cell type and brain region vulnerabil-ity in AD.

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Epigenetic Profiling of Chromatin Accessibility in MDD Identifies Glial Dysfunction in Reward-Processing Cortex

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Background: Although clinical symptoms of MDD are well-defined, the etiology is poorly understood and current treatment efficacy hovers around 50%. MDD is heterogeneous, with genetic and environmental determinants interacting through epigenetic mechanisms to increase vulnerability. We use ATAC-sequencing plus FAC-sorting to profile cell-type specific chromatin accessibility in human MDD. We focus on OFC as a key region in corticostriatal reward processing and anhedonia. Targets further validated in two preclinical depression models (monkey and rodent).

Methods: OFC tissue from sex/aged-matched control and MDD subjects (N=40) FAC-sorted into neuronal and non-neuronal (NeuN +/-) populations. ATAC-sequencing performed and differentially accessible gene targets determined through analysis pipeline. Cell-Type enrichment, GO, TF-motif analysis performed (Barres/ENRICHR/RSAT). Target validation for mRNA (rt-qPCR) and protein (WB). Further validation on NHP OFC (Variable Foraging Demand) and mouse PFC (Chronic Social Defeat).

Results: In non-neuronal population, ATAC-seq revealed 183 regulatory regions more open, 20 more closed in MDD vs. controls. In neuronal populations, 0 regions differentially accessible. 12 genes validated as differentially expressed at mRNA level (.0001<p<.04) in MDD vs. control human, 3 genes in CSDS mouse, 1 in NHP. 2 genes validated at protein level. TF binding sites determined.

Conclusions: ATAC-seq reveals loci-specific chromatin accessibility differences in non-neuronal cells of MDD. ATAC allows integration of genetic/epigenetic and -omics investigation by identifying gene expression changes, regulatory regions, and TFs that may coordinate complex disease states in vivo.

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Unravelling the epigenomic differences in histone modified regions in neurons in schizophrenia.

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Introduction: Identifying genetic and transcriptomic differences between schizophrenia patients and controls has yielded insight into disease etiology. Moreover, schizophrenia risk variants are enriched in regions with histone modification specifically in neurons.

Methods: We conducted H3K4me3 (H3K27ac) chromatin immunoprecipitation sequencing (ChIP-seq) on fluorescence-activated cell sorted (FACS) neuronal nuclei from dorsolateral prefrontal (PFC) region of 240(270) postmortem samples from SCZ and matched control brains.

Results: We compare epigenomic profiles between cases and controls in neurons to identify loci that are differentially modified in schizophrenia. Integrating histone modification profiles of individuals with their whole genome sequences, we identified histone quantitative trait loci (hQTLs). These loci (hQTLs) are set of genetic variants in neurons that correlate with variation in histone modification profiles in individuals. We intersected the hQTL set with genome-wide significant ($p \leq 5e-8$) variants associated with schizophrenia.

Discussion: These results yield novel insights into non-coding variants associated with schizophrenia and will help us in tracing the molecular mechanisms by which risk variants confer disease liability.

Funding: NIMH

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Underlying neuronal circuitry of attention in Fmr1-ΔKH1 rats

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Background: Fragile X Syndrome (FXS) is caused by the silencing of FMR1, which leads to a loss of Fragile X Mental Retardation Protein (FMRP), a regulator of mRNA translation. Patients have severe impairments in prefrontal cortex (PFC)-dependent attention and PFC anatomy. Despite this, the medial PFC (mPFC) has not been focused on in many Fmr1 knockout (KO) rodent studies. Therefore, we assessed the mPFC of the published Fmr1 KO rat. Importantly, we first found that this rat is not Fmr1 null, but instead has a specific knockout of KH1, a domain within Fmr1 responsible for RNA-binding.

Method: In order to determine whether a loss of the KH1 domain can lead to FXS-like phenotypes, specifically in the mPFC, we tested attention with the five-choice serial reaction time task, examined neuroanatomy with Magnetic Resonance Imaging, and assessed mPFC mRNA expression with RNA-seq in Fmr1-ΔKH1 rats and wild type littermates.

Results: Our data suggest that, similar to FXS patients, Fmr1-ΔKH1 rats have (1) impaired sustained attention, (2) deficits in neocortical white matter integrity, and (3) disrupted mPFC mRNA expression.

Conclusion: These findings emphasize the role that both the mPFC and KH1 domain of Fmrp play in three major impairments in FXS.

Funding: NIMH, Seaver Autism Center

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A Dose Response Relationship of Histone Deacetylases Inhibitor Drugs in a C. elegans model of Alzheimer's Disease

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Alzheimer's Disease is the sixth leading cause of death in the United States and is expected to cost Americans 1.1 trillion dollars by 2050. The purpose of this study is to investigate the potential of HDAC Inhibitors as therapeutic agents for Alzheimer's Disease. We assessed the efficacy of three different novel HDAC inhibitor drugs at 8 μM, 4 μM, and 2 μM. Caenorhabditis elegans (C. elegans) are an attractive model organism for the study of neurodegenerative disorders due to their fast reproduction rate and similar biochemical properties to humans. The worms were given the different drugs at different dosages to see not only which compound was the most effective, but at which concentration these drugs performed best at. Results indicated that drug #126040 had the highest efficacy of the compounds tested and significantly reduced the development of the Alzheimer's Disease phenotype. Furthermore, we found that that 4 μM was a sufficient enough concentration to prevent the paralysis phenotype of the C. elegans tested. The data gathered in this experiment could prove instrumental in furthering the use of HDAC inhibitor drugs in future clinical trials.

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Engineering CRISPR constructs as tools for gene-targeted transcriptional reprogramming in mammalian brain to elucidate the causal pathogenic mechanisms of drug abuse

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A major obstacle in efforts to understand and devise treatments for addiction stem from an inability to determine causality between enrichment of a transcription factor binding at a specific gene and the pathogenesis of addiction. In an effort to determine this causality, our group utilized CRISPR/dCas9 technology fused to pseudo-phosphorylated isoform of the transcription factor CREB (dCas9-CREB(S133D)) to determine the neural and behavioral effects of targeted in vivo transcriptional reprogramming in a locus-specific and cell-type specific manner. We initially targeted this to the Fosb gene locus, a locus implicated in drug addiction pathogenesis. We observe that viral delivery and targeting of dCas9-CREB(S133D) to the Fosb promoter is sufficient to up-regulate ΔFosB mRNA and protein levels in the NAc of mice as well as potentiate cocaine conditioned place preference, indicating a causal role for CREB binding to Fosb in the progression of cocaine responses. Having utilized these tools at the well-understood Fosb locus, we capitalized on the intrinsic flexibility of CRISPR to design gRNAs targeting dCas9-CREB(S133D) to the previously unexplored, CREB-regulated gene Zfp189 – which we have observed to be induced in NAc by cocaine self-administration. The targeted recruitment of CREB to Zfp189 will allow us to identify the causal transcriptional and behavioral consequences of this interaction within the brain's reward regions.

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Expansion Microscopy: Verification and Reproducibility

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Expansion microscopy is a technique in which proteins in biological samples are labeled with antibodies tagged with fluorescent molecules, anchored to a polymerizable substance, and then physically expanded. This technique is useful because it allows for particularly small samples to be resolved easily; it is inexpensive, simple and versatile which minimizes the need for costly and fragile equipment. This project focuses on first verifying the expansion technique and then making it as reproducible as possible across samples and across experiments. Cultured neurons were immunolabeled for a marker of the Golgi apparatus that was tagged with Alexa 488 and stained with DAPI, a marker for DNA that labels nuclei and the preparation was expanded using a gel. Images of the cells were taken using a Zeiss LSM 780 confocal microscope and analyzed using Fiji software. Based on the four trials that were performed, the expansion technique was successful but showed high variability. The nuclei of the samples, on average, expanded to double the size of the cells themselves and the physical gels increasingly expanded during experiments. Reproducibility, as shown in the last two trials out of four, became more apparent when the protocol was modified in order to get more consistent results.

Funding: The National Institute of Mental Health (NIMH)

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Absence of TYROBP in a mouse model of Alzheimer's amyloidosis recapitulates human Alzheimer's-predicted complement network and prevents functional deficits

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Background: Multiscale gene network approaches enable new avenues of exploration to identify causal genes in sporadic late onset Alzheimer's disease (LOAD) pathogenesis and to offer insights for drug discovery programs. We previously constructed a probabilistic causal network model of LOAD and identified TYROBP (=DAP12), a microglial transmembrane signaling polypeptide, as the most robust key driver gene in the LOAD network.

Methods: We crossed the amyloidogenic mouse model of AD (APP/PS1) with Tyrobp-/- mice. Using a panel of biochemical, physiological, behavioral, and transcriptomic assays, we sought to validate in vivo the driver role of TYROBP in AD.

Results: Absence of TYROBP in APP/PS1 mice recapitulated the characteristics of the expected human network and repressed the induction of genes involved in the switch from homeostatic microglia to disease-associated microglia, including Trem2, C1q, Clec7a, and Cst7. Importantly, absence of TYROBP in APP/PS1 mice prevented the electrophysiological and learning and memory alterations associated with the APP/PS1 mutant-bearing mice.

Conclusion: Our results suggest that TYROBP could represent a novel therapeutic opportunity to slow or arrest the progression of sporadic LOAD and validate the relevance of multiscale gene networks for identifying causal genes and pathways in complex diseases.

Funding: NIH; BrightFocus Foundation

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EARLY PSYCHOSIS RESEARCH PROJECT

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Background: This research project is clinically driven hewing to Bacon's Razor—paying attention to research the will benefit human kind and relieve suffering. Early psychosis research and research into the development of the schizophrenia spectrums disorders appears to have bogged down—stuck in a logjam of a mass of reductive neuro biological data.with a build up much of which is likely to turn out to be assigned to a category of artifacts of scholarship.

Methods: Viewing neuropsychiatric disorders as various disturbances in the construction of prediction—perhaps a premature scientific hypothesis—maybe a way forward for the field.

Results: Preliminary results suggest that an open dialogue initial diagnostic and therapeutic family group meeting may provide a way to collect a cohort of children and adolescents to study. Since prediction is constructed on sensory input, perceptual processing and memory this research project aims at studying the symptom expression of the several deficits in perception and perceptual processing that congregate in families vulnerable to psychosis and the schizophrenia spectrum disorders.

Conclusions: None

Source: None

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FUNCTIONAL ANALYSIS OF SCHIZOPHRENIA-ASSOCIATED GENES IN HIPSC 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/i) platform to NGN2-induced excitatory neurons, enabling manipulation of CMC gene expression in human neurons and examined functional roles of the CMC genes by presynaptic imaging, patch clamping and multiple electrode array.

Result: The decreased SNAP91 and TSNARE1 expression reduced SYNAPTOPHYSIN1+ puncta counts, having limited effect on the puncta size. Furthermore, decreasing SNAP91 expression reduced sEPSC frequency through its presynaptic and postsynaptic function.

Conclusion: We confirmed the presynaptic functions of SNAP91 and TSNARE1 in human excitatory neurons.

Source: NIH

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Systems Modeling of White Matter Microstructural Abnormalities in Alzheimer’s Disease

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Introduction: Microstructural abnormalities in white matter (WM) are often reported in Alzheimer's disease (AD) and may cause neuronal degeneration. We performed regional association analysis of diffusion weighted MRI (DTI)-derived nine features and AD-pathology related endophenotypes to identify significant features and regions which are relevant to disease progression using the Alzheimer’s Disease Neuroimaging Initiative (ADNI-GO/2). We also uncovered the multi-scale network structures of genes and DTI features.

Methods: We assessed diffusion MRI data to derive a number of DTI features from ADNIGO/2 (N=259). The correlation analysis of the DTI features and the clinical and cognitive traits systematically uncovered the relevance of 176 brain regions to disease severity. Weighted interaction network analysis (WINA) was further performed on the DTI and gene expression data to identify highly coordinated gene and voxel modules. GSEA was carried out to annotate each module with enriched pathways.

Results: Parahypocampal gyrus, saggital stratum, hippocampus were among the top ten regions most related to AD severity. Amyloid beta accumulation and tau pathology are highly correlated with longitudinal WM integrity in the top ten regions. Immune system, interferon signaling, lipid homeostasis are among the pathways enriched with modules with nine DTI features.

Conclusion: Enhanced understanding of the biological processes and key drivers related to WM microstructural changes could lead to novel therapeutic strategies for AD.

Funding: NIH

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A novel hypothalamic-to-thalamic circuitry controlling motivated reward seeking

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Introduction: Motivation can be broadly defined as a process whereby internal and external stimuli invigorate and hone on-going behavior. Evidence suggests that drugs of abuse come to exert control over behavior by usurping basic motivation and appetitive drive circuits in the brain. Orexin (hypocretin) neurons of the lateral hypothalamus (LH) have a major influence over appetitive behaviors and motivation, though how changes in the activity within discrete circuits of this distributed system contribute to drug reward seeking is unknown.

Methods: We have employed in vivo calcium imaging with fiber photometry to monitor the activity of orexin neurons in mice seeking food and nicotine to gain a better understanding of how dynamic fluctuations in orexin activity code different phases of motivated behavior. Additional experiments employ slice electrophysiology, local pharmacology in task performing animals, and pathway specific chemogenetics to identify the precise neural circuitry that underlies motivated nicotine seeking.

Results/Discussion: Our combined data suggests that nicotine fundamentally alters the recruitment of the LH orexin system, primarily by augmenting orexin neural activity which in turn maintains reward seeking even under conditions of increased effort. This behavioral effect is mediated by the actions of orexin on a small population of previously unidentified orexin-1 receptor expressing GABAergic neurons in the dorsal thalamus. The results of these studies identify a novel circuitry that regulates motivation, and thus a new target for the treatment of motivational disruption in drug addiction.

Funding: NIH

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Plexin-B2 promotes invasive growth of glioblastoma by lowering cell adhesion

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Background: The diffuse invasion of glioblastoma (GBM) cells into brain tissue is a main contributor to the lethality of this frequent brain tumor. Plexins are cell surface receptors for semaphorins that control cellular dynamics in developmental processes and in adult physiology. The plexin family member Plexin-B2 is upregulated in GBM cells, and its high expression correlates with shorter patient survival. Here, we sought to elucidate the cellular mechanism by which Plexin-B2 promotes malignancy of GBM.

Method: Plexin-B2 was knocked-out by CRISPR/Cas9 in GBM cells. Using these Plexin-B2 GBM cell lines, we performed a series of in vitro assay, in vivo intracranial transplants, and RNA-seq analyses.

Results: We found that Plexin-B2 regulates aggregation and dispersal of GBM cells. GBM cells with Plexin-B2 knockout showed increased cohesion to each other, and reduced invasion of host brain in vivo (and longer survival of mice transplanted with Plexin-B2 mutant cells). Plexin-B2 had no direct impact of cell proliferation. In RNA-Seq analysis of Plexin-B2 knockout cells, cells no obvious shift in gene expression program was observed, however, changes in expression of cell adhesion molecules was detected, suggesting that cells compensate Plexin-B2 loss with expression of other cell adhesion molecules.

Conclusions: We hypothesize that Plexin-B2 acts as a molecular clutch that lowers the adhesiveness of cells, facilitating invasive migration.

Funding: NIH/NINDS

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Neural correlates of auditory hyporesponsiveness in individuals with Phelan-McDermid Syndrome

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Phelan-McDermid Syndrome (PMS) is a rare disorder involving a mutation or deletion in the SHANK3 gene that affects synaptic and glutametergic function. PMS is characterized by global developmental delay, intellectual disability, delayed or absent speech, hypotonia, and confers high risk for autism. Based on observations of sensory hyporeactivity in individuals with PMS, we hypothesize that cortical response to auditory stimuli will be reduced, whereas habituation will be enhanced in this population.

EEG was recorded from 6 individuals with PMS (aged 13-18) and 7 controls (aged 14-32). Sequences of four consecutive 1000Hz tones separated by 500ms were repeatedly presented; inter-trial interval was 4000ms. Amplitudes of N1 and P2 event-related potentials (ERP) were extracted and compared between groups.

Compared to controls, the PMS group displayed a marked decrease in P2 amplitude to the initial tone (d=.932) and stronger P2 habituation (d=.720) when comparing the amplitude ratio between tone 1 and 4. N1 response to the initial tone and N1 habituation did not differ between groups.

Findings reveal a trend towards cortical hyporesponsiveness and more pronounced habituation to auditory stimuli in PMS; results are consistent with behavioral observations. Electrophysiological response during auditory habituation may offer a promising biomarker for use in measuring treatment effectiveness, and reveal underlying neural dysfunction in this neurodevelopmental disorder.

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Autism risk after prenatal exposure to medication affecting neurotransmission

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Background: Prenatal exposure to medications has been hypothesized to influence the risk of autism spectrum disorder (ASD). However, safety of the majority of pharmaceuticals has not been verified. We investigated the effects of all medications acting on the major neurotransmitter systems on the risk of ASD in offspring.

Methods: This is a case-cohort study using prescription data from Israel (nASD=1,405, ncontrols=94,573). We identified 55 groups of medications affecting neurotransmitter-relevant drug targets prescribed to pregnant women in our sample. We investigated the effects of exposure to those groups using Cox proportional hazard regression.

Results: After quality control, we tested 34 groups of medications, 26 of which showed no association with ASD. After adjustments, we observed higher rates of ASD among children prenatally exposed to antagonists of neuronal acetylcholine α receptor (p=0.02) or GABA transaminase inhibitors (p=0.09), and decreased rates among those exposed to cannabinoid receptor agonists (p=0.03), muscarinic receptor 2 agonists (p=0.04), opioid receptor κ and ε agonists (p<0.05).

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Plexin-B2 as a mechanoregulator during the neurodevelopment: an ancient function in control of cytoskeleton and cell adhesion

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Neural tube closure is a critical step in neurodevelopment, yet how neuroprogenitors sense biochemical cues to transmit into tensional forces in the developing neuroepithelium is unclear. The semaphorin receptor Plexin-B2 is required for neural tube closure and regulates neuroprogenitor proliferation and migration; however, a unifying mechanism underlying its multifaceted roles is lacking. Here, using cerebral organoids derived from human embryonic stem cells (hESCs), we demonstrate that Plexin-B2 mediates biochemical-mechanical integration during multicellular organization. Plexin-B2 deficiency disrupts the formation and architectural integrity of ventricle-like structures in cerebral organoids. Plexin-B2 also regulates traction forces during hESC colony expansion by orchestrating actomyosin contraction, intercellular adhesion, and cell-matrix attachment. Plexin-B2 directly interacts with integrin β-1 and requires its extracellular, Ras-GAP and RBD domains for mechanoregulation. Our findings provide a new understanding of Plexin-B2-mediated mechanomorphogenesis during the earliest stages of cell fate specification and human corticogenesis, and may have implication for stem cell-based regenerative strategies.

Source: NINDS; NY state and National Council for Scientific and Technological Development (CNPq, Brazil).

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Dynamics of sleep spindles and the slow oscillation across motor learning in adult mice

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Increased cortical sleep spindles during NREM sleep have been observed in offline improvement during human motor learning, particularly in topographically relevant cortical areas. Slow oscillations have been implicated in long term memory consolidation through cortical-hippocampal synchrony, but has yet to be investigated in motor learning.

Following handling, spindle count in all NREM sleep was significantly greater in female mice (1699 ± 32 spindles, n = 4) compared to male mice (904 ± 50 spindles, n = 7, t-test: $p < 0.001$). Sleep following rotarod learning was marked by an increase in spindle count (237 ± 18 following learning vs 272 ± 23 following handling, n = 11, $p = 0.023$) from 1 to 4 hours after NREM sleep onset, without significant change in spindle peak frequency, duration, coherence, or relative power in the spindle band (10-16 Hz). There was a significantly greater number of spindles in the first 1 to 4 hours of NREM sleep in female mice (304 ± 23 spindles, n = 4) compared to male mice (212 ± 10 spindles, n = 7, t-test: $p < 0.001$) following rotarod learning.
Ad libitum sleep following rotarod motor learning results in an early increase in spindle count and density compared to sleep without motor learning.

Source: The Friedman Brain Institute

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Validation of in vivo-Diffusion MRI Neuroinflammatory Markers against LN3 Immunostain.

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Background: Diffusion Weighted Imaging (DWI) and its quantitative measures of Fractional Anisotropy (FA), Free Water (FW) and Mean Diffusivity (MD) are widely used to characterize white matter microstructural pathology in various neuropsychiatric diseases. FA, FW and MD are believed to be indirect measures of axonal/myelin integrity and extra cellular space, however their biological specificity is poorly understood, as the histological validation studies of DWI are relatively rare. Animal models such as rhesus macaques open a new window towards exploration of changes in the white matter (WM) structure. In this study, we investigate relationship between age related changes of FW, and age related changes in the number and density of activated microglial cells.

Methods: MRI: Diffusion and T1-weighted images were collected in five rhesus macaques (Ages: 7-27). Floating sections of the macaque brains were immunostained with antibody for microglial cells (LN3). Stained activated microglial cells in the Cingulum Bundle were then counted.

Results: FW and microglial cells positive correlate with age.

Conclusion: Both increase of FW as well as increased number of activated microglia with age suggests possible involvement of inflammation in the aging process.

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Identifying Myeloid Genes and Functions Modulating Alzheimer's Disease

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Background: Genome-wide association studies (GWAS) have identified more than twenty loci associated with late-onset Alzheimer's disease (AD). The molecular mechanisms by which these disease-associated variants give rise to AD have yet to be elucidated, but several studies have implicated myeloid cells in the etiology of AD. To address this gap in our knowledge we undertook an integrative analysis of myeloid genomic datasets in the context of AD genetics.

Method: We integrated AD GWAS summary statistics and myeloid eQTLs to generate AD associated myeloid candidate genes. We explored the myeloid context of these by examining co-expression networks derived in three independent gene expression datasets. We tested the consistency of these relationships across different cell types (monocytes and macrophages) and treatments (interferon g, LPS).

Results: Several modules are discovered to be enriched for AD candidate genes. Amongst enriched modules preserved across datasets are modules corresponding to the response to type I interferon and response to oxidative stress.

Conclusion: Through an integrative analysis of expression and genetic datasets, we have identified various genes and biological processes to monitor in experiments to identify disrupted immune functionality by AD genetics. We hope to integrate these findings into a multi-scale and longitudinal picture of the development of AD pathology and cognitive phenotypes starting from disruptions in myeloid functionality.

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Trajectory of Human Habenula Volume and Location Through Adult Lifespan

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Background: The habenula, a small nucleus in the midbrain, plays a key role in reward and aversion processing. Due to the habenula's small size, segmenting it from MRI is challenging. We proposed objective automated human habenula segmentation schemes based on the high myelin content in the habenula. Here, we applied our habenula segmentation to the Cambridge Centre for Ageing and Neuroscience (CamCAN, Taylor et al., 2016, Shafto et al., 2015) data to examine left/right habenula asymmetry, and the effect of age on the habenula volume.

Methods: 652 healthy adults (age 18-88yrs, 330 females). We segmented the habenula from 3T 1mm isotropic resolution T1w/T2w images using our automated segmentation method and accepted 441 (68%) cases after visual inspection. The center-of-mass of habenula segmentation in the MNI coordinates, was averaged.

Results: The left/right habenula volume of all subjects were 18.3±5.6/17.9±5.5mm^3. The habenula volume was negatively correlated with age ($r<-0.2$, $p<0.01$). The habenula volume in males was larger than that in females only in the young group (18-30yrs). There is a trend ($p=0.08$) toward larger right than left habenula volume only for the young group. The habenula centers in the MNI coordinates in younger subjects located more medially and posteriorly than older subjects.

Conclusion: The habenula volume and center location in the MNI space are correlated with age. The habenula volume may differ between genders in young adults.

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Synergistic Effects of High Early-Life Stress Exposure and HIV Infection on Reaction Time Variability

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A recent report indicated that HIV+ adults with high levels of early-life stress (ELS) exposure, relative to those with low ELS, exhibit greater reaction time variability (RTV), a neurobehavioral marker of cognitive dysfunction. Yet, comparisons to HIV-negative samples are lacking. It thus remains unclear whether increases in RTV observed in HIV+ High-ELS adults reflect effects associated with high ELS exposure exclusively or the combined effects of high ELS and HIV. Gaining clarity on this issue is required to better characterize ELS-related risks to neurocognitive dysfunction in HIV+ samples. Hence, we examined RTV, assessed during a simple working memory task, in a sample of 60 HIV+ adults (34 High-ELS) and 70 HIV-negative control (HC) adults (33 High-ELS). We observed a significant interaction between HIV and ELS status, driven by RTV elevations in the HIV+ High-ELS group relative to all other groups, including HIV+ Low-ELS, HC Low-ELS, and HC High-ELS. In the HIV+ sample, degree of ELS exposure was significantly associated with RTV. By contrast, significant associations between ELS and RTV were not observed in HC. In conclusion, we find evidence for synergistic effects of HIV and high ELS on RTV, suggesting ELS-related mechanisms exacerbate HIV-related neural vulnerabilities leading to increased cognitive dysfunction. Such findings provide further evidence that high ELS exposure is a significant risk factor for cognitive dysfunction, particularly in the context of HIV.

Funding: NIH

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

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Background: Neuropeptides are widely expressed molecules in the brain that can act as transmitters. Little is known about this transmission in vivo. This is mainly due to lack of detection tools with good temporal resolution. We developed a method that allows real-time monitoring of peptide levels. It is an optical approach that relies on signal detection from genetically-engineered cells. These cells, transduced to express a peptide receptor and a Ca2+ sensor, convert peptide binding into a fluorescent signal.

Method: Somatostatin reporter cells (SSTR2 CNiFERs) were created by lentiviral transduction of HEK293 cells. Cells were then single-cell sorted and expanded. Clonal cells were screened for sensitivity and specificity for somatostatin on a fluorometric reader. Selected clones were further tested in vitro and in vivo for potential desensitization of the receptor.

Results: The clone selected after screening has nanomolar sensitivity to somatostatin (EC50=15nM). It had a detectable level of response after multiple exposure to saturating level of the peptide. Implanted CNiFER responded to externally applied peptide implying basal level of the peptide had not desensitized the receptor.

Conclusion: We have created a CNiFER with a physiologically relevant sensitivity to somatostatin. I am currently using this reporter to find out the optical stimulation parameters that would lead to somotastatin release from the cortical SST-interneurons.

Funding: NIH

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

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Schizophrenia, bipolar disorder, and major depression together affect over 16% of the worldwide population, but their etiologies are poorly understood. Gene expression variation is a common attribute of these disorders, so research to identify and target aberrant mRNA regulation may provide novel therapeutic benefit. mRNA can anneal to template DNA during transcription, forming a DNA/RNA hybrid known as an R-loop. New genome-wide mapping strategies have identified a connection between R-loops and transcriptional regulation, suggesting a role for R-loops in gene expression variation. However, R-loops have never been characterized genome-wide in human brain cells, precluding research exploring their role in neuropsychiatric illnesses. Here, using DNA/RNA immunoprecipitation followed by deep sequencing (DRIP-seq), we show that R-loops are abundant in human neural cells and display a distinctive distribution relative to non-neural cells. We find evidence that R-loops may be poising genes for transcription, particularly those genes involved in neural differentiation and cell type-specific function. We predict that aberrant R-loop regulation disrupts essential transcriptional pathways, and may be involved in the pathophysiology of neuropsychiatric illness. Our future studies will test this hypothesis by directly manipulating R-loop formation and examining the phenotypic consequences in neural cells both in vitro and in vivo.

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Appraisal of threat and related stigma in youths at clinical risk for psychosis

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Background: Face emotion recognition (FER) deficits and stigma characterize schizophrenia, including in prodromal stages. As stigma depends on perceived appraisal by others, we hypothesized it would be associated with FER deficits in clinical high-risk (CHR) youths.

Method: We obtained FER, stigma measures and prodromal symptom ratings in 28 CHR youths. FER was assessed using the Penn Emotion Recognition Task (ER-40; Kohler 2005). Link's measures of shame and discrimination in schizophrenia, adapted for CHR, were used to assess stigma (Link 1989; Yang 2015).

Results: A negative correlation was found between reported shame and accuracy in fear recognition (r=-0.41; p=.03), adjusting for prodromal symptom severity. Stratified by shame, the "high shame" subgroup had worse fear recognition than the "low shame" subgroup (p=.014). Negative stigma emotions and misperception of fear in non-fearful faces were correlated (r=0.37, p=.05).

Conclusions: The association between fear perception and reported shame in CHR youths has implications for prevention. Causal direction can be clarified in longitudinal study, and also by interventions that target each, such as cognitive remediation or oxytocin for FER deficits (Wolwer 2005; Fischer-Shofty 2013), or stigma reduction strategies (Yang 2014). Potential mechanisms for their association include disturbance in amygdala function for FER (Atkinson and Adolphs, 2011) and for stigma (Raij, 2014).

Source: NYSOMH, NIMH

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Effect of VTA GABA neuron activation on methamphetamine sensitization and CPP

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Background: Chronic psychostimulant exposure potentiates glutamatergic transmission onto VTA dopamine neurons, while GABAergic inhibition becomes weakened. Such plasticity contributes to hyperactivity of DA neurons during early drug withdrawal, which can promote drug seeking behavior. We test the hypothesis that enhancing the activity of local VTA GABA neurons can attenuate DA neuron firing and inhibit meth-induced behavioral adaptations.

Method: GAD2-IRES-Cre mice were injected with AAV expressing Cre-dependent excitatory DREADD (hM3Dq) or control fluorophore in the VTA. CNO was given i.p. to activate VTA GABA neurons during meth exposure in locomotor sensitization and conditioned place preference (CPP) tests. CNO was bath-applied in slice recording to evaluate its effect on VTA GABA and DA neuron firing.

Results: Chemogenetic activation of VTA GABA neurons suppressed basal locomotion as well as sensitized locomotor response to meth, but did not prevent the development of sensitization. Activating VTA GABA neurons during meth exposure abolished meth CPP, although activating VTA GABA neurons alone did not generate conditioned place aversion (CPA). Activating VTA GABA neurons in acute brain slices confirms inhibition of DA neuron spontaneous firing.

Conclusions: Chemogenetic activation of VTA GABA neurons acutely suppresses DA neuron firing. This leads to an inhibition in the expression, but not development of meth sensitization. In addition, VTA GABA neuron activation abolishes the rewarding effect of meth in the CPP paradigm.

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Pathological Diagnoses of Biopsied Samples in Intracerebral Hemorrhage

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Background: Neuropathologic analyses of parenchymal brain biopsies collected during open and endoscopic intracerebral hemorrhage (ICH) evacuation can provide a more definitive determination of hemorrhage etiology.

Methods: A single surgeon operating at Mount Sinai Hospital and Mount Sinai West collected parenchymal and clot biopsies for forty-three patients undergoing operation for ICH between October 2016 and March 2018 and sent them to the Department of Pathology for analysis. All demographic and pathologic data were collected prospectively.

Results: The average age of patients biopsied was 62.9 years. There were 27 males (63%) and 16 females (37%). Thirty-nine patients(91%) underwent endoscopic clot evacuation, whereas 4(9%) underwent open surgery. Hemorrhage location was categorized as basal ganglia(n=17, 40%), parietal(n=10, 23%), thalamic(n=7, 16%), frontal(n=6, 14%), temporal(n=4, 9%), occipital(n=3, 7%), and extreme capsule(n=1, 2%), with 8 patients having hemorrhage in more than one location. Pathological biopsy results were as follows: gliosis(n=6, 14%), amyloid(n=5, 12%), ischemic change(n=5, 12%), hypertensive etiology(n=3, 7%), reactive microglia(n=2, 5%), arteriosclerosis(n=2, 5%), arteriovenous malformation(n=1, 2%), tumor(n=1, 2%), and no pathological findings(n=22, 51%). Patients positive for amyloid had an average age of 80 years with the following bleed characteristics: parietal only(n=1), occipital only(n=1), frontal+parietal+occipital(n=1), frontal+parietal(n=1), and parietal+occipital(n=1).

Conclusions: Further analysis of CT/MRI imaging is needed to determine the predictive accuracy of various etiologies for ICH.

Funding: None

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IL-18 controls the habenular avoidance circuits of nicotine intake.

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IL-18 is a key pro-inflammatory cytokine acts in the immune system and the central nervous system. Uniquely, neurons in the medial habenula (MHb) produce IL-18. It has been established that MHb neurons and their projections to the Interpeduncular nucleus (IPN) play a critical role in controlling nicotine consumption. Here, we investigate if and how IL-18 produced by habenular neurons influence nicotine intake. First, we confirmed that neurons in the dorsal MHb produce IL-18. Second, we found that local infusion of IL-18 into MHb and IPN suppressed nicotine intake in rats. We confirmed that nicotine activates IL-18-producing neurons in the habenula by Fos immunoreactivity. Electrophysiological recordings from IPN show that IL-18 enhances local excitatory synaptic transmission. Together, these data suggest that IL-18 has excitatory effects on the habenula-IPN circuit that likely explains the inhibitory effects of this cytokine on nicotine intake. Paradoxically, nicotine intake was also decreased in Il18-/- mice. Moreover, the habenula-IPN circuit was hyper-responsive to nicotine in Il18-/- mice. Further, we observed lower levels of microglia and microglia-derived cytokines in the habenula of Il18-/- mice. These findings suggest that in addition to its acute stimulatory effects of transmission in the habenula-IPN, IL-18 also regulate the sensitivity of circuit to nicotine, perhaps through a mechanism involving pruning of excitatory synapses in these brain region.

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Modulation of hippocampus-prefrontal cortex neural oscillations in Shank3 rats through deep brain stimulation

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Background: The lack of effective treatments for disorders associated with fronto-temporal dysfunction suggests a limited understanding of the mechanisms supporting communication between these distributed networks. Synchrony of neural oscillations accompanies effective signaling between brain regions, and impaired interactions between the hippocampus (HPC) and prefrontal cortex (PFC) are accompanied by abnormal oscillations in schizophrenia (SCZ) and autism spectrum disorder (ASD). Deep brain stimulation (DBS) is increasingly studied to treat disorders affecting cognition. DBS can modulate local field potentials (LFPs), and fimbria-fornix (FFx) stimulation that increased theta-gamma power comodulation of hippocampal LFPs predicted improved memory performance in amnestic rats.

Methods: We hypothesize that specific DBS parameters (e.g. intensity, temporal pattern) modulate oscillations across structures and determine their functional effects. We tested our hypothesis by varying the magnitude (50-500μA) and temporal pattern (theta pulse/burst) of FFx stimulation in behaving rats while recording simultaneously in medial PFC and dorsal and ventral hippocampus (CA1).

Results: FFx theta burst stimulation modulated amplitude and phase of theta LFPs (4-12 Hz) by increasing the synchrony and reducing the phase differences of theta across all three recording sites. Compared to WTs, Shank3 heterozygous rats had reduced endogenous theta power, reduced HPC-mPFC theta coherence, and heightened sensitivity to FFx stimulation.

Conclusions: Future experiments will determine how DBS parameters alter cognitive performance in memory tasks.

Funding: NIH, Seaver Autism Center

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Role of APOE in the phagocytic clearance of brain tissue debris by microglia

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

Methods: Here, we began to investigate the impact of microglial APOE loss-of-function in response to brain tissue debris. In particular, we explored phagocytic uptake and clearance of fluorescently-labeled myelin debris using fluorescence-activated cell sorting (FACS) and IncuCyte imaging platform. Furthermore, we analyzed microglial transcriptional response using qPCR.

Results: Although APOE knock-down in BV2 cells had no effect on myelin debris phagocytic uptake, it is able to enhance clearance. Transcriptional analysis in BV2 cells with APOE knock-down impairs the ability of BV2 cells to down-regulate homeostatic genes in response to myelin debris and enhances their ability of up-regulate genes involve in lipid metabolism and phagocytosis.

Conclusions: This evidence supports that loss of microglial APOE does not affect myelin debris uptake of BV2 cells, however impairs microglia's homeostatic function.

Funding: BrightFocus Foundation

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The PFC and Learning to Learn

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Background: Behavioral flexibility is the ability to adapt to a dynamic environment (Kolb, 1990). This ability is embodied in reversal learning, where a previously rewarded choice is no longer rewarded, whilst a previously unrewarded choice becomes rewarded. At first, animals take some time to adjust responding. On the next reversal, however, they will adapt and thus learn to relearn (Harlow, 1949). We can dissociate two types of learning: relearning a contingency, and learning to relearn. Behavioral flexibility depends on the prefrontal cortex (Fuster, 2000). We propose that 2 subregions of the PFC, the orbitofrontal cortex (OFC), and the medial prefrontal cortex (mPFC), are the neural substrate of each type of learning, respectively.

Methods: Rats performed a spatial serial reversal task with either deterministic or probabilistic contingencies. We pharmacologically inactivated either the mPFC, or OFC.

Results: After animals are well trained, inactivating the mPFC results in deficits during reversal learning but not during the initial spatial discrimination. OFC inactivation does not. A model trained on early learning data was able to decode ~80% of trials of the mPFC inactivation sessions and vice versa. This suggests that the deficits observed during mPFC inactivation are due to a lack of knowing how to “relearn” efficiently, that “reverts” animals to their “naïve” state.

Conclusions: these results suggest the mPFC and OFC may cooperate in supporting adaptive behavior

Funding – NIH

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In-Vivo Population Activity of Neural Circuit Underlying Individual Alcohol Drinking Behaviors

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Background: The progression of alcohol-use disorders involves the dysfunction of dopamine (DA) neurons of the ventral tegmental area (VTA), an area critical to encoding the salience and reinforcing properties of drug stimuli. Our previous studies used an inbred C57BL/6J mouse line to demonstrate the existence of divergent alcohol drinking phenotypes. In order to understand the in vivo development of these individual behaviors and their neurophysiological mechanisms, we will use a combination of behavior/fiber photometry to perform real-time neural monitoring in mice.

Methods: 2BC-paradigm will be used to segregate LAD and HAD mice. Open-field test (OFT), lickometer, and fiber photometry will be employed to measure anxiety behaviors, drinking patterns and population activity of VTA DA neurons.

Results: (1) LAD mice exhibit higher scores of anxiety in the OFT as compared to controls and HAD mice. (2) LAD mice exhibit stronger locomotor sensitization to ethanol as compared to controls and HAD mice after I.P. injection in the OFT. (3) Preference (H20) encodes a strong reward signal in LAD and EtOH encodes a novel reward signal in EtOH naive control.

Conclusions: Using an isogenic mouse strain, we are able to experimentally assess the effects of chronic alcohol exposure separate from genetics. Future studies are needed to chronically monitor neural populations that affect the emergence of alcohol preference and addiction.

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Role of the Ventral Tegmental Area in Anxiety Following Chronic Stress Exposure.

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Background: Anxiety disorders are the most common psychiatric illness afflicting 273 million people worldwide. The symptoms of anxiety disorders are highly complex and the causes are poorly understood. Additionally, a substantial number of patients suffering from anxiety disorders also present depressive-like symptoms, making the diagnosis and treatment more complicated. Following chronic social defeat stress (CSDS), mice can be segregated into two subgroups based on their social interaction behavior: profound avoidance-displaying mice (susceptible) and non-avoidance displaying (resilient). However, CSDS also induces severe anxiety behaviors in both depression-susceptible and depression-resilient mice. We thus label them as anxiety/depression (A/D) and anxiety (A) subgroups. Previously, we observed that maladaptive firing activity occurred in the ventral tegmental area (VTA) dopamine circuitry projecting to the medial prefrontal cortex (mPFC) and VTA DA neurons projecting to the nucleus accumbens (NAc) selectively in A/D mice, but not in the A-mice.

Methods: Neural circuit-probing techniques, electrophysiology, behavioral assays, calcium imaging recordings.

Results: We found that the firing activity of VTA neurons projecting to amygdala (VTA-Amg) was dramatically decreased in both A/D- and A-mice, correlating with the anxiety phenotype.

Conclusions: Based on these findings, we aim to define the role of the VTA microcircuit and subcircuits in mediating anxiety-like behaviors observed in both A/D- and A-mice following

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Sex differences in rat lumbar intervertebral discs following annular puncture injury

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Background: Spine impairments are more common in women, yet most studies of intervertebral (IVD) degeneration do not address sex differences. The purpose of this study was to determine if sex differences exist in structural, morphological, and biomechanical properties of rat lumbar IVDs 6 weeks after annular puncture injury.

Method: 24 male & 24 female Sprague-Dawley rats were used. Lumbar IVDs were injured using a 26G needle either one (1x) or three times (3x) and injected with TNF-α. IVD height was measured by sagittal X-ray. IVD degeneration was assessed using structural staining with a semi-quantitative degeneration scale. Biomechanics were evaluated with loading protocols for axial tension-compression and torsion.

Results: 1x and 3x injury reduced IVD height at 6 weeks, with no sex differences. Female IVDs exhibited greater degeneration than male IVDs after 1x but not 3x injury. Neither 1x nor 3x injury changed compressive stiffness, tensile stiffness, or axial range of motion at 6 weeks, and no sex differences were observed. Male IVDs had greater torsional stiffness and torque range than female IVDs 6 weeks after 3x injury. Male 3x IVDs exhibited increased torque range compared to sham.

Conclusion: Males and females respond differently to IVD puncture injury, which may be due to different healing mechanisms, and may partially explain differences in spinal pathology rates.

Source: NIH.

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Prioritize risk genes for neurodevelopmental disorders using rare variant and pathway information

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De novo mutations (DNMs) have been successfully used to identify genes associated with neurodevelopmental disorders (NDDs) including autism spectrum disorders (ASD). These risk genes show strong enrichments of brain expressed and synaptic gene sets. We hypothesized that additional significant NDD risk genes could be discovered through the integration of rare variants and other data types including pathways and tissue specific gene expression. We have developed a Bayesian pipeline (gTADA) that integrates rare variants with pathway/tissue-expression information in order to identify risk genes and pathways involved in the etiologies of NDDs. gTADA is available at https://github.com/hoangtn/gTADA. gTADA prioritized multiple significant genes for NDDs. Meta-analysis of multiple types of epilepsy (EPI) identified 25 novel significant genes (posterior probabilities > 0.95), several of which replicate in an independent dataset. Top prioritized EPI genes have high protein-protein interaction network connectivity, and show expression in different development stages of the human brain. Finally, we saw more enriched drug-target gene sets for EPI than for other disorders, driven particularly by GABA signaling genes. Thus, integrative analyses, gene set enrichments and network analyses of novel risk genes provide biological insights across NDDs, particularly for epilepsy.

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Prefrontal top-down cortico-cortical projection in control of attentional behavior

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Background: Attention is a goal-directed process that facilitates the detection of sensory stimuli from our environment. Attention deficits are frequently observed in psychiatric disorders, yet the underlying neural circuits are not well understood. The frontal cortex—particularly the anterior cingulate cortex (ACC) — has been heavily implicated in contributing to top-down control of sensory processing in the visual cortex (VIS). We aim to examine the contribution of ACC->VIS projections in top-down control of visual attention.

Methods: We integrate circuit-based techniques, including chemogenetics, fiber photometry, and optogenetics, to monitor and manipulate top-down neural activity in mice performing freely moving attention behavior during the 5-choice serial reaction time task with a translational touchscreen system.

Results: Chemogenetic suppression of ACC->VIS projections impairs attention performance. Fiber photometry imaging in behaving mice points to a key role for this circuit in integrating sustained attention and visual processing. Optogenetic activation of top-down projections during period of sustained attention further reveals temporal- and frequency-dependent improvement of attention.

Conclusion: Frontal-sensory projections play a key role in top-down control of attentional behavior. Our findings may provide circuit-based insight into the pathophysiology and intervention strategy for impaired visual attention in neuropsychiatric disorders.

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LD Score regression of AD heritability partitioned by PU.1, MEF2C and epigenetic functional annotations reveals enrichment in human microglia

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Background: Multiple risk loci have been identified in genome-wide association studies (GWAS) of Alzheimer's disease (AD), and the majority of risk genes play important roles in myeloid cells including microglia, the brain-resident macrophages. However, an understanding of the mechanistic roles of relevant genes and transcriptional networks remains limited. Integrative data analyses can shed light on microglia-mediated mechanisms underlying AD pathogenesis.

Methods: LD Score regression was used to obtain enrichment of AD heritability partitioned on the human microglia PU.1 cistrome, proxy-MEF2C cistrome and ATAC-seq functional annotations. Enrichment of AD heritability was also obtained for active enhancer regions (as marked by H3K27ac) and promoter/enhancer regions (as marked by H3K4me2).

Results: Significant enrichment of AD heritability, partitioned by PU.1 cistrome (61.4-fold enrichment, P-value=4.8*10-4), H3K27ac (Ex vivo: 20.1-fold enrichment, P-value= 6*10-4 , in vitro: 11.5-fold enrichment, P-value = 3*10-3), H3K4me2 (21.9-fold enrichment, P-value=1*10-4) and ATAC-seq (47.7-fold enrichment, P-value = 8*10-3) functional annotations were observed. Proxy-MEF2C binding regions show significantly higher enrichment than open chromatin regions (138-fold enrichment, P-value=0.04).

Conclusions: Integrative analyses of AD GWAS, transcriptomic and epigenetic data point to a key role of microglia in AD pathogenesis.

Funding: NIH RO1: Understanding the mechanism of SPI1 dependent Alzheimer disease risk (NIA RF1AG054011) and JPB Foundation.

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Hypothalamic–>Habenular–>Midbrain Communication Regulates Food Preference

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Background: The lateral hypothalamus (LH) plays a critical role in energy homeostasis and reward sensitivity. A major output of the LH terminates in the lateral habenula (LHb) which has been described as a "preference center" and exerts a negative influence over motivated behaviors through inhibition of midbrain dopamine neurons. We tested the hypothesis that LH projections to LHb play an important role in food preference and food-related motivation through downstream influences on midbrain dopamine neurons.

Methods: Circuit mapping: Glycoprotein-deleted rabies and cre-dependent TVA–mCherry/glycoprotein viruses were injected into LHb. Retro-AAV-iCre was delivered to the ventral tegmental area (VTA). Recording neuronal activity: retro-AAV-iCre was delivered to VTA and cre-dependent GCaMP was injected into LHb. A fiber optic was implanted in LHb. Manipulation of LH inputs to LHb neurons: Retrograde AAV2/5-Cre-eYFP was delivered to LHb and Cre-inducible diphtheria toxin (DTA) or Cre-inducible (hM3Dq) DREADD was delivered to LH.

Results/Conclusions: Prominent innervation of midbrain projecting LHb neurons originated in LH. Activity of VTA projecting LHb neurons decreased in hungry animals during the retrieval of food rewards and in sated animals during palatable food consumption. Lesioning of LH inputs to LHb decreased general food motivation yet increased palatable food consumption. DREADD induced stimulation of these LH inputs produced the opposite effects. These findings identify the LH-LHb-VTA pathway as an important brain circuit involved in feeding and obesity.

Funding: NIH

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A Technical Comparison of Modern Minimally Invasive Intracerebral Hemorrhage Evacuation Strategies

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Background: Minimally invasive intracerebral hemorrhage (ICH) evacuation has gained popularity with success in early-phase clinical trials. This procedure, however is performed in very different ways around the world. A comparative analysis of these techniques can inform further improvements in the procedure.

Methods: Major authors of clinical trials evaluating each of the main techniques were contacted and asked to supply a case example and technical description of their respective surgeries.

Results: Five major techniques were identified including stereotactic thrombolysis (ST), craniopuncture, endoscopic, endoscope-assist, and endoport-assist. The diameter of the access corridor ranged from 3mm in craniopuncture to 13.5mm in the endoport-assist evacuation. A burr hole is created in ST and craniopuncture, a small craniectomy in endoscopic, and a small craniotomy in the other two. ST and craniopuncture rely on passive drainage from a catheter placed during surgery that remains in place for multiple days while the other three rely on active evacuation with suction.

Conclusion: Minimally invasive ICH evacuation is a procedure under development with five major techniques now performed around the world. Future comparative clinical trials will identify the advantageous components of each strategy and contribute to improved outcomes in this patient population.

Funding: Department of Neurosurgery

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Sex-specific effects of brain extracellular matrix genes in major depressive disorder

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The extracellular matrix (ECM) of the brain is a highly complex network of proteoglycans, glycoproteins, fibrous glycoproteins, and hyaluronic acid that surround neurons and glial cells. In the brain, the ECM is essential in providing structural support, driving developmental decisions, guiding cell migration, promoting cell maturation and differentiation, ensuring cell survival, and facilitating synaptic plasticity. Major Depressive Disorder (MDD), a costly and burdensome mood disorder poised to be the leading cause of disability in the world, is known to cause structural alterations throughout the brain. Despite this, the role of the brain ECM in MDD is poorly understood. In order to identify possible MDD-associated alterations in the ECM, we analyzed transcriptional profiles from the nucleus accumbens and prefrontal cortex in postmortem brain tissue of humans with MDD. In parallel, we analyzed RNA sequencing data from male and female mice exposed to chronic variable stress (CVS), a validated stress paradigm. We identified dozens of ECM-specific genes differentially-expressed in both data sets. Strikingly, we found little overlap between male and female differentially expressed brain ECM genes. To better understand the functional role of these sex-specific ECM target genes on stress responses, we are investigating their ability to influence stress susceptibility at the behavioral and molecular levels. Together, these findings implicate the ECM of the brain as a potential key mediator of stress responding that is impacted in a sex-specific manner.

Funding: NIMH and HDRF

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A preliminary report on a multiscale investigation of the living human brain

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In efforts to elucidate the complexities of human brain function, researchers have employed a number of interdisciplinary approaches including neuroimaging, neuromodulation, neuropharmacology, neurophysiology, clinical observation, and molecular-cellular biology to study the brain. However, due to the inaccessibility of the human brain, this diverse neuroscience toolkit is yet to be applied in its entirety to study a single large cohort of living individuals. The Living Brain Project, a multi-scale investigation of the human brain, circumvents this limitation by targeting individuals undergoing the deep brain stimulation implantation procedure. Here, we provide a preliminary report of this study where the full human-subject neuroscience toolkit will be applied to 500 living individuals. Data from each subject is generated using multimodal neuroimaging, neuropsychological testing batteries, electronic medical records, and molecular and cellular biology assays performed on multiple tissues, including the prefrontal cortex of the brain. For a subset of subjects, data is also generated using wearable mobile health devices and micro-electrode neural recordings. Currently, data has been collected from over 150 individuals, and single-cell RNA sequencing and next-generation genome mapping experiments on brain and blood specimens have been performed on a small subset. This presentation will provide an introduction to a novel, holistic approach to study the human brain.

University funding.

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The APOE-e4 Allele and the Risk of Alzheimer Disease and Related Traits Among Populations of Multi-ethnic Ancestry

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Background: The APOE e4 allele is a major risk factor for Alzheimer Disease (AD) in most populations. Despite the known APOE-e4 association, a comprehensive understanding of how the effect size varies across populations is lacking.

Method: We have obtained data from the National Alzheimer's Coordinating Center for over 20,000 (n=21,891) individuals across four ethnicities (European ancestry (EU) n=17539; African American (AA), n=2463; Hispanic (His), n=1414; East Asian (EA), n=475). Association between APOE genotypes and 527 traits was analyzed using logistic or linear regression, adjusting for covariates. HAPMIX was used to estimate local ancestry.

Results: We observed significant association of e4/e4 with several traits but the effect sizes vary across ethnicities. Compared with e3/e3, the relative risk (RR) for AD for e4/e4 are 7.08 (p= 1.6E-118), 4.88 (p=6.15E-24), 4.36(p=3.4E-05) and 8.10 (p=3.3E-04) for EU AA, His and EA, respectively. When accounting for local ancestry, E4 alleles on a European background were more associated with AD than those on an African background (p=0.002).

Conclusion: APOE ε4 had a significant, but weaker, effect on AD in AA and Hispanics. The APOE ε4 effect on AD on an African background shows significantly less effect than on European backgrounds, suggesting non-genetic factors may mitigate the effect of the e4 allele in different populations.

Funding: NIA/NIH & Alzheimer's Association.

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Emotional Content Modulates Brain fMRI and Cognitive Effects of Repetitive Exposure to Graphic Warning Labels in Adolescents

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Background: Adolescence is a critical period for smoking prevention, however, objective data on response to prevention efforts in adolescents lags behind data from adults. Graphic warning labels (GWLs) on cigarette packs are a common prevention strategy. However, its implementation in the US has been challenged on constitutional grounds, with image selection being one of the flashpoints of the debate. We experimentally tested how the emotional content of GWLs affects cognitive processing in adolescents.

Methods: Participants were exposed daily to GWLs previously rated high or low on the emotional reaction scale (High ER vs. Low ER) over a 4-week period via smartphones. Brain responses to GWLs were recorded using functional magnetic resonance imaging (fMRI) before and after the exposure period. Memory for GWLs images and texts was tested.

Results: After exposure, brain response to high ER GWLs was reduced in the amygdala, putamen, hippocampus, and superior frontal gyrus, while brain response to low ER GWL were reduced in the amygdala, hippocampus, anterior cingulate and thalamus. At baseline, images from High ER GWLs were better recalled but no difference in text recall. In High ER condition, recall of images and text remained unchanged after repeated exposure. In Low ER condition, recall of images improved significantly while recall of text was unchanged.

Conclusions: These preliminary results show the emotional salience of GWLs did not facilitate cognitive processing of textual warnings in adolescents, unlike adult smokers,. Translating adult GWL data to adolescents requires validation.

Funding: National Institute of Child Development (R00 HD084746)

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Repetitive Low-Level Blast Exposure Induces Chronic Hyperphosphorylation of Tau in Rat Brain

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Background: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease associated with repetitive mild traumatic brain Injury. CTE presents clinically as a progressive behavioral and cognitive syndrome, with pathological features of aggregates of phosphorylated tau. We previously showed that rats subjected to repetitive low-level blast exposure displayed anxiety and other post-traumatic stress disorder related behavioral traits many months after blast exposure.

Methods: Anesthetized rats were exposed to three 75 kPa blasts. 10 and 12 months after blast exposure rats were tested on a variety of behavioral tasks relevant to anxiety/stress and cognition and the phosphorylation status of tau (p-tau) was determined by Western blotting and correlated with behavioral performance.

Results: In hippocampus and anterior cortex tau phosphorylation was increased and showed strong positive correlations with anxiety parameters in the elevated zero maze (EZM), while there were no correlations in the amygdala.

Conclusions: Rats exposed to repetitive blast exhibit hyperphosphorylated tau in brain 10-12 months after the last blast exposure. Elevated p-tau levels correlated with anxiety in the EZM. The presence of a chronic progressive behavioral phenotype with affective and cognitive features suggests a relationship between blast injury and the later development of tauopathies.

Funding: VA MERIT

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

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Background: The genetic risk for sporadic Alzheimer's disease (AD) is polygenic, driven by more than 20 loci associated with different disease traits. Pathway analysis implicates immune response in the etiology of AD, and given that genetic risk alleles are enriched in myeloid cell types, it is proposed that impaired microglial function is a major contributing factor to AD progression. Microglial homeostasis is affected by the myeloid lineage-determining transcription factor SPI1/PU.1, which is associated with risk for AD through changes in expression levels based on genetic variation.

Methods: To understand how modulation of PU.1 expression affects microglial function we generated stable Spi1/PU.1 overexpression and knock-down BV2 microglial cells and assessed their response in functional assays under baseline and challenged conditions.

Results: Knock-down of PU.1 repressed the microglial homeostatic signature in a manner similar to that described in disease-associated microglia. BV2 cells with reduced PU.1 expression showed a reduction in phagocytic ability, while PU.1 overexpression resulted in increased phagocytosis and resistance to apoptosis. We are currently pursuing RNA sequencing of stimulated microglia with differential PU.1 expression to design experiments for rescue of defective phenotypes controlled by PU.1. These data will be compared to human datasets on monocytes/macrophages, while primary mouse microglia and mice will be used for validation.

Conclusion: PU.1 regulates the homeostatic signature of microglia and affects their phagocytosis and apoptosis response.

Funding: NIH (NIA RF1AG054011), JPB Foundation

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In Vitro Generation of Dopaminergic and GABAergic Neurons for 3-Dimensional Chromatin Analysis

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Abstract: Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the world population. While many different biological abnormalities have been implicated in the disease, altered dopaminergic and GABAergic neurotransmission are some of the best studied systems that contribute to Schizophrenia. Despite decades of research on the role of these two neurotransmitter systems in the disorder, the causal factors leading to their disruption have remained elusive. Across the genome, many of the variants that have been associated with Schizophrenia may disrupt normal gene-regulatory processes, including chromatin looping. Because chromatin looping is cell-type specific, we decided to investigate the role of this process in midbrain dopaminergic and GABAergic neurons generated from human induced pluripotent stem cells (iPSCs). Relatively pure populations of these two neuronal cell types were produced with lineage-specific transcription factor overexpression followed by antibiotic-mediated selection. These neurons will be used for subsequent in situ HiC analysis in order to catalogue their three-dimensional chromatin architecture.

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CRISPR-Cas9-Targeted SMRT Sequencing of Medically Relevant CGG DNA Repeat Expansions in the FMR1 gene

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Background: Fragile X Syndrome (FX) is caused by the expansion of a trinucleotide DNA repeat (CGG) in the FMR1 gene on the X chromosome. The severity of the FX disease phenotype is correlated with the number of CGG repeats in the locus, making it an important target for carrier screening tests. Current sequencing methods using short-read technologies cannot span the repeat in diseased individuals and hybridization capture methods utilizing PCR amplification, often favor enrichment of the shorter allele. Also,PCR-based methods are error prone in regions of high GC-content and amplification abrogates detection of important epigenetic modification events.

Method: Here we describe the (CRISPR-CAS9 Target Enrichment) technique using RNA-guided Cas9 enzyme to target the genetic locus containing the trinucleotide repeat expansion (TNR), facilitating the TNR enrichment and single molecule, real time (SMRT) Sequencing for higher resolution repeat and phasing purposes.

Results: Using this method we show replicable, single molecule resolution of CGG repeats in the FMR1 locus ranging from normal, pre-mutation, and fully expanded pathogenic alleles across a wide range of both control and clinical samples.

Conclusion: This novel method provides full resolution of genomic aberrations in the FMR1 locus, including AGG repeat interruptions, allowing more accurate assessment of the disease and understanding of the genomic underpinnings of Fragile X Syndrome.

Funding: IGMB

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Microglial autophagy-mediated α-synuclein clearance

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Background: Defective autophagy has been implicated in neurodegenerative diseases including Parkinson's disease (PD). Pathogenic mutations of PD-related genes directly affect autophagy-lysosome function, providing a support to the hypothesis that impaired autophagy-lysosome pathway contributes to the disease progression. Accumulation of α-synuclein is a major risk factor for both sporadic and familial PD; increasing evidence shows that autophagy prevents α-synuclein accumulation by degrading α-synuclein. However, the detailed mechanism that autophagy mediates the clearance of α-synuclein remains unclear.

Methods: Here we examined the entry and metabolization of recombinant α-synuclein protein in microglia. We applied multidisciplinary approach including biochemistry, primary cell imaging, and electron-microscopy (EM) in our studies.

Results: We showed that microglia mobilize selective autophagy pathway to clear the internalized α-synuclein. We found that autophagy receptors can specifically recognize monomeric form of α-synuclein but not pathological aggregated α-synuclein after the internalization. This suggests that specific conformation of aggregated α-synuclein escapes macroautophagy clearance due to lack of interaction with autophagy receptors. Additionally, we hypothesized that LRRK2 can modulate α-synuclein clearance by microglia.

Conclusion: Our study provides insight into the mechanism whereby microglial autophagy clears α-synuclein and maintains protein homeostasis of α-synuclein in the CNS. With increasing evidence implicating the transmission of α-synuclein in pathogenic PD pathway, our data assists to understand the molecular mechanism for synucleinopathies and identify novel therapeutics.

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Emotion Recognition in Cocaine Use Disorder: A Cross-sectional Exploration of Recency of Use and Long-Term Abstinence

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Emotion recognition is compromised in addiction. However, among stimulant users findings are mixed; some studies demonstrate that cocaine enhances functioning, while others show impairment with use. Inconsistencies may be due to varying lengths of abstinence. Therefore, we investigated the effects of cocaine recency on emotion recognition in cocaine use disorder (CUD) and explored whether task performance was related to structural brain integrity.

Emotion recognition performance was compared in users (CUD+, n=30; cocaine-positive urine), short-term abstainers (CUD −ST, n=26; abstinent<6-months), long-term abstainers (CUD-LT, n=21; abstinent≥6-months) and controls (n=46) (controlling for age, IQ). Functional outcomes were assessed using the Addiction Severity Index (ASI). A sample subset (N=73), received a structural MRI scan to assess gray matter volume (GMV) using voxel-based-morphometry. Relationships between GMV and emotion recognition were explored using regression analyses. GMV analyses controlled for age, and total intracranial volume.

CUD+ demonstrated poorer performance identifying happiness, sadness and fear than CTL ($p<0.01$); CUD-ST showed a similar pattern for fear ($p<0.01$). ASI interviewer severity ratings from the Family-Social subscale were higher in CUD+ than CUD-LT and CTL ($p=<0.03$). Reduced GMV in the right amygdala and bilateral cerebellum were found in CUD+ compared to CUD-LT and CTL (pFWE-corr<0.05). Lastly, there was a positive relationship between bilateral cerebellum and recognizing happiness ($p<0.05$).

Emotion recognition is impaired in current CUD, and for fear, deficits may persist for up to 6 months of abstinence. Specifically, cerebellar loss may underlie deficits in positive emotion recognition. Targeting these deficits may improve social functioning and help enhance treatment success for addiction.

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Hippocampal Tracking of Social Space is Related to Social Autistic Traits in healthy individuals

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Background: In a previous study, we found that participants with better social skills had a greater covariance between hippocampal activity and "movement" through "social space". Given that social dysfunction is a hallmark feature of Autism Spectrum Disorder (ASD), we sought to elucidate the relationship between ASD-related social impairment and hippocampal activation during a social navigation fMRI task.

Method: Healthy participants were lead characters in a role-playing game in which they were asked to navigate various real-life social situations during fMRI. Following the task, participants filled out the Autism Spectrum Quotient (AQ), a self-report measure that assesses autism symptom severity comprised of 5 subscales, including social skills.

Results: Hippocampal activity was significantly negatively correlated with scores on the AQ social skills subscale (R=-.562, P=.0098) and no other AQ subscale.

Conclusion: These results offer preliminary evidence suggesting that hippocampal dysfunction may underlie impaired social function in individuals with ASD.

Funding: This study was paid for by the NIH

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CREM- A mediator of Behavioral and Genetic Vulnerabilities to Substance Use Disorder

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Impulsivity is characterized as risky behavior that lacks forethought about consequences. Multiple lines of evidence from human studies and rodent models have implicated impulsivity as a risk factor for substance use disorder because it contributes to different stages of the addiction cycle. These findings show that an impulsive individual is more vulnerable to initial drug use, continued drug use, and relapse. Our previous study had identified the cAMP Response Element Modulator (Crem) gene as a possible genetic factor that influences impulsive behavior. The Crem gene is highly complex with multiple functional isoforms but limited information exist regarding the potential dysregulation of Crem isoforms in impulsive behavior. By utilization of a rodent ADHD model, that consists of the impulsive spontaneously hypertensive rats (SHRs) and non-impulsive Wistar Kyoto rats (WKYs), the current study investigates novel markers of impulsivity by characterizing Crem isoform patterns between SHRs and WKYs. Gene and protein expression results showed that a particular isoform, Inducible cAMP Early Repressor (Icer), is up-regulated in the nucleus accumbens shell, but not core, of SHRs. Studies are underway to interrogate chromatin modifications across the Crem gene in relation to epigenetic regulation of Icer and to determine whether manipulation of Icer expression may be a novel target for therapeutic intervention for treatment of impulsive behavior.

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Neuron-specific signatures in the chromosomal connectome are associated with schizophrenia risk

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Background: Spatial genome organization is highly regulated and critical for normal development, but not many datasets exist exploring this in the human brain.

Methods: We monitored chromosomal conformation changes between human neural progenitor cells (NPCs), glia and excitatory neurons using in situ Hi-C.

Results: Developmental 3D genome reorganization in neurons included massive pruning of chromosomal contacts, resulting genome-wide in a 40-50% reduction of shorter range contacts and a corresponding loss of many nested chromatin domains, compared to NPCs and glia. Neurons and NPCs exhibited the largest number of cell-type-specific chromosomal interactions anchored in common variant sequences associated with schizophrenia risk. This disease-related chromosomal connectome included hundreds of genes from other portions of the genome, providing a structural foundation for coordinated regulation of gene expression and protein levels in cell culture and adult prefrontal cortex, with significant protein-protein interactions enriched for regulators of neuronal connectivity and synaptic plasticity.

Conclusion: While the developmentally regulated reorganization of the brain's 3D genome includes large-scale loss of chromosomal contacts, the neuronal genome shows significant expansion of the genome space linked to risk sequences for schizophrenia.

Source: NIMH

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Tensor Decomposition Discovers Disease-specific Regulatory Networks in Myeloid Cells

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Background: Many studies have identified and characterized cis expression quantitative trait loci (eQTLs) in human primary cells and tissues. However, identifying distal regulation on gene expression (trans-eQTLs) are far more difficult to detect because of their smaller effect size and large number of tests for thousands of genes.

Methods: We implemented a Bayesian Tensor Decomposition Method to uncover sparse gene networks linked to genetic variation. This was applied to several large-scale induced human monocytes gene expression datasets (total number 1,022) simultaneously to discover context-specific trans-eQTLs.

Results: We identified 43 unique sparse components associated with genetic variants (1,564 trans-eQTLs at FDR < 0.15) at baseline and in response to LPS and interferon. We report robust evidence that some disease-associated variants affect expression of multiple genes in trans: the AD-associated SNP rs983392 (cis effect on MS4A4A/6A) increased expression of over 36 genes (FDR=5e-4) including several in interferon signaling pathway and complement cascade. We identified a PD-associated SNP rs1296028 (cis effect on CTSB) impacts expression of over 20 genes (FDR=9.5e-28) involved in myeloid lysosomal function (i.e., CTSB, AFMID, P2RY6, SPAG11A, ANTXR1).

Conclusion: This approach represents a powerful framework for understanding the effect of genetic variants on gene networks contributing to disease, and may help in elucidating the underlying biology of neurodegenerative disease.

Funding: This research was funded by NIH grants.

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Alzheimer's Disease Sequencing Project: Age Extremes x APOE Genotype Sampling for Genetic Discovery

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The APOE locus harbors the strongest genetic risk factor for Alzheimer's disease (AD). Clinical onset is delayed or absent in some APOE risk allele carriers, possibly due to protective alleles. To identify novel AD loci we undertook case-control association using age extremes sampling stratified by APOE genotype.

Discovery and replication were conducted among non-Hispanic whites in two strata: APOE4 extremes (young ε4+ AD cases vs old ε4+ controls) and APOE33 extremes (young ε3/ε3 AD cases vs old ε3/ε3 controls). Covariate-adjusted SKAT-O gene-based aggregation was undertaken.

APOE4 extremes discovery detected borderline study-wide significance for EIF2B3. APOE33 extremes discovery detected study-wide significance for TREM2 and HOXD4. Discovery signals were not replicated, and we are assembling expanded extremes cohorts to confirm these novel genes.

We have replicated the reported association between TREM2 and AD, but need larger sample sizes to leverage phenotypic extremes sampling in this disorder.

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Electrophysiological Biomarkers of Syndromic ASD

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Background: The current study evaluated patterns of excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission using visual evoked potentials (VEPs) in patients with syndromic ASD (sASD) and idiopathic ASD (iASD).

Methods: Data was obtained from 19 individuals with Phelan-McDermid syndrome, 4 with FOXP1 syndrome, 3 with ADNP syndrome, 69 with iASD, and 26 typically developing controls ages 4 to16. Transient VEPs were elicited using a contrast-reversing checkerboard condition. Time-domain variables included amplitudes and latencies. Frequency domain analyses applied the magnitude-squared coherence (MSC) statistic to examine six frequency bands: Band 1, 6-10 Hz, Band 2, 12-28 Hz, Band 3, 30-36 Hz, Band 4, 38-48 Hz, Band 5, 50-64 Hz, minus 60 Hz, and Band 6, 66-84 Hz.

Results: The PMS group displayed significantly weaker amplitudes compared to controls at P60-N75 and N75-P100 ($p<.001$) with no difference in latencies. The ADNP group showed a similar pattern at P60-N75 ($p=.027$) and N75-P100 ($p=.006$), and significantly longer latency at P100 ($p=.048$). There was significant individual variability in the FOXP1 group, corresponding to clinical phenotype. In the frequency domain, the PMS group displayed significant differences in Bands 2-5 (p values <.01 to .012). The ADNP and FOXP1 groups also showed weaker responses in Band 2 ($p=.034$; $p=.032$) and Band 3 ($p=.041$; $p=.016$).

Conclusions: Time-domain analyses revealed syndrome-specific phenotypes with differences in beta and low gamma activity present across all sASD groups.

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Neuromodulation by Combined Oxytocin and a Naturalistic Social Cognition Task

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Background: Oxytocin (OXT) is a neuropeptide hormone that may promote social cognition. In schizotypal personality disorder (SPD) and related disorders, OXT increases visual attention to social cues. We present pilot results from a functional MRI experiment during naturalistic viewing of the Movie for the Assessment of Social Cognition (MASC) after treating participants with OXT or placebo. Our hypothesis is that modulation of social gaze by OXT correlates to changes in functional connectivity in regions of OXT receptor expression, specifically amygdala and nucleus accumbens (NAcc).

Method: In a double-blind trial design, 40 IU of OXT or placebo were administered intra-nasally before brain imaging. In-MRI eye-tracking during MASC playback was acquired to evaluate the effects of OXT on social gaze. Connectivity of the NAcc and amygdala were compared for MASC and resting state data in the drug and placebo conditions.

Results: In the drug condition, gaze in SPD patients was normalized to view faces ($p<.01$). Functional connectivity during MASC viewing showed high connectivity between NAcc and ventro-medial prefrontal cortex (vmPFC) under OXT only. Compared to resting sate, connectivity with the NAcc under OXT showed substantially increased connectivity to vmPFC.

Conclusion: Results from this pilot study support the hypothesis that functional connectivity of two key areas expressing OXT receptors, NAcc and amygdala, is modulated by OXT. This may be linked to increased visual attention to social cues, as quantified by in-MRI-eye-tracking. We hope to further evaluate how OXT modulates the functional interaction of NAcc and amygdala to normalize deficits in social cognitive domains.

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D1 Agonist for Working Memory in Schizotypal Personality Disorder: Baseline Results

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Background: Schizotypal personality disorder (SPD) falls within the schizophrenia (SCZ) spectrum, characterized by subtle SCZ symptoms without apparent psychosis. Working memory function is a critical feature to the cognitive impairments exhibited by these patients. Enhancement of the prefrontal D1 dopamine receptor has been suggested as a novel approach to improve cognitive outcomes. In a previous proof-of-concept study, we performed a randomized, double-blind, placebo-controlled trial of the D1 agonist DAR-0100A in unmedicated SPD patients and observed significant improvement in working memory relative to placebo (Cohen's d=1.14). We aimed to characterize baseline cognitive deficits in SPD patients in a larger replication study.

Methods: Healthy controls (HC, N=54) and unmedicated SPD patients (N=30) were assessed with the Paced Auditory Serial Addition Test (PASAT), which ascertains working memory, and the MATRICS Consensus Cognitive Battery (MCCB), which captures many cognitive domains impaired in schizophrenia.

Results: SPD patients performed significantly worse than HC on the PASAT (SPD m=32.9; HC m=42.5, $t=3.96$; $p<0.001$) and on each of the domains of the MCCB.

Conclusions: SPD can be used to model SCZ, as they possess significant cognitive impairments across various cognitive domains, with a pattern similar to those found in SCZ.

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Effects of threat-related and deprivation-related early-life stressors on intrinsic amygdala activity in HIV+ adults

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Neuropsychiatric symptom elevations in HIV+ adults have been linked to early-life stress (ELS) related reductions in amygdala reactivity. Yet, it remains unclear whether these effects reflect underlying ELS-related elevations in intrinsic amygdala activity. Here, we examined whether ELS is associated with elevations in intrinsic amygdala activity, and whether this activity accounts for neuropsychiatric symptom elevations in HIV+ adults. Intrinsic activity in bilateral amygdala was assessed during resting-state fMRI in 44 HIV+ and 38 HIV-negative control (HC) adults. Neuropsychiatric symptoms and ELS exposure were quantified using a battery of validated self-report measures. Regarding ELS, threat-related stressors (violence exposures), known to impact affective functions, and deprivation-related stressors (poverty/neglect), known to have a greater impact on cognition, were examined independently. Across the entire sample, amygdala activity was significantly associated with threat exposure, but not with deprivation; a trend-level association between HIV status and amygdala activity was also observed. Follow-up analyses indicated that HIV+ adults with threat exposure exhibited significantly greater amygdala activity than HC adults without threat exposure. Although the HIV+ group exhibited elevated neuropsychiatric symptoms relative to HC, symptom levels were unrelated to amygdala activity in the HIV+ group. Collectively, these findings reveal that intrinsic amygdala activity is sensitive to specific types of childhood adversity and that ELS-related elevations in intrinsic amygdala activity do not account for neuropsychiatric symptom elevations in HIV+ adults.

Funding: NIH

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Quantifying Arousal: An Analysis of the Ascending Reticular Activating System in Intracerebral Hemorrhage Using Diffusion Tensor Imaging

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Background: We hypothesize that fractional anisotropy(FA) of the Ascending Reticular Activating System(ARAS) can be used to predict the state of consciousness of patients suffering intracerebral hemorrhage. To test this hypothesis, we performed a pilot analysis of the ARAS correlating NIH Stroke Score with quantitative assessment of the ARAS on DTI imaging.

Methods: 21 patients with spontaneous ICH admitted to the Mount Sinai Health System between October 2017 and February 2018 were evaluated with NIHSS and MRI-DTI at 24-48 hours and 7-10 days using a 1.5 T scanner. DTI and tractography were performed with the READY view software, quantifying mean FA(mFA) and density with a ROI in the ventromedial mesencephalon. We divided patients into 2 subgroups: “conscious”(NIHSS=0-15) and “unconscious”(NIHSS=16-42).

Results: Pearson's correlation coefficient demonstrated that quantitative DTI metrics (mFA and density)negatively correlate with the NIHSS at 7-10 days. The biserial correlation test demonstrated a significant association between mFA and NIHSS subgroups at 7-10 days. We assessed the probability for each patient of being in the subgroups given mFA using multivariate logistic regression model. Using a decision tree analysis, the mFA cut-off threshold between the two subgroups is 0.3765(sensitivity 93.3%,specificity 83.3%,ROC AUC=0.86).

Conclusions: The mFA measured by quantitative DTI at 7-10 days after onset of intracerebral hemorrhage strongly predicts NIHSS. Patients with lower mFA values in the ARAS are far more likely to be unconscious.

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EFFECT OF SCHIZOPHRENIA-ASSOCIATED COMMON VARIANTS ON GENE EXPRESSION LEVELS AND NEURAL CELL PHENOTYPES

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Schizophrenia (SCZ) is a highly heritable neuropsychiatric disorder for which pathogenic mechanisms remain largely unresolved. It is estimated that up to half of the genetic risk for SCZ may arise from common variants. Genome-wide association studies have identified 108 loci that are significantly associated with SCZ and subsequent expression quantitative trait loci (eQTL) studies recently identified the proprotein convertase FURIN as a likely causal contributor to disease risk. FURIN’s 3’UTR variant rs4702 is its strongest SCZ-associated eQTL and therefore the most likely candidate to affect gene expression and contribute to disease risk. Furthermore, FURIN knockout phenotypes in animal models include dendritic and synaptic defects, consistent with observations made in human SCZ post-mortem studies.

To substantiate the influence of the rs4702 risk allele on gene expression in vitro, we established a robust CRISPR/Cas9 single nucleotide-editing platform, in order to generate isogenic human induced pluripotent stem cell (hiPSC) lines from SCZ patients and controls. In parallel, we are using CRISPR interference to knock-down FURIN in neural progenitor cells and recapitulate the more subtle endogenous expression change, enabling us to elucidate the phenotypic consequences of FURIN down-regulation.

Overall, our hiPSC-based models are being applied to test the functional impact of manipulating FURIN genotype and expression in human neural cells.

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Formalin Tissue Fixation Biases Myelin Density Measurement by Quantitative Magnetization Transfer and Myelin Water Imaging

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Two common in vivo MRI biomarkers of myelin, quantitative magnetization transfer (qMT)-derived bound pool fraction and myelin water fraction (MWF), may be impacted by formalin fixation, casting doubt upon direct comparison of in vivo and post mortem measurements using these methods. The objective of this study is to quantify the effect of formalin fixation on these two biomarkers.

Two segments of unfixed human spinal cord were scanned at 9.4T using MT-prepared 3D spoiled-gradient-echo and 3D multi-echo-spin-echo sequences for qMT and myelin water imaging (MWI), respectively. QMT data were fitted to a two-pool MT model, which yields the bound pool fraction (F), a biomarker of myelin. Echo trains were fitted to generate a T_2 spectrum. The fraction of signal in peaks with T_2<30ms, the MWF, is another biomarker of myelin. The specimens were then fixed by immersion in 10% Formalin at room temperature for 24hrs, rinsed, and re-scanned using the same protocols.

After fixation, F increased by 37.5% ($p<0.005$), and MWF increased by 35.5-38.6% ($p<0.05$). Myelin-related contrast in all parametric maps is maintained after fixation. Cross-sectional area of the spinal cords decreased by 7%.

Fixation significantly biases myelin density measurements by qMT and MWI.

Funding: None.

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Microglia Activation After Addition of Neuroinflammatory Activators

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Background: Microglia activation plays a critical role in various neurological diseases including Alzheimer’s disease and intracerebral hemorrhage. We hypothesize that a comparative microglial de-activation assay may aid in the development of drugs that reverse activation from multiple disease processes.

Methods: A murine BV2 microglial cell line was seeded in 96-well plates with 5000 cells/well and treated with either: LPS (0.5µg/ml), hemin (30mM), or Aß (5µg/mL). After 6, 12, 24, and 48 hours of exposure, TNFα was quantified by ELISA.

Results: After addition of LPS, there was in an increase in average TNFα concentration between the 6-12 hours and 12-24 hours (+186.96pg/mL and +103pg/mL, respectively). After addition of hemin stimulation there was a similar trend with an increase in average levels between the 6-12 hours and 12-24 hours (+264.15pg/mL and +60.63pg/mL respectively). After the addition of Aß there was also a similar trend in average levels between the 6-12 hours (+335.5pg/mL). This suggests that microglia TNFα production is greatest 6-12 hours post activation.

Conclusions: After addition of the pro-inflammatory stimuli there is an increase in expression of pro-inflammatory cytokines such as TNFα, indicative of increased M1 microglia activation. Differences in microglial activation after addition of LPS, hemin, and Aß may indicate different neuroinflammatory responses to different neurological diseases. Future studies will investigate microglial epigenetics in response to neuroinflammatory mediators to develop a microglial de-activation assay.

Funding: Department of Neurosurgery

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Screening of AD associated genes via RNAi in a C. elegans Alzheimer's disease model

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Background: C. elegans provides a convenient, high-throughput system for modeling the molecular pathology of AD. The biochemical pathways in nematodes are highly conserved when compared with those of humans, and their short lifecycle coupled with a well characterized neuronal system make them an attractive model for the study of neurodegenerative disorders.

Methods: Using the CL2006 C. elegans model (dvIs2[pCL12(unc-54/human Abeta peptide 1-42 minigene)+pRF4]) expressing Aβ42 under the control of a muscle-specific promoter, we assessed the involvement of genes identified as network drivers in a multiscale network analysis of human AD brains on the paralysis phenotype via RNAi knockdown. RNAi was administered using dsRNAi vector feeder clones (pL4440-dest-RNAi Destination vector in the feeder HT115(DE3)E. coli).

Results: RNAi knockdown of proteins corresponding to the genes identified resulted in an accelerated paralysis phenotype, suggesting that they may play a role in AD pathology. These included genes encoding for ATPase subunits (ATP6VA1), proteins involved in glucose metabolism (PGM1), and a member of the glutamic acid decarboxylase family (GAD1).

Conclusions: C. elegans nematodes are an effective model for the study of AD via the silencing of genes using RNAi. This study has identified several genes that may have roles in the development of AD, which will be further studied in neuronal specific models.

Funding: NIH

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A novel role for class III phosphatidylinositol 3-kinase (Vps34) in synaptic vesicle exocytosis

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Introduction: Neuronal communication requires intricately controlled lipid metabolism to ensure proper regulation of synaptic vesicle exocytosis and endocytosis. While the functions of many phosphoinositide species have been extensively characterized in this process, a role for phosphatidylinositol 3-phosphate (PI3P) has yet to be established. Vps34 is the sole class III phosphatidylinositol 3-kinase that produces PI3P. Vps34 and PI3P are essential for various protein trafficking pathways including endocytic trafficking and autophagy.

Methods: We have used live imaging in cultured cortical neurons and electrophysiology in cortical slices treated with a pharmacological inhibitor of Vps34. Additionally, we have performed live imaging studies in neurons from autophagy-deficient mice.

Results: We have found Vps34 inhibition decreases both evoked synaptic vesicle exocytosis and spontaneous presynaptic activity. This decrease in presynaptic release correlates with lower calcium signaling within the presynaptic bouton and altered calcium signaling within presynaptic endoplasmic reticulum. We have determined that this function of Vps34 is independent of its role in autophagy.

Conclusions: Our studies have uncovered a novel role of Vps34 and PI3P in regulating presynaptic activity.

Funding: NIH

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New York Movement Disorders Study: A longitudinal clinical, genetic, and neuropathological study

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Emerging evidence indicates that neurodegenerative disorders have distinct and overlapping genetic and environmental risk factors. Studies have uncovered unique, and overlapping neuropathological signatures. We are systematically developing a large cohort of subjects in multiple institutes for collaborative translational research projects.

Subjects are recruited from MSHS. At the time of enrollment, they are asked to provide blood and access to their clinical records. Blood is subsequently processed into various fractions for further genetic and biomarker analysis. We have developed protocols for brain donation to generate neuropathological data.

We have recruited 221 individuals. The median age in the collection is 64 years with sex ratio roughly 2:1 towards men; including 41 controls and 135 with Parkinsonism. Other diagnoses include progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, and others. Genotyping is ongoing on the custom Illumina GSA chips.

We have developed a longitudinal cohort of extensively phenotyped patients with movement disorders and other neurodegenerative diseases. This resource will be critical for advancing our understanding these diseases and stratify risk.

Funding: Alzheimer's Association Grant, NIH/NIA R01, MJFF Grant, Tau Consortium, Departments of Pathology, Neuroscience and Neurology.

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Critical period plasticity-related transcriptional aberrations in schizophrenia and bipolar disorder

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Background. Childhood critical periods of experience-dependent plasticity are essential to develop environmentally appropriate behavior and cognition. Disruption of critical periods can disable development of normal function and confer risk for neurodevelopmental disorders. While genes and their expression relevant to neurodevelopment are associated with schizophrenia, the molecular relationship between schizophrenia and critical periods has not been assessed systematically.

Methods. We applied a transcriptome-based bioinformatics approach to assess whether genes associated with the human critical period for visual cortex plasticity are aberrantly expressed in schizophrenia and bipolar disorder.

Results. Across 24 schizophrenia and bipolar transcriptome datasets, we find that the majority show aberrations in expression of genes associated with the critical period. We observed both hyper- and hypo-critical period plasticity phenotypes at the transcriptional level, which mapped to computationally repurposed drug candidates. Chemogenomic enrichment analysis on clusters of candidates revealed unique drug targets per cluster (e.g. CB1).

Conclusions. Our findings indicate plasticity aberrations in schizophrenia and their treatment may need to be considered in the context of subpopulations with elevated and others reduced plasticity. Future studies should leverage ongoing large gene expression studies (e.g., CommonMind, BrainSeq) to tease out the underlying source of variation. This work urges direct assessment of cortical plasticity in humans using translational assays derived from rodent models to facilitate preclinical findings to humans with schizophrenia.

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Dietary polyphenols enhance optogenetic recall of fear memory in hippocampal dentate gyrus granule neurons subpopulations

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Background: Sleep deprivation (SD) is a common problem in our society and is linked to a number of co-morbidities including memory impairment. SD disrupts memory consolidation through impairments in CREB signaling and synthesis of de novo proteins in the hippocampus, which are attenuated by treatment with dietary polyphenols amongst other mechanisms. However, the mechanisms through which dietary polyphenols confer resilience in memory-bearing neurons are unclear.

Method: c-fos-tTA transgenic mice were injected with AAV9-TRE-ChR2-mCherry and implanted with optical fibers targeting the dentate gyrus (DG). Mice were pretreated with dietary polyphenols prior to training in the Contextual Fear Conditioning paradigm. After fear conditioning in Context B to label a neuronal subpopulation with ChR2-mCherry, mice were reintroduced to Context A under optical stimulation to record ChR2-mCherry-related fear recall.

Results: Mice pretreated with dietary polyphenols prior to training exhibited a higher increase in freezing under optical stimulation. Pretreated mice also showed an increase in the number of c-Fos and ChR2-mCherry immunoreactive neurons in the DG.

Conclusions: Increase in c-Fos expression is among the mechanisms through which dietary polyphenols promote memory function. Future studies will identify specific bioavailable metabolites and signaling pathways and synaptic changes that mediate improvements in memory function.

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A novel mechanism for treating depression: Efficacy of the potassium channel opener ezogabine in major depressive disorder

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Background: Major depressive disorder (MDD) is a leading cause of disability worldwide, yet current treatment strategies are limited in their diversity, thereby hindering the advancement of precision medicine. Recent preclinical evidence has highlighted a promising novel pharmaceutical target—the KCNQ-type potassium channel—for the treatment of depression.

Methods: The current translational study assessed the efficacy of the KCNQ channel opener ezogabine in attenuating depressive symptoms and modulating reward circuitry in patients with MDD. Patients were enrolled in an open-label study and received ezogabine over the course of ten weeks. Resting state functional magnetic resonance imaging data was collected at baseline and outcome to examine brain reward circuitry.

Results: Ezogabine significantly reduced depressive symptoms and also significantly reduced anhedonic symptoms, even when controlling for overall depression severity. This improvement in depression severity was associated with decreased functional connectivity between the ventral caudate and clusters within the mid-cingulate cortex and posterior cingulate cortex.

Conclusion: These findings highlight ezogabine as a novel pharmaceutical for the treatment of depression, implicating the KCNQ-type potassium channel as a promising target for future drug discovery efforts in mood disorders.

Source: National Institute of Mental Health

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Cell autonomous effects of APOE ε4/ε4 on human iPSC-derived astrocytes and microglia

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Homozygosity of Apolipoprotein E (APOE) increases Alzheimer's disease (AD) risk by >14-fold, however the mechanisms underlying this genetic risk on particular brain cell types is elusive. We hypothesized that the APOE ε4/ε4 genotype contributes to disease risk through cell autonomous mechanisms. We differentiated astrocytes, microglia, cortical neurons and brain microvascular endothelial cells from human induced pluripotent stem cells (iPSC) derived from non-isogenic and isogenic of cells selected based on APOE genotype and performed RNAseq. When APOE ε4/ε4 transcriptomes were compared with ε3/ε3 the most significantly enriched pathway is cholesterol biosynthesis in astrocytes and lysosomal pathways in microglia. Functional network analysis showed that APOE ε4/ε4 astrocytes and microglia significantly upregulates cholesterol biosynthesis. Lysosomal pathways of microglia are associated with phagosome maturation and autophagic function, defects of which lead to increased lipid accumulation and decreased lipid catabolism. Our data suggest a decoupling of cholesterol synthesis and degradation in APOE ε4/ε4 compared to ε3/ε3 glia. Together, human CNS cell type based iPSC models allowed us to elucidate APOE ε4/ε4 cell autonomous effects. Specifically in APOE ε4/ε4 compared to ε 3/ε3 astrocytes and microglia we observed deficits in lipid metabolism, leading to increased cholesterol biosynthesis, even in the face of decreased cholesterol efflux.

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Quiescent glioblastoma cells shift to an epithelial-mesenchymal transition (EMT)-like gene program

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Background: Quiescent stem cells of glioblastoma (GBM), a malignant primary brain tumor, are potential sources for recurrence after therapy. However, the gene expression program underlying the physiology of GBM stem cells remains unclear.

Methods: I have engineered human GBM cells with an inducible histone2B-GFP reporter by CRISPR/Cas9 knock-in. Quiescent GBM cells are labeled GFP-high after pulse-chase paradigm. I utilized a 3D GBM organoid system to isolate quiescent GBM cells, which were subjected to stem cell assays and RNA-Seq analysis. To elucidate therapy resistance of quiescent GBM cells, I exposed GBM organoids to radiation and TMZ. In a parallel strategy, I study quiescent GBM cells with in vivo intracranial transplants.

Results: RNA-Seq analysis of quiescent and proliferative GBM cells showed upregulation of EMT pathway genes and of genes that modify extracellular matrix. After exposure to XRT and TMZ, I observed an increase in the fraction of GFP-high population in live cells, demonstrating higher therapy resistance. Histological analyses of tumors growing in mouse host brains revealed the relative prevalence of quiescent cell populations near putative perivascular stem cell niches.

Conclusion: My findings connect quiescent GBM cells with an EMT-like shift, possibly explaining how GBM stem cells achieve high therapy resistance and invasiveness, and suggest new targets to abrogate the stem cell population of GBM.

Abstracts

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Proliferative glial pathology in drug resistant human epilepsy

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[1]Department of Pathology, [2]Neuroscience, [3]Neurosurgery, [4]Neurology at ISMMS

Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy. While current seizure medications target abnormal neuronal hyperexcitability, pathological epileptic tissue also shows reactive astroglial scar and dysregulation of myelin.

In this study, we aimed to characterize the pathological changes in astrocytes and oligodendroglia associated with epilepsy, using primary, electrode-mapped, epileptic cortical tissue from patients with drug resistant TLE and age-matched human autopsy temporal cortex (TL) as control. We developed a Fluorescence-Activated-Nuclei-Sorting (FANS) strategy to isolate nuclei from neurons, oligodendroglial progenitors (OPCs), and astrocytes from TLE and TL, and confirmed cell-type specificity of the isolated populations by nuclear RNA-seq. Differential nuclear transcriptome analysis revealed enrichment of functional gene sets related to cell growth/proliferation in epileptic astrocytes and OPCs, compared to normal TL counterparts. Increased proliferation in OPCs (OLIG2+) and astrocytes (GFAP+) in TLE was further confirmed in-vivo by Ki67 immunoreactivity. To isolate and functionally characterize proliferative epileptic glia, we FACS-sorted EGFR+ cells from fresh TLE tissue, a technique previously used to isolate neural/glioblastoma stem cell populations. Epileptic EGFR+ cells displayed abnormal neurosphere-forming immature phenotype in vitro and expressed both OPC and astrocytic markers in RNA-seq analysis, with preferential enrichment of the more harmful A1 (vs. A2) reactive astrocyte genes.

Our results implicate an immature and proliferative phenotype of epileptic astrocytes and OPCs, which might be detrimental to neuronal function. Further understanding of the glial-specific dysregulated pathways will allow design of better therapies for synapse restoration in this debilitating disease.

Source: NIH

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The Role of Innate Immunity in Parkinson's Disease

Evan Udine[1], Tamjeed Skider[1], Madison Parks[1], Elisa Navarro[1], Ying-chih Wang[1], Ritesh Ramdhani[2], Steven Frucht[2], John Crary[1] and Towfique Raj[1]

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Background: Recent studies implicate the role of the innate immune system in Parkinson's disease (PD) but the underlying genes, pathways, and biological mechanisms remain unknown.

Method: We have recruited over 221 PD patients from the Movement Disorder Clinic. In the pilot phase, we processed blood into plasma, buffy coat, and monocytes. We isolated CD14+ monocytes from 22 PD cases and 22 aged-matched controls. We generated gene expression profiles using RNA-seq and genotyping data to perform differential expression and expression Quantitative Trait Loci (eQTL) mapping. We also quantified tau protein abundance from plasma for 36 samples.

Results: Overall we identified 86 differentially expressed genes between PD cases/controls, and enrichment in cytokine signaling, autophagy, interferon signaling and phagocytosis pathways. We identified 12 significant cis-eQTL variants in LD with index variants in PD loci (i.e., CTSB, PTPN22, SNCA, TMEM175, and LRRK2). Additionally, we found a correlation between the protective H2 haplotype in MAPT and decreased tau.

Conclusion: We identified several known and novel genes differentially expressed between PD cases/controls, some of which are genetically regulated. We are currently extending our cohort to over 200 patients.

Funding: This work was funded by the NIH and MJFF.

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Biochemical and genetic predictors of amyloid deposition in brain aging

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Background: Alzheimer disease (AD) is the major cause of dementia worldwide. AD is characterized by plaques consisting of amyloid-beta (Aβ) and neurofibrillary tangles composed of hyperphosphorylated tau. Aβ deposition is common in non-demented aged individuals, but a subset of individuals reach advanced old age without apparent Aβ pathology. Understanding the factors that modulate Aβ accumulation during aging may provide insight into the pathogenesis of AD.

Methods: From a collection of autopsy brain tissue from subjects with mild or no amyloid pathology (n=104, average age = 78.9 yr, range 53-108 yr), we interrogated the levels of abnormal tau as well as amyloid precursor protein (APP) and its metabolites (sAPPα/β, Aβ40/42) using ELISA and immunoblot. We measured the activity of major APP proteases (ADAM10 and BACE1) using a fluorometric assay. Measurements were correlated with Aβ plaque counts from histological preparations using a multi-linear model with APOE genotype and age as covariates.

Results: Our model showed strong correlations between plaque deposition and APOE (p=8.3e-5) and total tau (p=0.03). We also observed trends towards differences in age (p=0.06), soluble Aβ42 (p=0.06), total Aβ42 (p=0.06), and phospho-tau/total tau ratio (p=0.07).

Conclusions: These findings provide strong support for the role of APOE genotype in amyloid deposition. Further studies addressing the role of APP processing on amyloid deposition are ongoing.

Funding: NIH R01NS095252

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Novel modulatory role of Plexin-B2 in neuroimmunity after spinal cord injury

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Semaphorins are membrane bound or secreted proteins that regulate a number of cellular functions by direct cell-cell contact. Most of their downstream signaling is carried out by the receptors Plexins. Cumulative evidence suggests that Plexin signaling may play a role in neuroimmune disorders. Macrophages and microglia-the resident immune cells of the CNS- form the myeloid lineage and are the first line of defense in CNS injury, contributing to neuroimmunity. Upon injury, we report upregulation of PlexinB2 protein at the lesion site, specifically in cells of the myeloid lineage. Deleting PB2 in Cx3Cr1+ microglia and macrophages led to impaired motor recovery, increased microglial branch points, and reduced motility; while other physiological functions of microglia, namely proliferation, phagocytosis and lipid metabolism, were unaffected. We report impaired corralling-a process in which scar formation for wound healing is hampered-as the cause of hindered motor recovery, and together with microglia RNA-Seq, immunohistochemistry, and two-photon imaging, intend to dissect a sub-optimal immune-glia crosstalk that may contribute to the phenotype.

This work was funded by grants from Hongyan Zou, NY State spinal cord injury repair post-doctoral fellowship (Shalaka Wahane) and the Govt. of China (Xiang Zhou).

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Striatal ELK1 is a key regulator of synaptic plasticity through modulation of proteasomal activity

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Background: Chronic heroin abuse alters synaptic plasticity in brain regions relevant to addiction. The mechanisms underlying heroin-induced synaptic alterations remain unknown. Prior microarray analysis revealed that a significant portion of genes downregulated in the striatum of human heroin abusers were targets of ELK1, a transcription factor downstream of μ-opioid receptor signaling. Additionally, phosphorylated ELK1 (pELK1), which influences its transcriptional activity, was reduced in this population and negatively correlated with heroin intake in self-administering rats. Moreover, ELK1 cellular localization influenced synaptic morphology. We currently interrogate the relevance of pEKL1 to cellular function and its potential role in heroin addiction.

Methods: Primary rat striatal-cortical neurons were transfected with ELK1 vectors that alter its phosphorylation status. Synaptic alterations were assessed using confocal microscopy. Proteasomal activity was measured using a fluorometric assay.

Results: Overexpression of unphosphorylated ELK1 (unpELK1) reduced striatal spine density similar to the effects of heroin. Additionally, unpELK1 increased synaptic protein levels. Interestingly, unpELK1 repressed expression of target genes relevant to the proteasomal pathway and reduced proteasomal activity.

Conclusions: In addition to altering synaptic morphology in heroin abusers, our data suggests that unpELK1 impairs proteasomal gene expression and the proteolysis of synaptic proteins. Together, these findings provide neurobiological insights suggesting an important link between ELK1 cellular localization and neuronal adaptations that underlie heroin-seeking behaviors. Studies are underway to identify such a causal link.

Funding: NIH

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Sensory reactivity as an outcome measure for clinical trials in autism spectrum disorder

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Background: Sensory symptoms represent a core feature of autism spectrum disorder (ASD). This study piloted the utility of electrophysiological and behavioral measures for assessing change in sensory reactivity during a clinical trial of insulin-like growth factor-1 (IGF-1) in children with Phelan-McDermid syndrome (PMS), one of the most common single-gene causes of ASD.

Methods: Six children with PMS 5-12 years of age enrolled in a placebo-controlled, double-blind, crossover design study. Transient visual evoked potentials (VEPs) and the Sensory Assessment for Neurodevelopmental Disorders (SAND) were collected at baseline and week 12 during both phases. VEPs reflect the sum of excitatory and inhibitory postsynaptic potentials and provide a window into the brain to examine excitatory/inhibitory balance. The magnitude squared coherence statistic (MSC) was used to examine coherence of high-frequency oscillatory responses. The SAND is a clinician-administered observation and corresponding caregiver interview that quantifies sensory reactivity according to DSM-5 criteria for ASD.

Results: There was a significant increase in low gamma (30-36 Hz) activity following IGF-1 relative to baseline (p=.048). Notably, MSC increased in 5 of 6 patients. Significant clinical improvement was observed on the SAND Hyporeactivity Domain following IGF-1 treatment (p=.037).

Conclusions: Our results suggest that VEPs and the SAND represent two novel outcome measures for use in clinical trials for individuals with ASD and related conditions.

Funding: Internal

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Prioritizing Parkinson's Disease genes using population-scale transcriptomic data

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[*] These authors contributed equally to this work.

Background: Genome-wide association studies (GWAS) have identified over 41 susceptibility loci associated with late-onset Parkinson's Disease (PD) but identifying putative causal genes and the underlying mechanisms remains challenging.

Methods: Here, we leveraged large-scale transcriptomic datasets to prioritize genes that are likely to affect PD by using a transcriptome wide association study (TWAS) approach. Unlike standard TWAS that associate imputed RNA expression levels to measured trait, our TWAS associates both imputed RNA expression and RNA splicing to measured traits.

Results: Using this approach, we identified 44 gene associations whose expression or differential splicing in prefrontal cortex is associated with PD. This includes many novel genes but also known associations such as MAPT, for which we found that variation in exon 3 splicing explains the common genetic association. Genes identified in our analyses are more likely to interact physically with known PD genes and belong to the same or related pathways including lysosomal and innate immune function.

Conclusion: Overall, our study provides a strong foundation for further mechanistic studies that will elucidate the molecular drivers of PD and suggests the utility of including RNA splicing effects in all TWAS.

Funding: This research is funded by NIH and MJFF grants.

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Dynamic balance between vesicle transport and microtubule growth enables neurite growth

Arjun Singh Yadaw, Mustafa M. Siddiq, Vera Rabinovich, Rosa Tolentino, Ravi Iyengar, Jens Hansen

Whole cell responses are complex because they involve many subcellular processes (SCPs) that function in a coordinated manner. Understanding of how different SCPs function together is essential for predictions of whole cell responses. We studied neurite outgrowth to understand how balance between SCPs is essential for this whole cell function. Neurite outgrowth involves three types of SCPs: production of membrane components, vesicle transport that delivers membrane to the growth cone and microtubule growth that regulates extension of the neurite shaft. Mathematical modeling and simulations show that redundancies between lower level sibling SCPs produce robustness of higher level SCPs. In contrast, higher level SCPs need to be strictly coordinated and cannot compensate for each other. From these models we predicted the effect of SCPs involved vesicle fusion as well as microtubule growth on neurite outgrowth. siRNA ablation experiments verified these predictions. We conclude that origins whole cell dynamics requires strict balance between the higher level SCPs involved.

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Amyloid-β Pathway Linking Traumatic Brain Injury and Alzheimer's disease

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Background: Large number of injuries from exposure to explosive blasts during the Iraq and Afghanistan wars motivate investigations of blast-related neurotrauma. Blast injury is the most common cause of mild Traumatic brain injury (TBI). TBI-induced neurovascular injuries accelerate amyloid-β (Aβ) production which is one of the causes of Alzheimer's disease (AD). Despite many studies on TBI and AD, TBI disease development mechanism that leads to AD-like pathology is not well understood. Therefore, identifying a pathway of Aβ acceleration yields insight into the disease pathology and link TBI to AD.

Method: For better understanding the mechanisms underlying TBI and AD through Aβ, we investigated effect of blast on gene-gene interactions. The study involved 32 individuals participating in a 2-week data collection cycle at U.S. Army. The blood samples of the individuals were collected pre- and post-training to profile transcript abundance. To assess changes of the interactions, we constructed co-regularity network of RNA-Seq data separately for pre- and post-transcripts.

Result: Comparison of the networks reveals changes in pathway of Aβ. These changes present consequences of TBI on the development of AD-like pathology through Aβ and provide potential intervention target.

Conclusion: The investigations through studies of training operations of individuals with exposure to blast offers a unique opportunity to establish a link between mild TBI and AD.

Funding: NIMH, VA

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Data Driven Approach Identifies Postnatal Lead (Pb) Disrupts Juvenile Critical Period Neuroplasticity

Priscilla E. Yevoo#, Milo R. Smith#, Masato Sadahiro, Manish Arora, Joel T. Dudley, Hirofumi Morishita

Background: Given that thousands of chemicals released into the environment have an unknown, but potentially significant capacity to harm neurodevelopment, there is an urgent need for systematic approaches to identify chemicals impacting neurodevelopment. Neurodevelopment is marked by critical periods of plasticity wherein neural circuitry is optimized by the environment. Perturbation of these critical periods by environmental chemicals may confer risk for neurodevelopmental disorders such as autism.

Methods: We developed an integrative bioinformatics approach to systematically identify chemicals that disrupt critical period plasticity. Scanning across 214 established human neurotoxicants within the Comparative Toxicogenomics Database, we assessed the ability of these neurotoxicants to dysregulate a critical period transcriptome-based gene signature from primary visual cortex (V1) of juvenile mice at the peak of the critical period. The functional impact of neurotoxicant exposure was validated by gene expression analysis to determine impact on critical period signature genes and in vivo electrophysiology to assess ocular dominance plasticity within visual cortex.

Results: We identified lead (Pb) as a top-ranked neurotoxicant to disrupt plasticity and confirmed that juvenile Pb exposure reversed critical period gene expression and suppressed critical period experience-dependent plasticity in vivo.

Conclusions: We show that a systematic, data-driven, transcriptome-based approach can effectively identify developmental neurotoxicants from public data, and that Pb suppresses critical period plasticity in developing animals.

Funding: Traineeship T32HD075735, NIH, and foundations.

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Integration of epigenomic information improves transcriptome prediction and identifies novel genes in large-scale gene-trait association study.

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Background: Novel machine learning approaches can generate models for "imputation" (prediction) of gene expression by using solely genetic data as input. These models can be integrated with GWAS to identify changes at the imputed gene expression with much greater power than examining single nucleotide variants. Here we developed a method that integrates epigenomic information to better estimate variants' effects on gene expression level.

Methods: We generated predictive models of gene expression across 14 datasets by using a weighted elastic net model that integrates epigenome data. We applied these models to 58 GWAS to identify genes that are dysregulated in each trait.

Results: Compared to previous methods, our model improves the accuracy of gene expression prediction in independent datasets. Integration of gene expression predictors with GWAS summary results identified novel trait-associated genes. These genes are enriched for: (1) biological pathways that are relevant to the etiopathogenesis of the trait, and (2) genes that have been associated with Mendelian syndromes for the disease.

Conclusions: Integrating epigenomic information into prediction of transcriptome can improve the performance of imputation and when applied in GWAS data reveals novel tissue-specific trait-associated genes.

Funding: NIH (R01AG050986 and R01MH109677) and VA (BX002395).

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Brain Insulin Lowers Adipose Tissue Inflammation by Reducing Lipolysis

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[1] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY
[2] Institute of Molecular Biosciences, University of Graz, Graz, Austria

Brain inflammation is implicated in the development and progression of obesity and diabetes, but also in neurodegenerative diseases such as Alzheimer's and Parkinson's. The mechanisms that induce and maintain brain inflammation in these conditions are incompletely understood. To what extend brain inflammation is due to altered metabolism is unclear. We have previously shown that insulin signaling in the hypothalamus controls adipose tissue lipolysis. Fatty acids are important energy substrates, but can also function as inflammatory mediators. Hence, we hypothesized that brain insulin signaling reduces the expression of proinflammatory cytokines in adipose tissue and that hypothalamic inflammation will be ameliorated if lipolysis in adipose tissue is reduced. We tested this through a series of genetic loss of function studies in mice, brain microinfusion of insulin in rats, and assessing inflammation through cytokine expression in peripheral organs and brain tissues. Our studies demonstrate an important role of the brain-adipose axis in peripheral and brain inflammation in several models of metabolic diseases. Preventing adipose tissue lipolysis can prevent brain inflammation. This suggests that hypothalamic insulin resistance induces inflammation in the periphery (adipose tissue and liver) and that in turn adipose tissue lipolysis is a major determinant of hypothalamic and brain inflammation.

Study is funded by NIH.

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HCN channel inhibitor induces ketamine-like rapid and sustained antidepressant effects in chronic social defeat stress model of depression

Yingbo Zhu, Mary Regis Shanley, Stacy M. Ku, Carole Morel, Hongxing Zhang, Yuan Shen, Allyson K. Friedman, and Ming-Hu Han

Department of Pharmacological Sciences, ISMMS, Department of Biological Sciences, Hunter College

Background: Repeated, long-term (weeks to months) exposure to standard antidepressant medications is required to achieve treatment efficacy. In contrast, acute ketamine quickly improves mood for an extended time. Recent work implicates that hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are involved in mediating ketamine's antidepressant effects. In this study, we directly targeted HCN channels and achieved ketamine-like rapid and sustained antidepressant efficacy.

Methods: C57Bl/6J mice were subjected to CSDS. Those exhibiting depressive-like symptoms received a VTA microinfusion or systemic intraperitoneal (ip) injection of HCN channel inhibitor DK-AH 269. In vitro recordings were used to assess HCN-mediated Ih current and firing frequency of VTA dopamine neurons post DK-AH 269 treatment.

Results: Our in vitro recordings first showed that DK-AH 269 decreased the pathological HCN-mediated current (Ih) and abnormal hyperactivity of ventral tegmental area (VTA) dopamine (DA) neurons in depressed susceptible mice in a CSDS model. Our in vivo studies further showed that acute intra-VTA or acute systemic administration of DK-AH 269 normalized social behavior and rescued sucrose preference in previously socially avoidant and anhedonic susceptible mice. The single-dose of DK-AH 269, could produce an extended 13-day duration of treatment efficacy.

Conclusions: This study provides a novel ion channel target for acutely acting, long-lasting antidepressant effects.

Source: NIH

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The Center for Excellence in Youth Education: A Best Practice Model for Developing Science Enrichment Pipeline Programs for Urban Minority and Disadvantaged Youth

Despite the overall improvement in public education, significant racial ethnic disparities in educational attainment outcomes continue to persist for youth in grades K-12. Black and Latino youth experience lower rates of completion of Science and Engineering undergraduate degrees due to lower rates of high school completion and college enrollment. Therefore, Black and Latino youth become underrepresented (URM) in science and medicine. As a result of these persistent disparities in educational attainment, 11% of the medical and graduate (PhD level) student graduates in 2015 were URM compared to 59% who were Caucasian. This trend also evident among MD/PhD graduates whereas 9.4% were URM students compared to 60% who were Caucasian. Early exposure and hands-on experiential learning within STEM is shown to promote interest in these career fields and have a positive impact on students' self-perception as a scientist.

The CEYE Program Model capitalizes on the medical school's research faculty workforce, its biomedical research lab footprint, its student-led youth focused groups and programs, and partnerships with NYC Public/Charter Schools. Theoretical frameworks inform specific program interventions including six-week classroom-based research projects, clinical internships, and 2-year biomedical research prep courses with corresponding research internships.

2014-2015, 98% of CEYE's graduating high school seniors matriculated to college with 85% declaring a STEM major
2015-2016, 100% of CEYE's graduating high school seniors matriculated to college with 70% declaring a STEM major

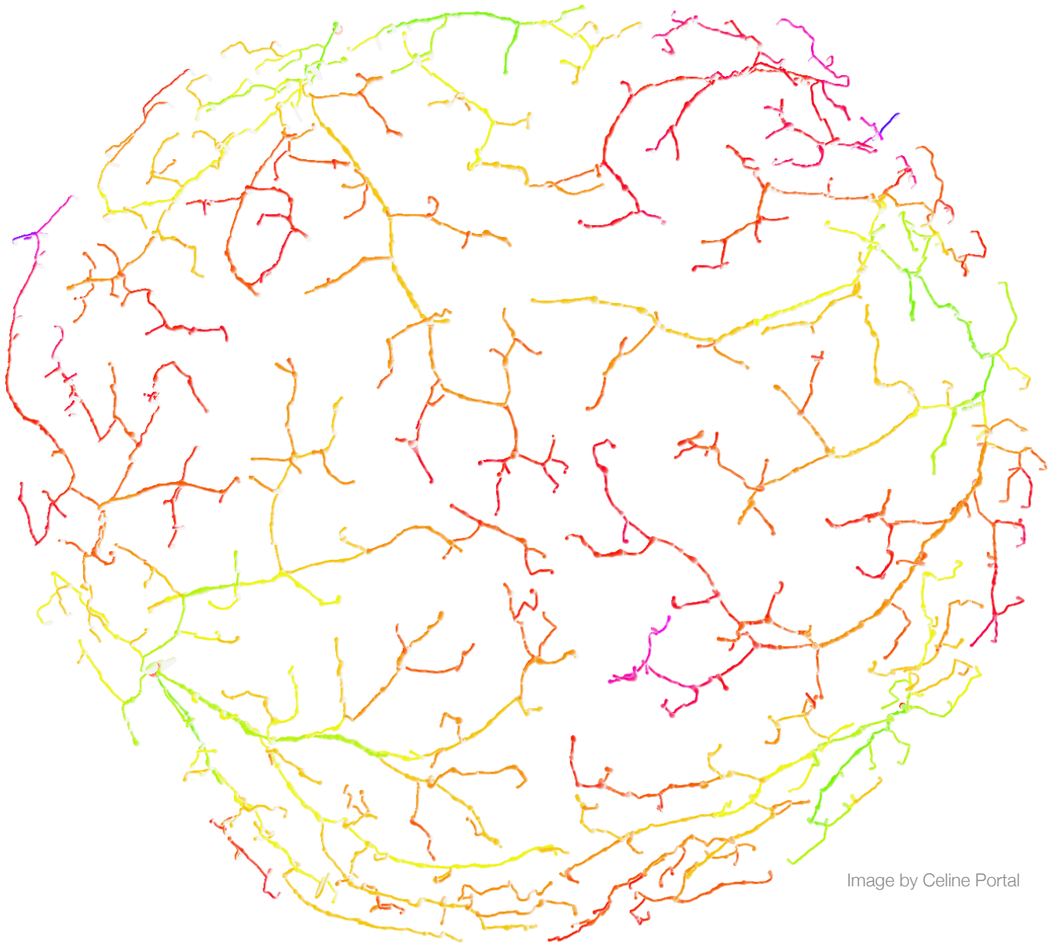

Image by Celine Portal

Neuroscience Graduate Training Program

It was another banner year for our Neuroscience graduate training program. We received a record number of Ph.D applications this year (174), and we welcome an as-yet unknown number of new MSTP students. As of this writing, we are proud to recognize 17 confirmed Ph.D matriculating students for the incoming class (Fall, 2018). This is noteworthy in several respects. It is a continued reflection of the ever-growing star power of our faculty. Without you, we would not be attracting the number and quality of these applicants. Telling too are the programs to which we lose applicants—Harvard, Yale, Hopkins et al.. all top-tier programs, among which we must now consider ourselves. The incoming class is also the most diverse—culturally and scientifically—that we have ever had. This is a tremendous strength. We are especially grateful to the many faculty, students and staff that made this year's admissions process so successful. Of course with these numbers come challenges—we must all work hard and be creative in finding the means to place these exceptional and highly motivated students into laboratories.

There is an important and noteworthy change to the Ph.D application process itself. Starting with Fall, 2018 applications, the GRE will no longer be required as part of the application process for either the Neuroscience or Biomedical Sciences programs. Mount Sinai joins a growing list of top-tier programs nationwide to dispense with the GRE requirement, and places Mount Sinai and Rockefeller as the only two NYC-area institutions to do so. The reason for eliminating the GRE requirement is simple—a substantial body of evidence indicates that the GRE has little or no predictive value in determining success in graduate school by a wide number of measures (e.g. time to thesis proposal, time to graduation, number of published papers, grades in graduate coursework, et al). More importantly, the GRE requirement discriminates against applicants who lack the means to prepare properly, to pay for the exam, or to access an exam location. Neuroscience led the effort on this initiative, and we are proud of the outcome.

There are no major changes planned for the curriculum. This past year was the trial run of a number of institution-wide changes, including shortened rotation schedules, accelerated Core course timeframes and others. This has been quite successful in getting students into labs earlier (with a goal of April-May of their first year) with a shortened time to their thesis proposal (with a hard deadline of June of their second year).

Finally, we salute the impressive success of our students in obtaining their own extramural funding, noting record numbers of successfully funded NRSAs, NSF grants and private foundation fellowships by our trainees.

George Huntley and Stephen Salton

Image by Jessica Johnson

2018 UPCOMING EVENTS

APRIL

Diversity in Neuroscience
Michelle Jones-London, Ph.D.
April 30, 2018

MAY

ISMMS commencement
May 11, 2018

Diversity in Neuroscience
Kafui Dzirasa, M.D, Ph.D.
May 31, 2018

CTE in the Female Brain: Researching answers for Women Athletes, Veterans and Brain Injury Survivors
May 23, 2018

JUNE

Diversity in Neuroscience
Uraina Clark, PhD
TBD

AUGUST

Grad School Classes Begin
August 14, 2018

SEPTEMBER

Annual Postdoc Day
Sept. 21, 2018

MD/PhD Retreat
September 14-16, 2018

White Coat Ceremony
September 13, 2018

OCTOBER

SinaInnovations
October 17-18, 2018

NOVEMEBER

Society for Neuroscience Meeting
November 3-7, 2018

DECEMBER

Grad School Winter Party
December 15, 2018

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

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#stemcells
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Notes