2015

THE Friedman Brain Institute

and the NEUROSCIENCE TRAINING AREA

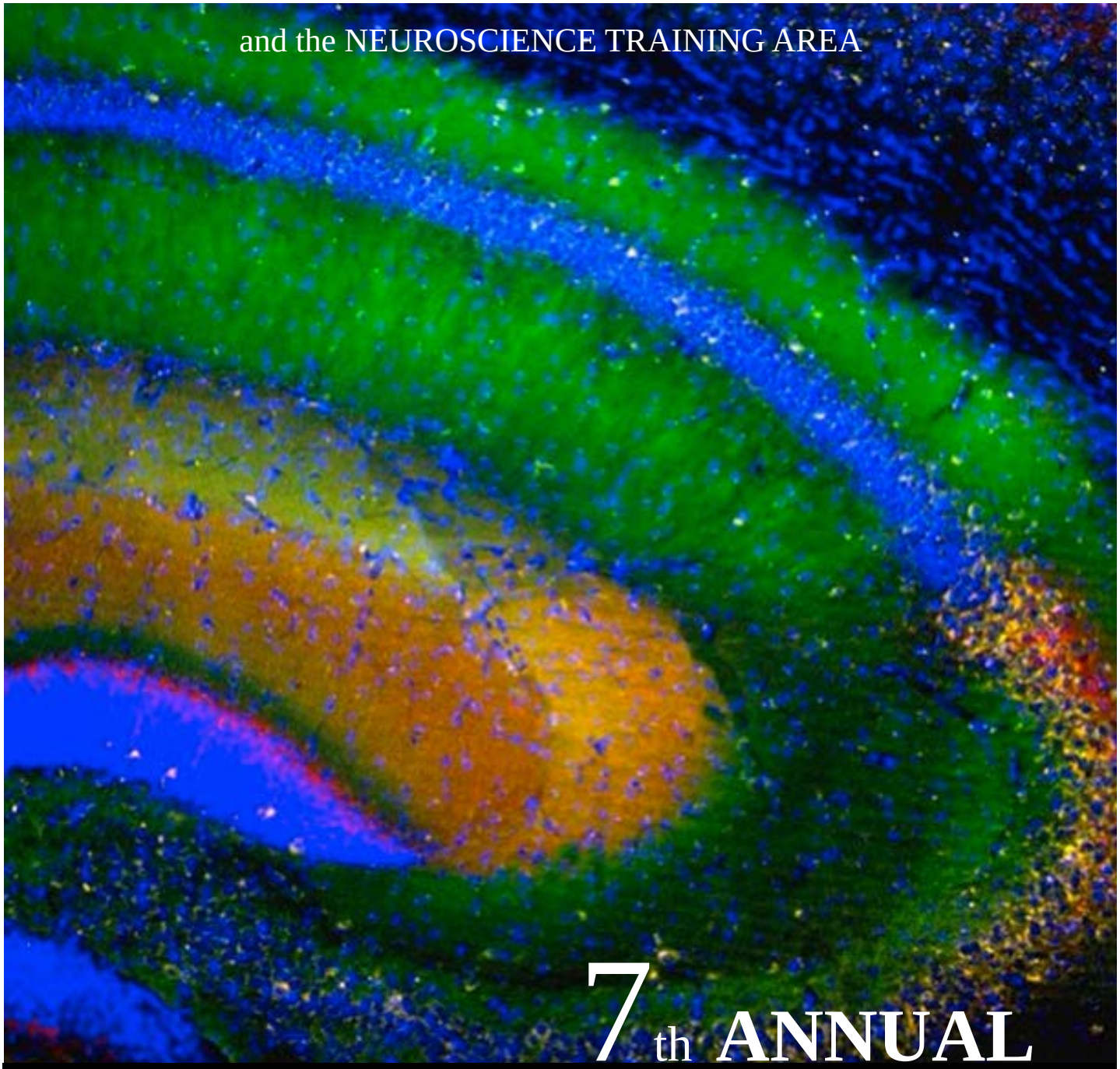

Photo by Erin Bobeck, Department of Pharmacology and Systems Therapeutics

7th ANNUAL NEUROSCIENCE RETREAT

Icahn School of Medicine at Mount Sinai

NEW YORK ACADEMY OF MEDICINE 1216 Fifth Avenue

THE Friedman Brain Institute

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7th Annual Neuroscience Retreat Committee

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The 7th Annual Neuroscience Retreat

NEW YORK ACADEMY OF MEDICINE 1216 Fifth Avenue (corner of 103rd Street)

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The 7th Annual Neuroscience Retreat

NEW YORK ACADEMY OF MEDICINE 1216 Fifth Avenue (corner of 103rd Street)

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Abstracts (Posters)

Retreat Schedule May 13, 2015

8:45am..... Sign in and Register (Lobby) Poster setup (Library, 3rd fl.) and Breakfast (Room 20, 2nd fl.)

OPENING REMARKS AND ANNOUNCEMENTS (HOSACK HALL):

9:30am..... **Kristina Simonyan, M.D., Ph.D.** (Neurology and Otolaryngology)

9:35am..... **Eric J. Nestler, M.D., Ph.D.** (Friedman Brain Institute and Neuroscience)

10:05am..... **George W. Huntley, Ph.D.** (Neuroscience)

10:15am..... **Keynote Address: Zhenyu Yue, Ph.D.** (Neurology and Neuroscience)

"How Shall I Eat Thee? - A Question of Autophagy and Neurodegeneration"

BREAK.....10:50am - 11:05am

SESSION 1

11:05am..... **Paula Croxson, Ph.D.** - Chair I

11:10pm..... **Peter Rudebeck, Ph.D.** (Neuroscience)
"Adjusting accordingly: the contribution of the orbital and ventral prefrontal to adaptive choice behavior"

11:25am..... **Yael Grossman** (Neuroscience)
"Preexisting differences in cortico-limbic functional connectivity predict resilience to social defeat"

11:40am..... **Mitra Heshmati** (Neuroscience)
"Neuroligin---2 in nucleus accumbens regulates social behavior"

11:55am..... **Christienne Damatac** (Neuroscience)
"Structural and functional network changes associated with cognitive training in memory"

12:10pm..... **Stefan Fuertinger, M.Sc., Ph.D.** (Neurology)
"Dopaminergic neuromodulation during speech: A combined iEEG and neural modeling study"

LUNCH.....12:25pm - 1:35pm, Room 20, 2nd fl.

SESSION 2

1:40pm..... **Rafael O'Halloran, Ph.D.** - Chair II

1:45pm..... **Panagiotis (Panos) Roussos, M.D., Ph.D.** (Psychiatry)
"Dissecting the cis regulation of gene expression in schizophrenia"

2:00pm..... **Cesar Moreno** (Neuroscience)
"Inhibition of hypothalamic Creb---binding protein produces obesity and hypothalamic molecular reprogramming away from glucose toward lipid metabolism"

2:15pm..... **Jenna Short** (Psychiatry)
"Adolescent suppression of prefrontal nicotinic signaling shapes attentional function"

2:30pm..... **Keren Bachi, Ph.D.** (Psychiatry)
"Characterizing atherosclerosis in asymptomatic cocaine addicted individuals"

2:45pm..... **Joo–won Kim, Ph.D.** (TMII)
"Human Habenula Myelination Extent and Relationship with Mood"

POSTER SESSION Library 3rd fl.

3:00pm.....Poster Session and Reception Begin

5:00pm.....Award Ceremony (Best Poster, Best Oral Presentation, "Call for Images" Award and 2015 BRAIN Award)

5:30pm.....Reception Ends

PLEASE REMEMBER TO RECYCLE YOUR NAME TAGS

Presenters

Preexisting differences in cortico-limbic functional connectivity predict resilience to social defeat

Yael Grossman, Rachel E Waldman, Natasha Qureshi, William G Janssen, Junqian Xu , Dani Dumitriu

Depression is a neuropsychological disorder afflicting millions of people. There are currently no predictors for susceptibility and a large proportion of afflicted individuals are resistant to available treatments. Therefore, the ability to predict psychosocial vulnerability and resilience to stress holds great promise in preventing this debilitating disorder. Social defeat (SD) is a highly validated mouse model of depression. We developed a model of acute SD for elucidating the neurocircuitry involved in establishing divergent behavioral phenotypes. To probe the neuroactivation correlate of the establishment of the divergent phenotypes, we analyzed cFos expression in various cortical and subcortical regions following SD and found that resilient animals have higher correlative activation between prefrontal and temporal regions while susceptible animals exhibit anti-correlative activation patterns within the same circuits. To investigate the synaptic mechanisms underlying these activation differences, we used a GFP-expressing virus to isolate amygdala-projecting prelimbic neurons (a circuit involved in the establishment of fear) that are active during the exposure to SD. We found that in this subpopulation of neurons that are active during the establishment of response to social defeat, resilient animals have lower densities of mushroom spines compared to susceptible animals. Together, these results suggest that susceptible animals have pre-existing higher synaptic connectivity of amygdala-projecting prelimbic neurons, which may be one of the mechanisms involved in their higher vulnerability to social defeat stress.

Neuroligin-2 in nucleus accumbens regulates social behavior

Mitra Heshmati[1], Hossein Aleyasin[1], Caroline Menard[1], Meghan E. Flanigan[1], Madeline L. Pfau[1], Peter H. Goff[1], Georgia E. Hodes[1], Ashley Lepack[1], Lucy Bicks[1], Ian S. Maze[1], Sam A. Golden[2] and Scott J. Russo[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY
[2]National Institute of Drug Abuse, Baltimore, MD

Background: Dysregulation of excitatory/inhibitory balance is suggested to be a common mechanism of neuropsychiatric disease. Neuroligin-2, a postsynaptic cell adhesion protein, supports the functional integrity of the inhibitory synapse and may play a role in the inhibitory balance. While the neuroligin gene family has been implicated in autism, little is known about the role of neuroligin-2 in social behavior.

Methods: Using a Cre-conditional RNA interference approach, we knocked down neuroligin-2 in the nucleus accumbens (NAc) of young adult mice expressing Cre in either dopamine D1 receptor-positive or dopamine D2 receptor-positive cells. We then explored the contribution of neuroligin-2 in the NAc to social behavior.

Results: We demonstrate that neuroligin-2 knockdown in D2+ cells stimulates increased home cage aggression and heightened dominance. Knockdown in D1+ cells promotoes susceptibility to social defeat stress with no significant change in baseline aggression.

Conclusions: Together, these findings suggest a novel, cell-specific role of nucleus accumbens neuroligin-2 in aggression and stress-induced social interaction.

R01MH090264 (to S.J.R.)
5F30MH100835 (to M.H.).

Structural and functional network changes associated with cognitive training in memory

Christienne Damatac, Jamie Nagy, Lazar Fleysher, Rafael O'Halloran, Paula Croxson

Department of Neuroscience, ISMMS

Age and pathologically related cognitive decline correlate with changes in brain structure and connectivity. However, there has yet to be a longitudinal study that demonstrates long term positive effects of cognitive training. We investigated the effect of cognitive training on structural and functional plasticity in memory networks in macaque monkeys using structural and diffusion weighted MRI (DWI) combined with behavioral measures.

We trained 6 monkeys on two object discrimination learning tasks. We compared 3 monkeys that formed a discrimination learning set (DLS), reliant on frontal-temporal connections, with 3 controls whose task involved concurrent discrimination learning (CDL), which utilizes only temporal lobe structures. We assessed transfer of learning to an untrained task through assessment on a third task of episodic memory. High-resolution structural (MP2RAGE, 0.5 mm isotropic voxels) and DWI (68 directions, 1.0mm isotropic voxels) scans were performed on a 3 Tesla Siemens Skyra MRI scanner using a custom-built 8-channel head coil. Scans were acquired before and after each stage of cognitive training. Data were analyzed using FSL.

DLS-trained monkeys learned more quickly than CDL-trained monkeys. Comparison of pre- and post-training MRI data revealed changes in grey matter volume and DWI changes in fractional anisotropy associated with cognitive training. These findings that cognitive training is accompanied by distinct structural changes may be translated into therapies for Alzheimer's disease, multiple sclerosis, and normal age-related cognitive decline.

Dopaminergic neuromodulation during speech: A combined iEEG and neural modeling study

Stefan Fuertinger[1], Joel Zinn[1], Walter Hinds[2], Ashwini D. Sharan[3], Farid Hamzei-Sichani[4], Kristina Simonyan[1,5]

[1]Department of Neurology, [4]Neurosurgery, and [5]Otolaryngology, ISMMS, New York,
[2] School of Biomedical Engineering, Science, & Health Systems, Drexel University, Philadelphia,
[3] Department of Neurosurgery, Thomas Jefferson University, Philadelphia

Background: In order to assess the modulatory influences of dopamine (DA) on speech production, we combined intracranial EEG recordings with simulations generated using our recently developed neural population model.

Methods: We analyzed two 11-second segments of iEEG recordings (1kHz sampling frequency) from the laryngeal/orofacial motor cortex in the resting state and while speaking and compared the results to simulations obtained from a physiologically detailed large-scale neural population model. DA modulation was quantified as changes in the analytic amplitude (AA) of empirical and simulated neural signals.

Results: Voltage amplitudes in the motor cortex were consistently higher before speech onset and during pausing in-between words but were down regulated while speaking. In the simulations DA induced a decrease in the magnitude of neural potentials similar to the empirical findings (correlation between simulated DA modulation and empirical data: $r = 0.69$).

Conclusions: The high agreement between voltage modulations in iEEG recordings and simulated DA influences during speech production suggests a driving role of DA in shaping the neuro-electrophysiological footprint of human speech control.

Funding: KS and SF were supported by the NIDCD/NIH (R01DC011805, R01DC012545 to KS).

Inhibition of hypothalamic Creb-binding protein produces obesity and hypothalamic molecular reprogramming away from glucose toward lipid metabolism.

Cesar Moreno, Linda Yang, Penny Dacks, Fumiko Isoda, Charles Mobbs

Obesity and diabetes are major challenges to public health in the 21st century. We reported a correlation between hypothalamic expression of Creb-binding protein (Cbp) and lifespan, and found that inhibition of Cbp prevents protective effects of dietary restriction, suggesting that hypothalamic Cbp plays a role in responses to nutritional status and energy balance. The present studies examine this further by inhibiting hypothalamic Cbp in mice using a cre-lox strategy. Inhibition of hypothalamic Cbp results in profound obesity and impaired glucose homeostasis, which is associated with increased food intake and decreased energy expenditure. These metabolic impairments parallel molecular evidence of a shift from hypothalamic glucose metabolism toward lipid metabolism, as well as reduced leptin receptor, and POMC. Based on evidence that decreased hypothalamic fatty acid metabolism inhibits feeding, and the observation that CBP inhibition increases fatty acid metabolism signatures, we tested the hypothesis that increasing fatty acid oxidation would similarly increase food intake. We used AAV-mediated gene transfer to increase hypothalamic expression of carnitine palmitoyltransferase 1 (Cpt1a), a rate-limiting enzyme in fatty acid oxidation. Similar to CBP deletion, enhanced hypothalamic Cpt1a increased food intake, weight gain, and decreased POMC expression. These data support that hypothalamic substrate partitioning towards fatty acid oxidation predisposes to obesity and that CBP regulates these targets.

Supported by NIA FAG042299A and F31AG042299.

Adolescent suppression of prefrontal nicotinic signaling shapes attentional function

Jenna Short*, Michael Demars*, Elisa Nabel, Hiroyuki Koike, Hirofumi Morishita

Department of Psychiatry, Neuroscience, Ophthalmology

Introduction: Attention is a cognitive function impaired in various neurodevelopmental disorders, but the developmental mechanism essential to shape attentional function is poorly understood. In the visual cortex, a well-characterized model of a developmental critical period, adolescent suppression of nicotinic acetylcholine receptors (nAChRs) by increased expression of an endogenous nAChR inhibitor, Lynx1, is essential for cortical maturation. Since the nAChR system is also implicated in attention, we tested a hypothesis that Lynx1 plays a key role in establishing frontal cortex-dependent attentional function.

Methods: By employing a 5-choice serial reaction time task on an automated touchscreen system, we combined genetic, viral, pharmacological, and histological approaches to investigate when and where in the brain Lynx1 exerts its effects to establish attention in mice.

Results: Lynx1 knock-out (KO) mice have attention-deficits in adulthood and reduced task-dependent-activation of anterior cingulate cortex (ACC) neurons. Viral knock-down of Lynx1 specifically in the ACC, beginning from peri-adolescence, phenocopied the attention deficit. Strikingly, the attention deficit was rescued by pharmacological suppression of nAChRs during peri-adolescence, but not acutely in adulthood.

Conclusions: These data suggest that excessive nAChR signaling during adolescence, normally limited by peri-adolescent increase in Lynx1 expression, causes long-lasting impairment in the frontal cortex and attention related behaviors. Our study provides mechanistic insight into neurodevelopmental disorders characterized by disrupted nAChR signaling, such as autism, ADHD and schizophrenia.

Funding: NINDS5T32DA007135-29 (M.D.), MCHDI (H.M.).

*equal contribution

Characterizing atherosclerosis in asymptomatic cocaine addicted individuals

K. Bachi[1], V. Mani[2], R.Z. Goldstein[1], Z. Fayad[2], N. Alia-Klein[1]

[1]Brain Imaging Center, [2]Translational Molecular Imaging Institute
Icahn School of Medicine at Mount Sinai

Cocaine, a powerful vasoconstrictor and a nonspecific voltage gated sodium channel blocker, induces an immune response including cytokine elevations. Chronic cocaine use, as in cocaine use disorder (CUD), associates with functional brain impairments potentially mediated by vascular pathology. We hypothesized that individuals with CUD are prone to vascular inflammation despite having no history of vascular and/or cardiovascular disease (CVD). Therefore, we imaged the common carotid arteries with PET/MR for inflammation markers (18F-FDG) and anatomical indices (MR) in 10 individuals with CUD aged 43 to 58. Results were compared with a population at risk for CVD aged 64.6 (SD=7.8). Individuals with CUD had more (mean, SD) inflamed plaque in arteries measured by target-to-background ratio (TBR) [TBRmax. Right (1.89, . 35) Left (1.7, .33); TBR ≥ 1.6 is considered inflamed plaque] and vessel and wall area and thickness [e.g. normalized wall index (56.3%, 4.2) versus (47%, 1.0)]. These inflammation and structural markers correlated significantly with cocaine use indices where the more severe the CUD the greater the carotid abnormalities (.63 ≤ r ≤ .97, p<.01). Thus, results demonstrate carotid disease markers in individuals with CUD and have clinical significance for combating silent disease progression. Our future studies will explore whether carotid abnormalities associate with brain impairments in CUD as they channel the majority of blood flow to the brain.

Funding: NIDA 1R21DA034954 (RZG), T32-DA007135-31 (KB).

Human Habenula Myelination Extent and Relationship with Mood

Joo-won Kim[1], Benjamin Ely[2], Emily Stern[2,3], Junqian Xu[1,2]

Departments of [1]Radiology, [2]Neuroscience, [3]Psychiatry, ISMMS

Background: The habenula is a pair of small diencephalic nuclei serving an important role in aversion and reward system regulation. Despite evidence suggesting a role in mood and anxiety disorders, the habenula is challenging to localize and segment in vivo because of its small size.

Methods: We used 0.7mm isotropic resolution T1w and T2w structural MRI data from 100 unrelated healthy young adults in the WU-Minn Human Connectome Project (HCP). Data were pre-processed using the HCP pre-freesurfer pipeline. Myelin maps were calculated using the ratio of T1w/T2w images.

A novel segmentation approach was employed, consisting of a region growth algorithm with intensity thresholding, geometric limit, and partial volume correction, for objective estimation of highly myelinated portion of the habenula, henceforth referred to as habenula myelination extent.

Subjects' NIH Toolbox sadness and anxiety scores were correlated with habenula myelination extent, normalized by total brain volume.

Results: Habenula segmentations results of 94 subjects passed visual inspection. The left and right habenula volumes, defined by the proposed myelin contrast based segmentation, were 17.8 ± 5.3 and 20.3 ± 5.9 mm3, respectively. Anxiety scores were negatively correlated with volumes of right ($r = -0.24$, $p = 0.020$) and left ($r = -0.21$, $p = 0.045$) normalized habenulae. No relationship was found with sadness.

Conclusions: Extent of habenula myelination is potentially related to human mood.

Abstracts

1 Heterogeneity of Microglia in the Mammalian Brain

Pinar Ayata, Fan Zhang, Ana Badimon, Zefa Sullivan, Melanie von Schimmelmann, Anne Schaefer

Microglia, the resident macrophages of the mammalian central nervous system, execute the primary response to pathophysiological brain insults. Recent studies reveal an emerging role for microglia in neuronal surveillance, synapse remodeling, and neurotrophin release, and point out their importance for normal neuron development and function. These functions require microglia to precisely communicate with their surveyed neurons. Given the highly heterogeneous nature of the brain, we hypothesized that the specific communication between various types of neurons and microglia would require specialized microglial subpopulations. The existence of microglial heterogeneity is suggested by their regional differences in cell number and morphology as well as their molecular properties in vitro. We use translating ribosome affinity purification method to compare gene expression profiles of microglia from various brain regions in vivo. This reveals two types of region-specific genes: microglia functional genes and genes shared with the specific neuron types resident to the respective region, such as neurotransmitter receptors. We confirm our results by single microglia nuclei RNA expression analysis and describe microglial subpopulations within each region. In summary, our analysis reveals for the first time a remarkable transcriptional heterogeneity of microglia. Deciphering this heterogeneity is critical for understanding the role of microglia in health and disease and will provide valuable insight into their potential therapeutic use.

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

2 Interleukin 34 As A Regulator of Direct Neuron-Microglia Interaction

Ana Badimon and Anne Schaefer

Icahn School of Medicine at Mount Sinai

Proper brain function is dependent on microglia-driven elimination of dead neurons and pruning of afunctional synapses. It has previously been shown that neuronal release of interleukin 34 (IL34) and subsequent binding on colony stimulating factor 1 receptor (CSF1R) on microglia is required for microglial survival. Utilizing transgenic mouse lines to deplete IL34 production, we show a dose-dependent reduction in microglia numbers. We propose that neuronal release of IL34 not only controls microglial number, but also prompts microglia to directly survey local neurons and maintain synaptic health. To better understand this physical interaction, we have generated a D1-specific IL34 knock out mouse that enables us to investigate if a reduction in IL34 and the resulting reduction in microglia number in the striatum has a region-wide effect or more precise cell type-specific effects. Immunofluorescent labeling will be used to visualize and quantify cell-to-cell contact. Cell filling, tracing, and spine analysis will determine gross morphological changes as well as spine density variations. We will combine these techniques with translating ribosome affinity purification (TRAP), in which GFP-tagged ribosomes are affinity purified and sequenced to analyze mRNA expression, to determine gene expression changes in D1 or D2 neurons resulting from the loss of Il34 and reduction in striatal microglia surveillance. Using these approaches we will better understand the underlying communication that governs healthy neuron-microglia interactions.

NIH 2012 Director's New Innovator Award

3 Resting-state phenotype-specific alterations in spasmodic dysphonia

Giovanni Battistella[1], Kristina Simonyan[1]

[1]Department of Neurology, Icahn School of Medicine at Mount Sinai

Spasmodic dysphonia (SD) is a primary task-specific focal dystonia of unknown pathophysiology, which is characterized by involuntary spasms in the laryngeal muscles during speech.

We investigated differences in the resting-state functional connectivity (rFC) in sporadic SD patients (ABductor and ADductor) and familial patients compared to healthy volunteers (HV). Secondly, we assessed phenotype-specific differences in ABSD and ADSD patients and in sporadic Vs familial cases.

Resting-state fMRI images were acquired in 30 ADSD, 30 ABSD, 23 familials and 30 HV and analyzed using Independent Component Analysis (MELODIC). A dual-regression analysis examined the group differences in rFC in the sensorimotor and frontoparietal components based on a one-way ANOVA at an FWE-corrected $p \leq 0.05$.

Compared to HV, sporadic and familial patients showed decreased connectivity in the sensorimotor cortex but increased connectivity in the frontoparietal and temporal cortices. Direct comparisons between the sporadic and familial SD indicates that the sensorimotor network had greater impairment in familials than in sporadics. In contrast, the frontoparietal component showed decreased rFC for both groups, with sporadic patients exhibiting more disperse alterations in rFC. Within the sporadics, ABSD patients showed decreased connectivity in the right premotor, parietal cortices, left inferior frontal and supramarginal gyri.

Our findings demonstrated abnormal organization of resting-state networks related to speech sensorimotor control in SD patients, which may underlie abnormal functional connectivity during dystonic task production and be associated with different genetic variants.

Funding: R01DC011805 to KS.

4 GPR171, a newly deorphanized hypothalamic G protein-coupled receptor is involved in the regulation of stress and reward-related behaviors

Erin Bobeck, Ivone Gomes, Wakako Fujita, & Lakshmi Devi

Recent neuropeptidomics studies have demonstrated that ProSAAS-derived peptides, including BigLEN (b-LEN) are abundant in the hypothalamus and enriched in the agouti related peptide (AgRP) neurons of the arcuate nucleus. Additional studies have implicated b-LEN in acute feeding. Recently we deorphanized GPR171, as a G protein-coupled receptor for b-LEN. Overexpression of GPR171 leads to an increase and knockdown to a decrease in b-LEN binding and signaling. Lentiviral shRNA-mediated knockdown of GPR171 in the hypothalamus leads to alterations in food intake and metabolism. To further investigate the role of GPR171, we used a DREADD approach to activate AgRP neurons to the release of b-LEN. As expected, activation of these neurons with clozapine-N-oxide leads to increases in food intake. This increase is attenuated by co-administration of a GPR171-selective small molecule antagonist. Given the known hedonic effects of activating these neuropeptide systems in the hypothalamus, we investigated additional reward-related behaviors. We find that activation of AgRP neurons leads to a reduction in anxiety and depression. In addition, we find that stress alters GPR171 mRNA expression. However, knockdown of GPR171 in the basolateral amygdala does not alter anxiety despite attenuating morphine conditioned place preference and fear conditioning. In conclusion, GPR171 is the receptor for b-LEN and plays a role in stress and reward-related behaviors.

Funding: NS026880 and DA019521 to L.A.D and T32 grant DA007135 to E.N.B.

5 Epigenetic Control of Transcriptional Changes Implicated in Defective Learning and Memory in HIV-infected Mice and Prevention by Valproic Acid Treatment

Borjabad A[1], Gu CJ[1], Kim BH[1], Wang J[1], Arancio O[2], Brooks AI[3], Morgello S[1], Murray J[1], Volsky DJ[1].

[1]Icahn School of Medicine at Mount Sinai, [1]Columbia University,
[3]Environmental and Occupational Health Science Institute

Despite the success of antiretroviral therapy in preventing AIDS-associated dementia, many treated individuals manifest milder neurocognitive diseases (HAND) that impair daily functions and worsen with age. There is no animal model to study mild HAND. We have shown that mice can be infected with chimeric HIV, EcoHIV. Here we report that EcoHIV-infected mice suffer neurocognitive impairment (NCI) shown by impaired learning and memory in behavioral tests. NCI persisted in infected mice for at least 6 months. Genome-wide gene expression profiles of brain tissues from behaviorally impaired mice were compared with profiles of patients with HAND, revealing common dysregulation of pathways controlling neuronal functions involved in learning and memory. Potential epigenetic control of these functions was assessed by chromatin immunoprecipitation with H3K9m3 antibody and sequencing. We found high correlations between chromatin hypermethylation and transcriptional dysregulation for genes associated with synaptodendritic functions. Down-regulation of selected proteins was confirmed by Western blotting. Immunohistochemical analysis of MAP2 revealed diffuse dendritic damage similar to the patients with HAND. Treatment of infected mice with valproic acid prevented NCI, down-regulation of selected synaptic genes and hypermethylation of their promoters. These findings establish EcoHIV-infected mice as a model for brain studies in HAND.

MH083627, DA017618, DA037611

6 Development of Prefrontal Cortex-Amygdala Synaptic Connectivity

Maithe Arruda-Carvalho and Roger L Clem

Icahn School of Medicine at Mount Sinai and the Friedman Brain institute, New York, NY, USA

Background: Early life is marked by high onset and incidence of mental disorders and intense changes in specific brain areas. Prefrontal cortex (PFC) and basolateral amygdala (BLA) form a circuit involved in emotional learning believed to underlie many of these disorders. Anatomical and morphological changes occur in PFC, BLA and their connections during early life, nevertheless how these changes affect PFC-BLA function and plasticity within this circuit is currently unknown.

Methods/Results: Aiming to achieve a more functional understanding of how the maturation of these sensitive areas might underlie normal and pathological brain function, we used optogenetics and whole cell patch clamp to characterize changes in PFC-BLA synaptic connectivity during different stages of development. We infused PFC with adeno-associated virus (AAV) expressing the optogene channelrhodopsin2 (ChR2) and examined the functional output of these neurons by optically stimulating PFC axon terminals in the BLA. C57/BL6 mice were assessed at different developmental stages: infancy (P15), juvenility (P21), early adolescence (P30), late adolescence (P45), and adulthood (P60).

Significance: Understanding how these emotional regulatory circuits functionally mature will help identify the mechanisms responsible for the high incidence of mental disorders during early life and provide tools for earlier and more targeted interventions

Funding: Young Investigator Grant from the Brain and Behavioral Research Foundation (RLC), Icahn School of Medicine (RLC), and Human Frontier Science Program (LT000191/2014-L) (MA-C).

7 High fat diet modulates onset of Multiple Sclerosis through methylomic alterations

Kamilah Castro[1], Mar Gacias[1], Jimmy Hyunh[1], Tamjeed Sikder[1], Yadira Bencosme[1], Corey Watson[2], Andrew Sharp[2], Ilana Katz Sand[3,4], Patrizia Casaccia[1,2,3,4]

[1]Department of Neuroscience, [2]Department of Genetics and Genomic Sciences, [3]Department of Neurology, [4]Corinne Goldsmith Dickinson Center for Multiple Sclerosis,
Icahn School of Medicine at Mount Sinai, New York

Epidemiological studies show that obesity, which correlates with high dietary fat consumption, increases risk of Multiple Sclerosis (MS). In collaboration with the CGD MS Center at Mount Sinai, we investigated the relationship between dietary composition and disease course in MS patients and then used a mouse model of MS, known as experimental allergic encephalomyelitis (EAE) to validate the findings. Our preliminary studies showed that BMI and saturated fat intake positively correlated with circulating monocyte counts in female MS patients but not male. Infiltration of monocytes in the CNS has been linked to lesion formation and MS pathogenesis. As confirmation, we found that female mice given high fat diet had precocious onset of EAE compared to their low fat counterparts. We hypothesize that high fat diet modulates disease onset by activating lipid signaling pathways that alter gene expression, possibly through epigenetic modifications. We have shown that changes in DNA methylation contribute to MS pathology in humans. Mice on high fat diet also show methylomic changes that alter gene expression related to immune function and cell survival. In conclusion, high fat diet modulates the methylome to induce earlier onset of MS.

NIH 2T32MH087004-06

8 Regulation and role of E2Fs in cocaine-elicited behavior

Hannah M. Cates, Elizabeth Heller, Rosemary Bagot, Deena Walker, Catherine Peña, Efrain Ribeiro, Eric J. Nestler

Icahn School of Medicine at Mount Sinai

The underlying mechanism of cocaine abuse and eventual addiction has been studied for decades, and findings have demonstrated hereditary predisposition to drug abuse. It has been posited that this heredity may be due in part to epigenetic regulation of genes in the brain, specifically in the mesolimbic dopamine reward system. Long-lasting changes in neuronal gene expression in the mesolimbic dopamine system appear to underlie some of the persistent neurophysiological changes in the addicted brain. Our group and others have demonstrated that alteration of transcription factor expression regulates drug sensitivity. Our lab has recently performed ChIP- and RNA-sequencing experiments on mouse NAc tissue after repeated investigator-administered cocaine. In depth analysis of these unbiased, genome-wide data deduced members of the E2F family as some of the most prominent upstream regulators of cocaine-induced changes in gene expression and splicing in this brain region. The E2F transcription factors are involved in chromatin modification, gene regulation, and RNA processing. Here we show regulation of E2F expression by cocaine administration, as well as binding of E2F transcription factors at multiple genes. Manipulation of E2F expression in vivo in specific reward brain regions leads to differences in target gene expression as well as regulation of cocaine behavioral response. These findings suggest a crucial role for the E2F family of proteins in the regulation of gene expression underlying cocaine-elicited behavior.

9 Adolescent THC exposure impact on prefrontal cortex structure and function

Benjamin Chadwick[1,2], Dara L. Dickstein[1], Michael M. Miller[1,2], Joseph Laundry[1,2], Tess Veuthey[1], Patrick R. Hof[1], Mark G. Baxter[1] and Yasmin L. Hurd[1,2].

Departments of [1]Neuroscience and [2]Psychiatry

Human studies have linked adolescent cannabis use with increased risk of developing schizoaffective disorders and addiction. Rodent models of adolescent cannabis exposure suggest these associations may be causative. The prefrontal cortex (PFC) is an intriguing locus for such insults as it is continues to develop during adolescence. We utilized our rodent adolescent THC exposure paradigm, which mimics the common pattern of cannabis use in humans, to explore the consequences of THC exposure on the PFC. Our studies focused on neuronal morphology, gene expression and behaviors that are mediated by the PFC. THC exposure altered the arborization and spine density for PFC pyramidal neurons both immediately following treatment in late adolescence and after a period of abstinence in early adulthood. The molecular phenotype of the prelimbic neurons captured by laser microdissection are currently being examined to provide insights about potential mechanisms contributing to the long-term morphological alterations. Behaviorally, THC-treated animals did not exhibit overt changes in decision making behaviors assayed in early adulthood, however, slight changes in components of impulsive action are suggested. Overall, the data to date demonstrate protracted structural alterations in the PFC induced by adolescent THC exposure and ongoing studies will examine the causal relationship to behaviors predictive of vulnerability to schizoaffective disorders and addiction.

Supported by: NIH grant DA030359

10 Nicotine self-administration affects MHb-IPN pathway in rodent

Zuxin Chen and Paul Kenny

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Backgrounds: Nicotine is the major rewarding component in cigaret. But recently more and more evidence show that nicotine is toxic and can cause brain damage. When injected with high dose nicotine for about 1 week, massive degeneration in Medial Habenula-Interpeduncular nucleus pathway was observed in mice or rats brain. But whether nicotine can cause neuronal degeneration or not when it`s volitionally taken by animal is unknown. In this study, we explore this question in a nicotine self-administration model which more accurately mimic nicotine intake in smokers.

Methods: nicotine self-administration model with rats using Med associate operate chamber, MRI (T1 and DTI); Immunostaining and western blot; brain slices electrophysiology recording

Results: Our T1 imaging show that nicotine self-administration rats have smaller volume of Medial habenula, DTI show that that fasciculus retroflexus in these rats have a smaller FA value.

Conclusions: Our data suggest that nicotine also cause neuronal degeneration of the MHb-IPN pathway in this volitional nicotine intake model.

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11 Understanding the Phenotypic Spectrum Underlying Comorbid Epileptic Encephalopathies and Autism Spectrum Disorders (ASD) Using Complementary Genomic and EEG Approaches

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Neurodevelopmental disorders, such as ASD and epilepsies, often present in a comorbid fashion, with ~30% of ASD patients developing epilepsy, and a likewise compelling portion of epilepsy patients presenting with ASD symptomology. Under a neurodevelopmental model of susceptibility, multifactorial mechanisms dynamically incur risk over critical developmental time periods. We suggest that underlying highly comorbid presentations of clinical phenotypes, there are central risk factors that are each highly penetrant and sufficient to produce a disorder in an individual, and that additional loci influence shared neural networks by acting in concert to produce a heterogeneous phenotype. Through analysis of electroencephalographic (EEG) data as well as genomic array, or sequencing data, for 30 patients with epileptic encephalopathies plus behavioral disturbances, or ASD with concurrent epilepsy, we are investigating the role that GABAergic inhibitory-excitatory regulation mechanisms play in the neural infrastructure that precipitates a comorbid phenotype. The chronology of comorbid disease acquisition will be addressed by grouping participants based on age-of-onset and overarching clinical applications, such as early intervention strategies, will be discussed.

Funding Sources: NIMH & ISMMS

12 A functional 3'UTR polymorphism (rs2235749) of prodynorphin affects miR-365 binding and gene expression to influence novelty seeking behavior and positive reinforcement learning

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Genetic factors impact behavioral traits relevant to numerous psychiatric disorders and risk-taking behaviors, and recent studies have indicated that discrete neurobiological systems contribute to such individual differences. In this study, we explored individual genetic differences of the prodynorphin (PDYN) gene relevant to behavioral traits of positive reward sensitivity. Our multidisciplinary approach revealed that rs2235749, a SNP in the 3' UTR of PDYN, significantly affects the binding of miR-365, and is associated with PDYN mRNA stability as well as striatal PDYN mRNA expression in the postmortem human brain. Interrogating a possible functional role of this SNP in vivo, we found a selective association of rs2235749 with novelty-seeking and a strong genotype-dose association with positive reinforcement behavior. Using DREADD in rats we showed that cell-specific inhibition of the activity of NAc shell Pdyn-expressing neurons directly influenced novelty seeking and facilitated self-administration of a natural reward. Overall, this translational study suggests a contribution of ventral striatal PDYN circuitry to novelty seeking and positive reinforcement traits that are influenced by individual genetic differences functionally linked to miRNA epigenetic regulation.

13 Using Genome Editing Approaches to Elucidate the Epigenetic Role of DNMT1 in hiPSCs Derived From a Patient with Schizophrenia

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Background: Schizophrenia (SZ) is a highly heritable (80-85%) neuropsychiatric disorder with a worldwide prevalence of 1%. Genetic studies have identified several genes thought be important in the study of SZ. In particular, a damaging de novo mutation in DNA (cytosine-5)-methyltransferase 1 (DNMT1) was found in one patient with SZ, which in mice has been implicated to play a role in prefrontal cortex neurogenesis, however the molecular details are not fully understood.

Methods: We directly reprogrammed fibroblasts from a SZ patient with a de novo missense mutation in DNMT1 into human induced pluripotent stem cells (hiPSCs). We will characterize the role of DNMT1 in SZ using genome editing technology CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9 (CRISPR-associated nuclease 9).

Results/Conclusion: We will characterize epigenetic DNA methylation and neuronal function in isogenic pairs of DNMT1 hiPSCs derived neurons from a patient with SZ.

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14 Histone monoaminylation in the CNS: implications for novel roles for serotonin in the development and treatment of major depressive disorder

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Antidepressants, such as SSRIs, although reasonably effective, are not always successful in treating major depressive disorder (MDD), hinting at neurotransmission independent mechanisms contributing to its etiology. We recently identified a novel role for extravesicular monoamines in the nucleus of monoaminergic cells, whereby monoamines can be posttranslationally modified to histone proteins. Based on preliminary data, we hypothesize that serotonin accumulation in the nucleus of dorsal raphe serotonergic neurons in MDD leads to alterations in genomic histone serotonylation and depressive behaviors owing, in part, to aberrant patterns of gene transcription in brain. Employing a wide range of biochemical, molecular and behavioral approaches, we are now fully characterizing functions for histone serotonylation, as well as other histone monoaminylation states in the brain to elucidate its role in the context of both normal neurodevelopment and in mental illness. Such novel insights may shed light on the heterogeneous efficacy of standard antidepressants and warrant potential targets for the development of alternative therapeutics aimed at treating MDD.

15 The Role of Lateral Habenula Orexin Recptor 2 in Aggressive Behavior

Meghan Flanigan, Hossein Aleyasin, Mitra Heshmati, Sam Golden, Madeline Pfau, Caroline Menard, Georgia Hodes, and Scott Russo

Many prevalent neuropsychopathologies are characterized by abnormalities in social behavior, including autism, schizophrenia, and mood disorders. In this investigation, we sought to determine the role of lateral habenula orexin receptor 2 in aggressive social behavior. Here we have shown that orexin receptor 2 mRNA is increased in the lateral habenula of aggressive mice four hours following social interaction with respect to non-aggressors. Furthermore, orexin positive neurons in the lateral hypothalamus of aggressors were colocalized with the immediate-early gene cFos to a significantly greater degree than those of non-aggressors 1 hour following social interaction. Subsequent histology experiments revealed that parvalbumin interneurons (PV) in the lHb highly express OxR2, thus providing a putative mechanism by which the generally excitatory neuropeptide orexin can drive the decreases in lHb activity previously associated with aggression. Presently, our data suggest an association between aggressive behavior and increased OxR2 signaling in the lHb and provide a possible mechanism by which increased orexin signaling could serve to dampen lHb excitability during social interactions.

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16 A novel protocol for characterizing long non-coding RNAs in autism spectrum disorders

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Long non-coding RNAs (lncRNAs) are key components of gene regulatory networks and may play a role in autism spectrum disorders (ASD) and other neurodevelopmental disorders. We are developing a novel protocol to sequence full-length lncRNAs in postmortem brains of ASD cases and controls as a first step towards incorporating lncRNA expression profiles into the analysis of gene regulatory networks underlying these disorders.

We have designed a lncRNA capture-seq protocol for sequencing full-length transcripts to identify splice variants and novel isoforms of lncRNAs, particularly those in the vicinity of protein-coding genes implicated in, or candidates of, ASD, intellectual disability or epilepsy.

We are generating full-length cDNA libraries using total RNA extracted from a neuroblastoma cell line and sequencing entire transcripts within single reads on the PacBio RS II platform. We will also hybridize full-length cDNA libraries to lncRNA capture probes to enrich for lncRNA transcripts present in our samples.

Our multi-library sequencing strategy to profile full-length transcripts has been successfully applied in an SH-SY5Y cell line, which is allowing us to refine our lncRNA capture-seq protocol as well as tools for the discovery and characterization of lncRNAs genome-wide.

Our strategy and tools developed for profiling lncRNA expression in ASD brain tissues will be widely applicable to other neurodevelopmental disorders.

Seaver Graduate Fellowship

17 The common functional neural architecture of the major psychiatric disorders

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Background: Epidemiological, phenomenological, family and molecular genetic studies suggest that the five major psychiatric disorders have overlapping aetiology and pathophysiology. The aim of this study was to identify the common neural functional architecture of schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), obsessive compulsive disorder (OCD), and anxiety disorders (ADs).

Methods: We extracted brain coordinates from 542 task-related fMRI case-control studies in SZ, BD, MDD, OCD and ADs comprising observations from 25,626 participants. We used quantitative meta-analytic and meta-regression techniques to identify the common neural nodes implicated in all five disorders and define contribution of age, sex, individual study and cognitive task domains.

Results: Shared transdiagnostic functional alterations (regardless of direction) were observed in three clusters encompassing bilaterally the amygdala, hippocampus, thalamus, striatum, insula perigenual anterior cingulate cortex, posterior cingulate cortex, entromedial prefrontal and the entire lateral prefrontal cortex. There was little evidence for disease specificity and the direction of functional change within the regions identified was primarily attributed to the task being performed.

Conclusions: Our findings suggest that major psychiatric conditions share a common neural architecture and provide a neurobiological explanation for their shared clinical and genetic features.

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18 Signaling states of allosteric crosstalk in mGlu2R/2AR mediated by glutamate antipsychotics

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The mechanism of action of glutamate antipsychotics, a recently-discovered class of drugs to treat schizophrenia, is largely unknown. Glutamate antipsychotics might target the G protein-coupled receptor (GPCR) complex formed by the Gi-coupled metabotropic glutamate 2 receptor and the Gq-coupled serotonin 2A receptor (mGlu2R/2AR), which has been shown to be dysregulated in schizophrenic patients. Glutamate antipsychotics, such as LY379268 (LY37), bind mGluR2 to activate Gi and are also able to activate Gq through the mGlu2R/2AR complex. However the molecular underpinnings of this allosteric crosstalk remain to be elucidated. In this study, we expressed the mGlu2R/2AR complex in Xenopus oocytes together with a reporter ion-channel sensitive to both Gi and Gq activity, and recorded macroscopic current traces elicited following treatment with LY37. We then used a combined analytical and computational approach to derive a molecular kinetic scheme of the mGlu2R/2AR signaling states elicited in response to LY37. Our results suggest that binding of LY37 can push the mGluR2/2AR complex to a Gq signaling state without transitioning through a Gi signaling state first, consistent with a cis model of activation of mGluR2/2AR complex.

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19 Circuit mechanisms of social buffering of chronic stress

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Background: The protective effect of social support for mental health disorders has been widely clinically recognized. Consistently, in rodents the robust benefits of an affiliative conspecific, termed social buffering has also been demonstrated. Primarily, these studies have demonstrated the overwhelming benefit of social support in reducing malfunction of the hypothalamic-pituitary-adrenocortical (HPA) system, the noradrenergic system, and central oxytocin pathways. However, despite the vast clinical evidence of the positive effects of social support in the face of either psychological stress, relatively little (experimental) physiological studies have been performed. Specifically, little is known about changes in intrinsic ionic mechanisms and how resulting circuit functions are beneficially altered within the mesocorticolimbic circuit.

Methods: Chronic social defeat stress (CSDS) is a powerful model of social stress induced changes. It induces a long-lasting behavioral syndrome that includes social avoidance and anhedonia. Utilizing retrograding viral labeling I have examined intrinsic changes in neuronal function in response to social buffering.
Results: Subjects provided with a littermate companion throughout CSDS paradigm are significantly more able to maintain healthy social behaviors, including avoiding developing social avoidance. Preliminary data reveals a reduction in mPFC-BLA activity.

Conclusion: This raises the exciting possibility that a deeper understanding of the cellular mechanisms and circuits underlying this behavioral model of social buffering will reveal novel sites for beneficial pharmacological intervention.

Funding: NARSAD Young investigator Award

20 Genome Wide Analysis of Cell-type Specific Chromatin Structure in Schizophrenia

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Background: Schizophrenia (SCZ) is a polygenic disorder resulting from the combined action of alleles of more than one gene. Genome Wide Association Studies (GWAS) have, thus far, identified 108 genetic risk loci associated with SCZ, the vast majority of which (>90%) are found within non-coding sequences of the genome, and are hypothesized to exert their effect on genes through the modulation of cis-regulatory elements such as promoters, enhancers and silencers. In order to better understand the mechanism through which non-coding variants increase risk for SCZ, we sought to study cell-specific regulatory elements of SCZ patients compared to controls.

Methods-Results: Assay for Transposase Accessible Chromatin (ATACseq) is a technique used for determining genomic regions associated with regulatory activity. We carried out ATACseq on populations of neuronal and glial nuclei isolated by Fluorescence Activated Cell Sorting (FACS) from frozen post-mortem brain tissue. Analysis of our ATACseq libraries indicate high enrichment for brain specific enhancer and promoter sequences. In addition, we observe disease and cell type differences between cases and controls and between neurons and glia, respectively.

Conclusions: By comparing chromatin architecture of glia and neurons from controls to those of SCZ patients, we hope to further our understanding of the genetic mechanisms underlying this complex disease.

Funding: Veterans Affairs Merit grant BX002395 (P.R.)

21 Gold nanoparticle-ligand contrast agents for sub-micron imaging of synaptic features

Jason H. Fuller

PI: Russell W. Hanson

Our ability to better understand neurological disease progression and measure the connectome accurately is hampered by the lack of safe, non-destructive, non-invasive in vivo imaging tools. MRI and PET imaging do not provide the sub-micron resolution needed to image receptor densities or create intricate maps of neural circuitry. In addition, in vivo contrast agents presently used are limited by their specificity, uptake, resolvability, and clearance.

NanoCT can provide 1,000-fold better resolution than current MRI and PET imaging techniques and allows for imaging of new features. Presently we are creating highly-specific nanoCT neurological contrast agents using functionalized gold nanoparticles. We have conjugated to a variety of validated affinity ligands to gold nanoparticles to target various receptors of interest. Currently we are optimizing blood brain barrier traversal and our results are presented here. We hypothesize that development of such reagents can provide a route to quantitatively measure neurotransporter and neuroreceptor distributions non-invasively and non-destructively.

Funding: Icahn School of Medicine at Mount Sinai

22 Exploring the complex interplay between environmental stressors, the gut microbiome and behavior

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Several epidemiological studies have demonstrated that psychiatric disorders are largely influenced by genetic factors. Yet in addition to the genetic predisposition, there is now compelling evidence to support the idea of an interaction between genetic background and environment to ultimately determine the individual response to stress and the vulnerability to developing a mental illness. Recent findings have shown that exposure to physical environmental stressors can impact the stability and diversity of the gut microbiota. Alterations to the composition of the “gut microbiome,” or “dysbiosis,” can result in behavioral changes, due to alterations of the gut-brain axis and subsequent modulation of CNS function. We show here that two different inbred mouse strains with distinct baseline behavioral patterns, differentially respond to the same mild environmental stressors. Depletion of intestinal flora through oral administration of broad-spectrum antibiotics ameliorated depressive-like behaviors in in a strain specific manner. Moreover, fecal transplantation experiments were effective to transfer the behavioral responses of the donors. Collectively, these results suggest that altering the composition of the gut microbiome alone is sufficient to overcome the individual genetic predisposition to develop mood disorders in response to environmental stressors.

23 Reward versus Retaliation and the Hyperactive Mesocorticostriatal Salience Network

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Background: In healthy individuals, impulsive aggressive traits have been linked to hyperactivity of the brain's reward network. Here we asked, is the opportunity to obtain monetary reward more salient than the opportunity to retaliate?

Methods: We compared button presses to obtain money versus button presses to retaliate in 9 males with reactive aggression (RA) vs. 9 male controls, using the functional MRI-adapted Point-Subtraction Aggression Paradigm (fMRI-PSAP), personality tests were also administered. To elicit retaliatory responding, a fictitious player infrequently subtracted money from the participant's earnings. On each trial, participants could choose to increase their own earnings (monetary-reward) or to subtract money from their opponent (retaliate, no monetary gain).

Results: In comparison to controls, RA reported elevated trait anger and negative emotionality (ps<.001), worked more for monetary-rewards (p=.015), but not for retaliation (p>.7). When engaging in reward-driven behavior vs. retaliating, RA individuals exhibited hyperactive brain responses in bilateral putamen and anterior insulae compared with controls (cluster-corrected: puncorrected<.005; >= 86 voxels).

Conclusions: RA individuals were willing to work more for money than for retaliation and exhibited hyperactivity of the brain's mesocorticostriatal salience network. Our findings, in a clinically reactive aggressive sample, lend support to potential interventions in this population to change aggressive behavior through positive reinforcement.

Funding: NIMH (NAK: R01MH090134)

24 Alcohol inhibition of a chemically-activated GIRK2 channel

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Alcohol is widely used and often abused. Yet, the molecular understanding of its action on brain function is poorly understood. Alcohol directly modulates the activity of several ion channels, including the G protein-gated inwardly-rectifying potassium (GIRK) channel. Currently, however, the molecular mechanism underlying alcohol activation of GIRK is poorly understood. We recently created a channel (GIRK2-L257C) that could be chemically activated with alcohol-like cysteine-reacting reagents. Here, we studied the channel gating properties of purified GIRK2-L257C channels in a defined reconstituted system that allowed precise control of the lipids, G proteins and ions. We expressed a truncated cys-less GIRK2-L257C(GIRK2Δ*-L257C), reconstituted purified protein into liposomes and studied its function using a high-throughput potassium flux assay. Reconstitution of GIRK2Δ*-L257C into liposomes exhibited a basal, barium-sensitive flux that was activated by three distinct ligands, Gβɣ G-proteins, alcohol and MTS-HE. Interestingly, MTS-HE-activated GIRK2Δ*-L257C channels were inhibited by propanol in a dose-dependent manner. Inclusion of TCEP (tris(2-carboxyethyl)phosphine), which reduces disulfides, decreased MTS-HE activation but converted the propanol response from inhibition to activation. These experiments reveal that GIRK2 channels can also be inhibited by alcohol, perhaps through a different site, depending on the level of basal channel activation. Elucidating the details underlying alcohol's effects on channel proteins is paramount to developing selective pharmacological tools that could be used in the treatment of alcohol abuse and addiction.

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25 Nuclear export inhibitors avert progression in preclinical models of inflammatory demyelination

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Axonal damage has been associated with aberrant protein trafficking. We examined a newly characterized class of compounds that target nucleo-cytoplasmic shuttling by binding to the catalytic groove of the nuclear export protein XPO1 (also known as CRM1, chromosome region maintenance protein 1). Oral administration of reversible CRM1 inhibitors in preclinical murine models of demyelination significantly attenuated disease progression, even when started after the onset of paralysis. Clinical efficacy was associated with decreased proliferation of immune cells, characterized by nuclear accumulation of cell cycle inhibitors, and preservation of cytoskeletal integrity even in demyelinated axons. Neuroprotection was not limited to models of demyelination, but was also observed in another mouse model of axonal damage (that is, kainic acid injection) and detected in cultured neurons after knockdown of Xpo1, the gene encoding CRM1. A proteomic screen for target molecules revealed that CRM1 inhibitors in neurons prevented nuclear export of molecules associated with axonal damage while retaining transcription factors modulating neuroprotection.

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26 The role of the nuclear lamina in oligodendrocytes

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Background: The differentiation of oligodendrocytes from progenitor cells entails nuclear morphological changes that include extensive chromatin condensation. These changes are lineage specific and distinguish oligodendrocyte nuclei from other cell types in the brain. The nuclear lamina is known to modulate nuclear structure and therefore we hypothesized that it plays an important role in driving the nuclear morphological changes that take place during differentiation.

Methods: In vitro and in vivo models of oligodendrocyte differentiation; Lmna knockout mice; shRNAs; PCR; TRAP-seq; DamID; Confocal imaging.

Results: We show that A-type and B-type lamins are differentially regulated during oligodendrocyte differentiation. To address the role of the nuclear lamina during myelination in vivo, we used the LAMIN A/C knockout mouse. These mice exhibit clinical signs such as tremors and locomotor defects at p21 and p50, suggesting functional defects in the myelin sheath. At the ultra-structural level, the spinal cord of these mice becomes hypo-myelinated at older ages, which is preceded by the loss of heterochromatin in oligodendrocytes. A transcriptional profiling of oligodendrocytes in vivo reveals that the loss of LAMIN A/C causes an increase in transcription factors transcripts levels and a decrease in lipid- and ion- binding proteins.

Conclusions: A-type lamins are important for myelin function and promote the nuclear structural changes that take place during oligodendrocyte differentiation.

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27 Pyramidal cell morphology in seizure onset zone, seizure spread zone and silent cortical areas in patients with parietal lobe epilepsy

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Genetic and acquired abnormalities of neuronal connectivity are thought to underlie many types of human epilepsy. We present detailed, high-resolution structure of human neocortical pyramidal neurons in three salient cortical areas associated with seizures, namely the seizure onset zone (SOZ), the seizure spread zone (SSZ) and the silent area with no seizure propagation, all within the inferior parietal lobule of two patients with epilepsy. The type of seizure locus was determined based on intracranial EEG recording and mapping by stimulation of each subdural electrode. Structural data for layer II/III and layer V neurons were obtained through morphometric analysis of Lucifer Yellow filled neurons obtained from epilepsy surgery. Using confocal laser scanning microscopy, the neuronal morphology, dendritic arbor, and dendritic spine morphology were extracted from scanned image stacks using a custom-designed algorithm (NeuronStudio). Results found the head diameter of thin, and the length of mushroom dendritic spines, to be significantly smaller in the SOZ and SSZ compared to the silent area. The head diameter of mushroom dendritic spines was significantly higher in the SOZ compared to SSZ and the silent area. The volume of mushroom dendritic spines was significantly higher in SOZ compared to SSZ and in SSZ compared to the silent area. The length of thin dendritic spines was significantly lower in the SOZ compared to SSZ and the silent area. These findings provide morphological evidence on how and why the SOZ is more prone to seizures, a necessary step to understand the pathophysiology of this common nervous system disorder.

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28 Role of VGF in Depression-Related Behavior and Antidepressant Efficacy

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Background: VGF (non-acronymic) is a secreted protein and neuropeptide precursor that is robustly regulated by BDNF, NGF and NT-3 in CNS neurons.

Methods: We utilized germline VGF knockout mice and viral-mediated VGF knockdown to explore the global and region-specific roles of VGF in the response to ketamine, a rapid acting glutamatergic antidepressant. We employed intrahippocampal cannulation and infusion to delineate the potential roles of different VGF peptides in social defeat stress, sucrose preference, and the forced swim test (FST).

Results: Mice with germline VGF ablation or viral-mediated VGF knockdown in dorsal-hippocampus show attenuated responses to acute ketamine treatment in FST. Intrahippocampal infusion of antibodies to VGF peptides AQEE-30 and TLQP-21 are pro-depressant and anti-depressant, respectively, in FST and microdefeat stress.

Conclusions: This impaired response to ketamine, in mice with germline VGF ablation or viral-mediated dorsal-hippocampal VGF knockdown, provides direct evidence for a role of VGF in mediating ketamine efficacy, perhaps via the BDNF/TrkB pathway. Varied pro-depressant and anti-depressant effects of anti-AQEE-30 and anti-TLQP-21 antibodies suggest that differential processing of the VGF peptide precursor in the hippocampus may give rise to peptides with opposing effects on depressive behavior.

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29 Histone H3K9me3 methyltransferase Setdb1/Eset/Kmt1e, a potential therapeutic target in psychiatric disorders

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Histone H3K9me3 methyltransferase Setdb1 is associated with repressive chromatin remodeling, but its potential role on neuronal function and behavior remain largely unexplored. We previously reported that transgenic mice (CK-Setdb1) with increased Setdb1 in adult forebrain show antidepressant-like phenotypes, here, we further explore the neuronal function of Setdb1 in a loss-of-function model. Conditional knockout mice (Setdb1-CK-cKO) with ablation of Setdb1 in postmitotic neurons, which are opposite to CK-Setdb1 mice, showed elevated level of anxiety and depression-like phenotype. Strikingly, such phenotype were reversed back to normal in Setdb1-rescue mice, in which Setdb1 was re-introduced to knockout neurons. Interestingly, Setdb1-CK-cKO brain showed both neuronal and glial pathology, including gliosis and loss of perforant path (PP) axonal projection to hippocampus. RNAseq revealed differential transcriptome in Setdb1-CK-cKO brain as compare to wildtype, and GO analysis identified a group of genes highly enriched in Cadherin family including 12 protocadherin-beta (Pcdhb) genes. Ongoing work including H3K9me3 ChIP-seq is to compare epigenomic profiling between Setdb1 knockout and wildtype neurons. In conjunction with data from RNAseq, our goal is to identify genes or functional genomic elements that contribute to affective behaviors through Setdb1-mediated repressive chromatin remodeling in mature brain.

Supported by grants from the NIMH, including P50 Epigenetic Mechanisms of Depression (Dr. Nestler) and R01 Chromatin remodeling in mouse models of depression (PI Dr. Akbarian) and a NARSAD Young Investigator Award to Yan Jiang.

30 Intrinsic Adaptations Underlying Individual Alcohol Drinking Behaviors

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Background: Dopamine (DA) neurons of the ventral tegmental area (VTA) projecting to the nucleus accumbens (NAc) are critical mediators of initial alcohol preference behaviors and can ultimately facilitate the transition into pathological alcohol consumption. We hypothesize that projection-specific cellular adaptations in VTA DA neurons projecting to the NAc (VTA-NAc) underlie individual alcohol drinking behaviors.

Methods: We use a combination of tyrosine-hydroxylase (TH)-Cre mice, viral-mediated gene transfer and electrophysiological techniques to specifically examine cellular adaptations to VTA-NAc DA neurons. We injected retrograding Cre-inducible eYFP into the NAc of TH-Cre mice. Mice then underwent a 2-bottle choice alcohol drinking paradigm that results in low and high alcohol drinking groups. Patch-clamp electrophysiology were performed in eYFP positive cells to determine cellular adaptations.

Results: Low alcohol drinking mice have increased firing in VTA-NAc DA neurons, whereas high alcohol drinking mice have firing rates similar to ethanol naïve mice. Underlying this “normal” firing in high alcohol drinking mice is a new balance between the excitatory hyperpolarization-activated Ih and inhibitory K+ currents. Low alcohol drinking mice have increased excitability to current injections.
Conclusion: These results suggest that following the alcohol drinking paradigm, intrinsic alterations may underlie the cellular adaptations observed in VTA-NAc DA neurons. Further investigations into how DA release and uptake are altered in the NAc are currently being performed.

31 Treatment of EcoHIV-infected Mice with Intranasal Insulin Abrogates Cognitive Impairment and Normalizes Energy Metabolite Alterations Associated with HAND

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HIV-associated neurocognitive disorder (HAND) remains among the most prominent features of chronic infection with HIV, despite almost universal use and success of antiretroviral therapy (ART). Growing evidence supports insulin-mediated signaling pathways as key components in normal cognitive processes. We hypothesized that intranasal insulin administration may also be effective in improving cognitive deficits in HAND. We evaluated this hypothesis using EcoHIV-infected immunocompetent mice, which were shown to reproduce the HAND such as seen in patients on effective ART and manifest neurocognitive impairment (NCI) when tested for learning and memory acuity in water maze. Although insulin treatment (2.4 IU for 9 days) had no effect on virus burden in the brains of EcoHIV-infected mice, it completely reversed their NCI. Similar to human HIV, EcoHIV-infected mice exhibited altered brain metabolite levels including citrate, creatine, myoinositol and glutamate which were partially normalized by insulin. The results highlight the relevance of the EcoHIV model to mild HAND and support the use of intranasal insulin for the treatment of HAND.

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32 Chemogenetic inactivation of anterior cingulate cortex neurons disrupts attentional behavior in mouse

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Background: Attention is a major cognitive function impaired in many psychiatric disorders, but its neural basis is poorly understood. The anterior cingulate cortex (ACC) has been implicated in this process by lesion, pharmacological manipulation, and electrophysiology studies in primates and rats. However, no study has directly tested the causal role of neural activity of the ACC on attentional behavior in mice, where genetic manipulations are possible.

Methods: We developed a novel chemogenetic approach that combines cell-type specific manipulations of neural activity with a translational touchscreen-based attentional behavioral task. Specifically, we virally expressed inhibitory hM4Di designer receptor exclusively activated by a designer drug (DREADD) in the ACC neurons in mice, and examined the effects of this inhibitory action with the 5-choice serial reaction time task.

Results: DREADD inactivation of ACC neurons impaired attention and processing speed. Interestingly, specifically inactivating excitatory neurons in the ACC induced more severe attentional deficits.

Conclusions: We demonstrate that the neural activity of the ACC, especially that of excitatory neurons, contributes to attentional and cognitive behaviors. Our results highlight excitatory-inhibitory balance in the ACC as a key pharmacologic target for modulating attention. This study establishes a foundational chemogenetic approach in a genetically tractable species to dissect specific cell-type and circuit mechanisms underlying attentional behaviors in future studies.

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33 Dissecting Lateral Hypothalamic Input to Midbrain Neurons and its Role in Social Defeat Stress

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Background: Hypocretin (hcrt) originates from the lateral hypothalamus (LH) and regulates reward and stress in the ventral tegmental area (VTA), a region known to mediate depression behaviors.

Method: To study the role of neurons that project from the LH to the VTA (LH-VTA), we use chronic social defeat stress (CSDS), a model of depression that produces susceptible and resilient mice, with electrophysiological, optogenetic, pharmacological and behavioral techniques.

Results: Following CSDS, we found increased firing activity in LH-VTA neurons of susceptible mice when compared to control and resilient mice. Chronically mimicking the increase in firing activity of LH-VTA neurons using channelrhodopsin-2 promotes susceptibility in stress-primed mice. Also, microinfusion of hcrt-1 into the VTA of stress-primed mice induces susceptibility.

Conclusions: These findings suggest that LH-VTA and hcrt may be involved in mediating VTA responses to CSDS. Further studies will define the contribution of LH-VTA hcrt signaling to CSDS-induced depression phenotype.

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34 PsychENCODE: Cis-Regulatory Epigenome Mapping in Schizophrenia

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The majority of genetic risk factors for psychiatric disorders reside in non-coding regions of the genome with largely unknown functions. Recently, the Encyclopedia of DNA Elements (ENCODE) project has characterized functionally relevant parts of the human genome in multiple cell lines and peripheral tissues showing that gene regulatory regions are often cell- and tissue-specific. This led to launching an NIMH-funded PsychENCODE consortium aiming to identify non-coding functional genomic elements relevant to neurodevelopment and mental disorders. The goal of our PsychENCODE project is to construct detailed maps for multiple chromatin modifications in human neurons and glia and subsequently assess the relationship of two of these marks (H3K4me3/H3K27ac) to genetic risk factors for schizophrenia (SCZ) in a cohort of 338 SCZ cases and 315 controls. We focus on post-mortem brain tissue including the prefrontal cortex and anterior cingulate cortex as the most likely sites of the pathological changes related to SCZ. As the cellular milieu of the human brain is complex, our project includes epigenomic profiling of neurons and glia using FACS-based separation of neuronal and non-neuronal nuclei followed by ChIP-seq. These data will be integrated with DNA variation and RNA sequencing profiles from the same brain specimens. The findings of this project will provide an extraordinary opportunity to improve our understanding of gene regulation in the brain and schizophrenia-relevant pathology.

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35 New Optical CNiFERs to Detect Neuropeptides

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Neuropeptides are essential participants in the regulation of neural activity. Although neuropeptides are widely expressed, the mechanisms, dynamics and consequences of neuropeptide release in vivo remain largely unexplored, largely due to a lack of analytical approaches for neuropeptide detection We are developing new biophotonic tools to monitor the release of neuropeptides in real-time in awake animals. We have previously created a cell-based neurotransmitter fluorescent engineered reporter (CNiFER) for detecting acetylcholine (Nguyen, Schroeder et al. 2010, Nature Neuroscience 13:127). CNiFERs are HEK293 cells engineered to express a specific GPCR and a genetically encoded FRET-based Ca2+ sensor, TNXXL. Activation of GPCRs that couple to endogenous Gq G-proteins trigger an increase in cytosolic [Ca2+] through the PLC/IP3 pathway, leading to an increase in FRET. Here, we report on the development of CNiFERs for detecting three neuropeptides; orexin, somatostatin and vasoactive intestinal peptide (VIP). These new CNiFERs provide a unique means to measure neuropeptide release in vivo, which in addition can be combined with complementary imaging techniques, such as genetically encoded Ca2+ indicators.

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36 Characterization of molecular and cellular phenotypes associated with a heterozygous CNTNAP2 deletion using patient-derived hiPSC neurons

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Neurodevelopmental disorders, such as autism and schizophrenia, are complex disorders with a high degree of heritability. Genetic studies have identified several candidate genes associated with these disorders, including contactin-associated protein-like 2 (CNTNAP2). Traditionally, in animal models or in vitro, the function of CNTNAP2 has been studied by genetic deletion or transcriptional knockdown, which reduce the expression of the entire gene; however, it remains unclear whether the mutations identified in clinical settings are sufficient to alter CNTNAP2 expression in human neurons. Here, using human induced pluripotent stem cells (hiPSCs) derived from two individuals with a large (289kb) and heterozygous deletion in CNTNAP2 (affecting exons 14-15) and discordant clinical outcomes, we have characterized neuronal migration and CNTNAP2 expression patterns in hiPSC neural progenitor cells (NPCs), two independent populations of hiPSC-derived neurons and hiPSC-derived oligodendrocyte precursor cells (OPCs). First, we observed exon-specific changes in CNTNAP2 expression in both carriers; although the expression of exons 14-15 is significantly decreased, the expression of other exons is upregulated. Second, we observed significant differences in patterns of allele-specific expression in CNTNAP2 carriers that were consistent with clinical outcome. Third, we observed a robust neural migration phenotype that correlated with diagnosis and exon- and allele-specific CNTNAP2 expression patterns, but not with genotype. In all, our data highlight the importance of considering the nature and precise location of mutations when attempting to connect GWAS studies to gene function.

37 Regional electric field generated by tDCS for the treatment of hallucinations in schizophrenia

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Background: Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that selectively modulates cortical excitability, has been used to ameliorate auditory verbal hallucinations (AVH) in schizophrenia. The aim of this study was to evaluate regional electric field (E-field) in regions of interest (ROIs) previously identified as key nodes in the functional network underpinning AVH. Specifically we examine the E-fields in the dorsolateral prefrontal (DLPFC), anterior cingulate cortex, parahippocampal gyrus, superior temporal gyrus, insula, and hippocampus.

Methods: We simulated the E-field generated by tDCS using an anatomically realistic head model derived from structural T1-weighted MRI images. We sampled the E-field in specific brain ROIs thought to be implicated in AVH.

Results: High E-field occurs in brain regions between the left DLPFC and the left temporoparietal cortex. Our results indicate inward current flow mostly over the left DLFPC induced by anodal stimulation, and outward current flow within the left temporoparietal and occipital regions induced by cathodal stimulation.

Conclusions: This study demonstrates the capability of computational E-field models to provide quantitative insight in the mechanisms of tDCS effects in the treatment of hallucinations in schizophrenia. Such models may help the interpretation of clinical tDCS studies and explore different tDCS montages for improved efficacy in the treatment of the symptoms of schizophrenia.

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38 Bipolar Disorder and Anxiety Disorders show overlapping functional neural signatures

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Background: There is considerable evidence for increased comorbidity between bipolar disorder (BD) and anxiety disorders (AD). Epidemiological studies suggest that up to 45% of patient with BD may meet lifetime criteria for comorbid AD. There is less information about whether this association between BD and AD reflects shared neural underpinnings. The aim of this study was to synthesize evidence from functional magnetic resonance imaging (fMRI) studies in BD and AD to investigate whether there is support for their association at the level of neural circuitry.

Methods: We conducted voxel-based quantitative meta-analysis of the anatomical coordinates of activation from 93 fMRI studies that employed affect processing paradigms and that compared healthy individuals to patients with BD or AD (combining studies of generalized anxiety and panic disorders).

Results: Abnormal hyperactivation in the amygdala/parahippocampal gyrus complex, ventral anterior cingulate, the insula and thalamus were observed both in BD and AD. Additionally, both disorders showed decreased activation in the inferior frontal gyrus and the caudate.

Discussion: Our findings suggest that during affect processing the most consistent abnormalities in BD and AD implicate the same key nodes of the affect processing circuitry and provide a biological explanation for the observed clinical comorbidity.

39 Functional significance and molecular mechanism of protein arginine methyltransferase 5 in oligodendrocyte progenitor cell differentiation

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Symmetric dimethylation of arginine residues on proteins is mediated by protein arginine methyltransferases (PRMTs), is essential for many cellular processes, including transcriptional regulation and RNA processing. In the oligodendrocyte lineage, PRMT5 has been reported to be required for oligodendrocyte differentiation in vitro, but its functional significance and molecular mechanism remains largely elusive. In this study, we identify substrates of PRMT5 in oligodendrocyte progenitors (OPCs), using a proteomic approach. We identified core histones H2A and H4, and the transcription repressor myelin expression factor 2 (MYEF2), the chromodomain helicase DNA binding protein 4 (CHD4) as nuclear binding partners for PRMT5. Using a lentiviral CRISPR/Cas9 system, we validated these interactions. Work in progress utilizing the Plp1-creERT transgenic mouse line will assess the functional importance of PRMT5 at different stages of oligodendrocyte development in vivo. Meanwhile, comprehensive analysis using ChIP-seq and RNA-seq data in cultured cells before and after CRISPR , will provide molecular insights into the genomic distribution of H2AR3me2s and H4R3me2s.

40 Dietary and pharmacological manipulations serve as potential strategies to diminish depressive-like behavior in socially isolated mice

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Depression is the most prevalent mental disorder in the United States. However, only 40-50% of patients respond to current antidepressant treatments, highlighting the need for targeting novel strategies. Using a rodent model of depression, we and others have previously demonstrated that social isolation induced behavioral, transcriptional and ultrastructural changes in oligodendrocytes of the prefrontal cortex (PFC). However, whether such behavioral and molecular changes could be reversed remains unexplored. Here we explored two different strategies, a dietary manipulation and a pharmacological approach. Mice were fed with ketogenic diet or administered a recently identified pro-myelinating compound, clemastine. Both strategies successfully reversed behavioral changes in socially isolated mice. However, while clemastine normalized transcriptional and ultrastructural changes of myelin in PFC, those levels were unaffected when mice were fed with ketogenic diet. Furthermore, clemastine, but not ketogenic diet, induced higher levels of repressive histone methylation, H3K9me3, in oligodendrocyte in vivo. Interestingly, mice fed with ketogenic diet displayed enhanced transcript level of brain-derived neurotrophic factor (Bdnf) in the PFC. Taken together, these results suggest two novel therapeutic approaches in improving depressive-like behavior in mice, yet possibly through distinct molecular targets in different cell types.

41 Emotional learning blunts parvalbumin-interneuron signaling in the basolateral amygdala

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Background: The basolateral amygdala (BLA) is a critical locus of emotional memory encoding. BLA parvalbumin-positive interneurons (PV-INs) have been implicated in fear memory encoding in male animals; however, no studies have investigated whether emotional learning alters synaptic plasticity in BLA PV-INs.

Methods: We utilized conventional and optogenetic-assisted in vitro electrophysiology to measure BLA PV-IN plasticity 24 hours after auditory fear conditioning. Naïve and unpaired animals were used as controls.

Results: We found nucleus-specific alterations of PV-IN plasticity in the BLA. In the lateral nucleus (LA), we found a decrease in the frequency of EPSCs onto PV-INs accompanied by an increase of paired pulse ratios of EPSCs evoked from the cortical pathway. In the basal nucleus (BA), we found an increase in the frequency of IPSCs; current studies are underway to determine the presynaptic source of this increased inhibition. A reduction in intrinsic excitability of PV-INs was observed in both nuclei. In LA pyramidal cells, these effects were accompanied by a reduction of IPSCs as well as reduction in GABA release from PV-INs.

Conclusions: We report for the first time that emotional learning induces plasticity in BLA PV-INs. Although LA and BA PV-INs undergo different forms of plasticity, synaptic alterations in both nuclei serve to blunt PV-IN signaling. We hypothesize that these effects serve to enhance fear memory consolidation by enhancing BLA pyramidal cell ouput.

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42 Aberrant LRRK2 modifies excitatory inputs to dorsal striatal medium spiny neurons at early postnatal ages

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Mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2) strongly predispose humans to an autosomal dominant form of Parkinson's Disease (PD). LRRK2 is enriched in medium spiny neurons (MSNs) of the dorsal striatum, the principal target of dopaminergic neurons that degenerate in PD, but paradoxically LRRK2 expression in striatum peaks during synaptogenesis in early postnatal life. We hypothesize that LRRK2 influences the formation of striatal input-output synaptic circuits such that PD-causing LRRK2 mutations lead to aberrant striatal synaptic development. We evaluated synaptic physiology and molecular organization in dorsal striatum of mice expressing an endogenous G2019S mutation (the most prevalent mutation seen in PD patients, known to cause an increase in kinase activity), mice lacking LRRK2, and mice expressing an endogenous D2017A mutation rendering LRRK2 kinase-dead. At postnatal day 21, MSNs from LRRK2-KO or expressing the G2019S mutation display a significant increase in the frequency of spontaneous excitatory postsynaptic currents compared to WT and D2017A mice. G2019S mice display an increase in the frequency of synaptic release of glutamate onto MSNs, as well as an increase in corticostriatal action-potential mediated activity. These data suggest that at P21 cortical innervation of the striatum yields greater excitation of medium spiny neurons in the presence of mutated LRRK2. These experiments reveal early dysfunction that may predispose the system to degeneration later in life.

43 Striatal RGS4 modulates feeding, metabolism, and obesity susceptibility

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Regulator of G-protein signaling 4 (RGS4) is densely expressed in striatum where it modulates opioid, glutamate, cannabinoid, acetylcholine, and dopamine signaling. Here we demonstrate a novel role for striatal RGS4 in regulating feeding and glucose metabolism associated with vulnerability to diet-induced obesity (DIO). DIO-susceptible rats exhibited increased palatable feeding, decreased locomotor activity, and decreased glucose tolerance relative to DIO-resistant rats. In vivo behavioral imaging via positron emission tomography was used to profile differences in whole-brain metabolic activity between the two strains and revealed significantly lower brain activity in the dorsal striatum in DIO-susceptible rats. Next, transcriptional and protein/receptor profiling in this region revealed significantly greater RGS4 mRNA and protein in DIO-susceptible rats. siRNA-mediated transcriptional downregulation of RGS4 led to significant decreases in feeding, increased locomotor activity and increased glucose intolerance, implicating a causal role for striatal RGS4 in behavioral and metabolic disturbances observed in DIO-susceptibility. Altogether, accumulating data plus our identification of a key functional regulator of RGS4 opens up novel targets for anti-obesity therapies.

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44 Striatal CREM mediates impulsive action and associates with fatal overdose in heroin abusers

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Drug addiction is a complex brain disease influenced by genetic and environmental factors. These factors not only contribute to addiction per se, but also to associated behavioral traits such as impulsivity. In order to determine the neurobiological substrates of impulsivity in the context of addiction, we studied the nucleus accumbens of two rat strains with differing levels of impulsivity and drug self-administration. In the nucleus accumbens core, Crem was significantly reduced in impulsive animals. Furthermore, viral overexpression in the core decreased motoric impulsivity suggesting that Crem region-specifically contributes to behavioral aspects of impulsivity. Next, we sought to determine CREM's role in human impulsivity and substance abuse. A non-coding polymorphism associated with impulsivity, and this relationship was particularly strong in individuals with known substance abuse disorder. In our extensive post-mortem brain collection of heroin abusers, we found an interaction between this polymorphism and CREM expression in the nucleus accumbens. While heroin abuse significantly increased CREM expression overall, this adaptive response was absent in carriers of the variant allele. Additionally, this polymorphism was associated with elevated risk of over-dose and a more rapid progression to fatal overdose. These studies suggest that dysregulation of CREM contributes to impulsivity and potentially accelerates addiction-associated mortality. (Supported by DA033660.)

45 Gut microbiota modulates schizophrenia-related synaptic and behavioral abnormalities induced by prenatal insults

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Schizophrenia affects perception, emotion, and cognition. It has been shown that environmental factors during pregnancy, such as viral infections and severe adverse life events, contribute to the onset of schizophrenia later in life. Signaling through serotonin 5-HT2A receptor (5HT2A) is implicated in cognitive processes. Previous results indicated that the 5HT2A receptor is up-regulated in postmortem frontal cortex of schizophrenic subjects, a pattern that could predispose to schizophrenia. We found up-regulation of 5HT2A expression in three mouse models of prenatal insults: maternal infection with influenza, maternal variable stress, and maternal immune activation. This occurred in association with schizophrenia-related phenotypes. Reduction in dendritic spine density has been reported in the cortex of schizophrenia patients. Our data suggests that up-regulation of 5HT2A occurs in association with a reduction in mushroom spine density on apical dendrites of cortical neurons. This neuronal alteration could be responsible for part of the schizophrenia-related behaviors observed in the adult offspring. Previous findings demonstrate that gut microbiota communicates with the CNS to influence brain development and behavior. Our results suggest that altering the gut microbiota by prenatal insults has behavioral consequences in the adult offspring. These results may help to understand the mechanisms whereby maternal/fetal gene-environment interactions contribute to the onset of schizophrenia later in life.

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46 Evidence Map Linking Plasticity to Working Memory and Psychosis

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Background: Neuroplasticity is the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections. We aimed to derive an evidence map for plasticity dysfunction relating to working memory and psychosis to identify the overlap/gaps in the evidence space.

Methods: We used a multistep process involving (a)interrogating literatures across NCBI databases, (b) identifying all available papers that included the combination of MESH terms “Neuronal-Plasticity”, “Memory-short term”, “Working-memory” and “Psychotic-disorders”, and then (c)using the Protégé system to map both convergence and gaps in knowledge at four levels of plasticity-associated correlates: 1)genetic/molecular processes; 2)synaptic morphology/strength; 3)neuronal excitability; 4)neural network connectivity.

Results: We identified 652 original research articles on working memory and neuroplasticity with most of the evidence converging on level2(62%) followed by level1(39%), level4(2.6%) and level3(0.6%). Within each level evidence focused on the glutamatergic pathway (level1); long-term potentiation(47% level2); firing rate(100% level3) and prefrontal connectivity(29%). Only 77 studies were in humans where the emphasis has been on genetic variation in the COMT and BDNF genes(level1), glutamatergic receptors(level1) and on neural network alterations(level4). The literature that examined the above in connection to psychosis was limited to 5 original papers.

Conclusions: The available evidence base linking working memory dysfunction to plasticity and schizophrenia is woefully limited, identifying a clear gap between animal and human research in this area.

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47 Effect of amygdala lesions on local field potentials in the primate prefrontal cortex during a reward-guided task

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Reward-guided behaviors require functional interactions between the amygdala and the orbital and medial prefrontal cortex (OFC and MFC). In monkeys, bilateral excitotoxic lesions of the amygdala attenuate reward-related and value-related signals of individual neurons in the OFC and MFC (Rudebeck et al., 2013). The responses of single neurons only reflect the local processing and output of an area -- local field potentials (LFPs), however, provide information about population dynamics and the inputs to an area. To better understand the dynamics of the amygdala-MFC-OFC network, we performed time-frequency analysis on LFPs recorded from the OFC and MFC of three monkeys engaged in a stimulus-choice task. Data were recorded before and after bilateral excitotoxic lesions of the amygdala. Our preliminary data reveal that visual stimuli evoke a response in the LFP in the prefrontal cortex. This response is composed of three frequency bands (<2 Hz, 4-20 HZ, 80-200 Hz) and importantly, the LFP power and phase correlates with the reward-value of the visual stimuli. Following bilateral, lesions of the amygdala, the magnitude of the evoked response decreases and its timing is delayed. Future analysis on spike-field coherence will determine the relationship between the activity of single units and the LFP, potentially allowing us to characterize the input and the outputs of this network.

48 Dnmt1-dependent transcriptional control of progenitor differentiation

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Development of the central nervous system requires the generation of multiple cell types, in correct sequence and number. DNA methylation is likely involved in this process, although its role is incompletely understood. Here, we study DNA methylation in oligodendrocyte progenitor cells (OPC), the last one to develop and therefore characterized by fewer rounds of replication prior to differentiation. Lineage-specific excision of Dnmt1 (but not Dnmt3a) in the mid-embryonic period was compatible with survival, but severely impaired proliferation and differentiation, while later ablation did not alter normal development. The role of methylation in OPC was highlighted by high-resolution methylomics and network analysis, revealing the integration of cell cycle and transcription and by the detection of repressive protein complexes containing DNMT1 and the cell cycle regulator E2F4. We suggest a dynamic role of DNMT1 in brain development modulating survival in highly proliferative cells and coordinating proliferation and lineage-specific programs in slower dividing progenitors.

49 Wilm's Tumor 1, a transcriptional regulator, modulates memory flexibility in mice

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Memories can decay through an active form of forgetting called memory interference, although the mechanism for this process is not understood. We identified Wilm's tumor 1 (WT1) as a key protein involved in active forgetting. Loss-of-function WT1 transgenic mice showed enhanced hippocampal LTP, suggesting that WT1 acts as a plasticity suppressor. These mice performed better than wildtype littermates in two hippocampus-dependent tasks: contextual fear conditioning (CFC) and novel object placement (NOP). Interestingly, in a two-task sequential learning protocol (NOP followed by CFC), transgenic mice showed better memory retention for NOP but impaired learning for the subsequent CFC when tested 24 hours (but not 10 days) later. Blockade of receptors for the chemokine CCL2 and IGF2, both of which are regulated by WT1, normalized LTP in WT1 transgenic mice, and the CCL2 receptor antagonist suppressed memory enhancement in the NOP test. These results show that WT1, by regulating CCL2, IGF2, and other possibly other diffusible signaling molecules, actively suppresses plasticity after learning, thereby preserving the ability of hippocampus to encode new memories and maintaining normal memory flexibility.

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50 Developmental nicotinic signaling regulates attention-dependent modulation of long-range frontal-posterior cortical circuits

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Introduction: Visual scenes contain more information than can be processed at a single time. Visual attention, the ability attend salient visual stimuli, is largely modulated through nicotinic acetylcholinergic signaling. Disruptions in this neurotransmission are observed in many neurodevelopmental disorders and result in visual attention deficits. How these perturbations alter activity in neural circuits remains unknown. We recently observed that knock down of Lynx1, an endogenous nicotinic inhibitor developmentally expressed in the anterior cingulate cortex (ACC), induces adult visual attention deficits measured by a translational five choice serial reaction time task (5CSRTT). Here we aim to identify specific ACC circuits contributing to this impairment.

Methods: We assayed attention-dependent neural activity via c-fos immunostaining in Lynx1KO mice subjected to the 5CSRTT and Lynx1 expression with in situ hybridization. For circuit-specific analysis, we injected cholera toxin B subunit (CTb) to produce retrograde circuit labeling.

Results: Correlative c-fos activity mapping revealed disrupted co-activation between the visual cortex (V1) and ACC during the 5CSRTT. CTb-labeled neurons projecting from the ACC to V1, which developmentally express Lynx1, showed decreased c-fos activity in Lynx1KO mice compared to WT matched controls.

Conclusions: Our results suggest that excessive adolescent nicotinic signaling, normally suppressed by Lynx1, disrupts adulthood functional modulation of top-down circuits, as found in ADHD and schizophrenia. Interventions targeting Lynx1/nAChR signaling may facilitate optimal top-down cortical circuit development in such disorders.

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51 Does sex matter? A meta-analysis of higher cognitive function

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Sex differences in human brain structures are often correlated with the development of neuropsychiatric conditions. Brain structures involved in higher cognitive functioning are specifically impaired in cognitive disorders, and these structures have also been suggested to differ in size between the sexes. However, the existing literature on sexual dimorphism is limited and contradictory, raising questions regarding whether sex differences play a role in higher cognitive functions and their associated brain structures.

We carried out a meta-analysis of behavioral data from a large cohort of macaque monkeys from two behavioral tasks testing higher cognitive function. The first was a test of episodic memory dependent on interactions between prefrontal cortex and temporal cortex and the second was a strategy implementation task dependent on ventrolateral prefrontal cortex.

For our current study, we combined data from animals in several experiments tested under identical task conditions and further examined the data by looking at sex as a factor. Our analysis did not show an effect of sex on episodic memory (45 males, 11 females) or strategy implementation (19 males, 6 females). Because we did not find sex differences in our higher-functioning cognitive tasks for monkeys, our research indicates that sex can be ruled out as a factor potentially influencing our behavioral results. This suggests that other aspects of higher cognitive function may be studied independently of sex with the correct study design.

52 Central Control of the Autonomic Nervous System

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Many behavioral disorders, including autism spectrum disorder, schizophrenia, general anxiety disorder, attention deficit disorder, and psychosis, may involve a fundamental deficit in the processing of internal (viscero-sensory) and external (sensory) stimuli. Core deficits in the processing of autonomic nervous system (ANS) signals may cause tonic and/or reflexive autonomic dysfunctions of these disorders, and may contribute to social and behavioral deficits. A better understanding of central autonomic networks may provide greater insight into the neuropathology of behavioral deficits in these disorders. This study aims to identify the neural networks associated with the central control of autonomic regulation and the influence of these networks on mental processes by integrating functional magnetic resonance imaging and physiological monitoring during rest and behavioral tasks. We examined the network-level connectivity patterns attributed to physiological fluctuations at baseline (rest), during sensorimotor processes, and during higher-order behavior with a socioemotional task in neurotypical adults between 18-39 years old (n=20). We found that various regions of the cingulate cortex were commonly recruited in each task and that connectivity between the cingulate cortex and other subcortical structures implicated in ANS regulation were context-dependent.

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53 Role of Helicobacter Pylori (HP) in Gastrointestinal Bleeding (GIB) in Patients Hospitalized for Acute Ischemic Stroke (AIS) in the Nationwide Inpatient Sample

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Background: HP is a well-established risk factor for GIB. Although it is known that the risk of GIB in AIS patients is increased due to exposure to tissue plasminogen activator (tPA), anti-platelets, and anticoagulants, the role of HP is not known.

Objective: To ascertain the relationship between HP and GIB in patients hospitalized with AIS.

Methods: In the Nationwide Inpatient Sample (NIS,years 2000 to 2011), adult hospitalization for AIS was identified by primary diagnosis using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 433.xx-437.1. HP and GIB were identified using ICD-9-CM codes 041.86 and 530.xx-535.xx respectively.Comorbidities were defined by Deyo's modification of Charlson's Comorbidity Index (CCI). Multivariable regression models with outcome of upper GIB were adjusted for age, gender, ethnicity, primary payer, teaching status, location, bed size, CCI and use of NSAIDs and treatment with aspirin, tPA, anti-platelets and anti-coagulants.

Results: Overall 5220246 AIS hospitalizations were identified, out of which 81066 (1.55%) had upper GIB and 4589 (0.09%) had HP. Among the GIB group, prevalence of HP was markedly elevated (19.27% vs. 0.49%, $p<0.0001$). In multivariable analysis, HP was associated with markedly elevated odds of GIB (odds ratio 29.8, 95% CI 24.4-36.5, $p<0.0001$).

Conclusion: Among patients hospitalized for AIS, those with HP had increased risk-adjusted occurrence of GIB. HP examination may assist risk stratification for GIB in stroke patients.

Funding: No

54 ESF-AP1 and KMT1E associated epigenetic mechanisms regulate axon development and connectivity in Cerebral cortex.

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Methylation of histone H3 at lysine 9 (H3K9) is one of the most abundant and stable epigenetic modification involved in gene repression and heterochromatin formation. In mammalian cells H3K9 methyltransferase SETDB1 is in complex with MCAF1 and KAP1, trimethylates H3K9 (H3K9me3). Transgenic mice with increased expression of Setdb1 show antidepressant-like phenotypes in behavioral paradigms (Jiang et. al., 2010). Similarly mice deleted for KAP1 in the adult forebrain exhibit heightened levels of anxiety-like and exploratory activity and stress-induced alterations in spatial learning and memory (Jakobsson et. al 2008). These studies indicate neuronal Setdb1/KAP1 epigenetic silencing machinery participates in the regulation of mouse behavior. To better understand SETDB1 mediated epigenetic mechanism we purified SETDB1 complex from human cells and identified a potential cognitively important factor ESF-AP1.

ESF-AP1 is enriched in cerebral cortex neuronal nucleus. ESF-AP1 is in complex with components of H3K9 methylstransferase KMT1E/MCAF1/KAP1 in human brain and cognitive disease mutation found in ESF-AP1 mutation disrupted this protein complex. Alterations in the expression of axonal connectivity genes were identified in human derived ESF-AP1 haploinsufficient lymphoblastoid cells and mouse NSC34 expressing ESF-AP1 shRNAs. Furthermore, shRNA mediated depleting of Esf-ap1 in mouse somatosensory cortex reduced terminal arborization of callosal axons. We propose that ESF-AP1/KMT1E complex epigenetically regulate genes critical for axon growth and connectivity in cerebral cortex and thus this mechanism is critical for cognitive development.

55 Intrinsic functional connectivity of cognitive networks in Primary-Progressive Multiple Sclerosis

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In Primary-Progressive Multiple Sclerosis (PP-MS) a wide range of cognitive deficits have been reported, affecting processing speed, attention, executive function, working and verbal memory. An inefficient cortical reorganization might play a role in cognitive impairment.

We explored the functional organization of resting state networks (RSNs) involved in cognition in 25 PP-MS patients. All subjects underwent MRI on a 3T scanner. A seed-based analysis of RS functional connectivity and variability was conducted using AFNI for the dorsal attention network-DAN; salience network-SN; executive control network-ECN and default mode network-DMN in the standard (0.01-0.1Hz) and slow (Slow 4: 0.027-0.073Hz; Slow 5: 0.01-0.027Hz) frequency bands.

In the standard frequency band a disrupted connectivity was identified in the DAN (between left_frontal_eye_field and thalamus); SN (between sACC - supragenual_ant_cingulate_cortex - and left_cingulate_gyrus, left_middle_frontal_gyrus, left_inferior_frontal_gyrus). In Slow 5, reduced FC was identified in the DMN (between ACC and thalamus); ECN (between dorsomedial_prefrontal_cortex and left_anterior_cingulate_gyrus); SN (between sACC and left_superior_temporal_gyrus, right_precuneus). In Slow 4 a reduced FC was identified in the DMN (between ACC and thalamus) and in the SN (between sACC and right_posterior_cingulate_gyrus). PP patients showed a significantly higher variability in all the above mentioned RSNs.

These results suggest that in PP-MS patients is present a widespread dysfunction of cortical organization, that involves several RSNs which control cognitive processes.

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

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Background: We have previously identified circulating Interleukin-6 as an important mediator of behavioral response to chronic social defeat stress (CSDS), a stress paradigm that produces susceptible and resilient phenotypes. As microRNAs (miRs) are important regulators of cytokine expression, we sought to examine their role in mediating inflammatory and behavioral response to CSDS.

Methods: Mouse blood was collected following CSDS and four populations of leukocytes were isolated via fluorescence-activated cell sorting (FACS): Ly6chigh and Ly6clow monocytes, neutrophils, and T cells. Total RNA was extracted and miR expression was profiled via quantitative real time PCR (qPCR).

Results: We find that, in both susceptible and resilient mice, CSDS produces an increase in circulating neutrophils coupled with a decrease in B and T cells. Ly6chigh monocyte levels are increased only in susceptible mice. Within this cell population, we identified several miRs that are differentially expressed in susceptible and resilient mice and predicted to target proinflammatory cytokines.

Conclusions: Our results suggest a role for miRs as regulators of stress-induced inflammation and behavioral susceptibility and resilience. We also identify candidate miRs for functional study and potential therapeutic applications.

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57 Sex-Specific Roles of Aromatase in the Human Amygdala

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Background: The enzyme aromatase converts androgens to estrogens and is found in brain regions that play a role in cognitive functions and behaviors across species. Aromatase expression in the human brain has been characterized in-vivo in males and females of different ages, showing a high density of the enzyme in the amygdala in both sexes. Here, we documented the degree to which aromatase availability in the amygdala was related to cognition and personality, positing a sex specific role.

Method: Twenty seven healthy participants (15 females) were recruited from the community for a PET scan with [11C]vorozole to obtain the brain distribution of aromatase availability. Participants preformed verbal memory, non-verbal intelligence, and personality tests prior to imaging. To obtain quantitative data, regions of interest were placed over the amygdala bilaterally.

Results: Results reveal that individual differences in brain aromatase availability in males predicted verbal and non-verbal cognitive performance. However, in females cognitive performance was not related to aromatase availability in the amygdala. The personality trait, Constraint, was related to amygdala aromatase in both sexes, yet driven by sex differences in motivation for Constraint.

Conclusion: For the first time, we demonstrate clear sex-specific roles of aromatase in cognitive performance and personality in humans.

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58 Thalamo-Striatal Dysfunction may underlie comorbidity between OCD and Schizophrenia

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Background: Several lines of evidence suggest that obsessive compulsive disorder (OCD) and schizophrenia (SZ) may be related. Patients with SZ have a lifetime risk of 12% for OCD while patients with OCD carry a 6-fold increased risk for developing SZ. Magnetic resonance imaging (MRI) studies suggest that dysfunction within distributed neural networks is central to the pathophysiology of both disorders. In this study we focused specifically on affect processing and tested the hypotheses that OCD and SZ may present with overlapping pathology within the corresponding neural network.

Methods: We conducted voxel-based quantitative meta-analysis of the anatomical coordinates of activation from 299 functional MRI studies comparing healthy individuals to patients with SZ or OCD.

Results: Within the core affect processing network involving the medial prefrontal cortex (PFC) and limbic and paralimbic regions (anterior cingulate, insula, amygdala complex), patients with SZ and OCD showed similar topographic distribution of abnormalities but in the opposite direction. SZ was associated with widespread under- engagement and OCD was associated with overactivation. Additional activation in OCD was also present in the precentral cortex. Both disorders showed hypoactivation in the caudate nucleus and the thalamus.

Discussion: Our findings highlight dysfunction within the thalamo-striatal system as a possible shared feature between SZ and OCD. This finding is consistent with the role of this system in generating, maintaining and switching between motor and non-motor mental functions.

59 The G-domain of the Joubert syndrome protein ARL13B is required for anchoring to the axoneme and uniform distribution along the cilium

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ARL13B is a membrane-associated small G-protein that localizes along the cilium and functions in ciliary protein transport and signaling. In human, mutations of ARL13B cause Joubert syndrome, a ciliopathy characterized by underdevelopment of the cerebellar vermis and the brainstem.
Using a tandem affinity purification approach and mass spectrometry, we found that ARL13B interacted with tubulin. Mapping of the ARL13B tubulin–interacting region revealed that it is located in the G-domain.
To address the function of the G-domain within the ciliary compartment, we obtained an ARL13B mutant lacking the G-domain (ARL13B-ΔGD). In contrast to the even distribution along the whole cilium in wild-type cells, in Arl13b null (hnn) MEFs ARL13B-ΔGD accumulated at the distal tip and dramatically diminished along the cilium. While the overexpression of ARL13B-ΔGD caused cilium elongation in wild-type cells, it failed to rescue shortened cilia in hnn MEFs.
To test whether ARL13B G-domain is required for anchoring ARL13B to the ciliary axoneme, we performed in vitro pull down using purified axonemes and showed that ARL13B interacts with axoneme through its G-domain. We conclude that the G-domain of ARL13B is not required for trafficking to the cilium but it is indispensable for proper axonemal distribution of ARL13B.

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60 Prediction of ion channel differences between young and aged pyramidal neurons

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Electrophysiological recording and morphological reconstruction of pyramidal neurons from layer 3 prefrontal cortex of young and aged adult rhesus monkeys reveals higher firing rates in aged neurons. Here we use compartmental models to provide insight into the ion channel parameters that underlie excitability differences between these neurons.

We optimize ion channel parameters in a stereotypical pyramidal neuron model. We use differential evolution (DE) to tune parameters that shape the model's response to subthreshold current injection. Then we add 7 voltage- and calcium-dependent channels with free conductance and kinetic parameters and simulate a space-filling set of parameter combinations, providing an overview of potential model outcomes that we use to weight error functions for the suprathreshold optimization. Finally, we perform suprathreshold optimization using DE, resulting in populations of models that fit the target neuron.

We have generated populations of models for 1 aged and 3 young neurons. Linear discriminant and principal component analyses reveal that all neurons can be discriminated in parameter space, and that all models of the aged neuron are separable from all models of the young neurons along the first principal component. Preliminary differences between parameters reveal enhanced L-type calcium and persistent sodium activation in the aged neuron. This result can be associated with the increased firing rates in the aged group.

61 Nicotinic modulation of somatostatin interneurons reactivates plasticity in adult visual cortex

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Background: A network of cortical inhibition is critical for plasticity in visual cortex. Although the role of Parvalbumin (PV)-interneurons on plasticity has been extensively studied, contributions of other GABAergic neurons such as those expressing somatostatin (SST) had largely been ignored. Here we aimed to identify the first molecular and circuit mechanisms governing the regulation of plasticity through SST-interneurons. Enriched in SST-interneurons, Lypd6, a positive nicotinic modulator belonging to the same family as known nicotinic plasticity brake, Lynx1, represents an ideal candidate for plasticity regulation. Here we tested the role of Lypd6 in SST-cells on adult V1 plasticity.

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

Results: Lypd6 expression in SST-interneurons declined dramatically after critical period in V1. Viral over-expression of Lypd6 specifically in adult SST cells, but not in pyramidal neurons, reactivated V1 plasticity, and required α2 nicotinic acetylcholine receptor which is highly enriched in Lypd6+SST-neurons. Lypd6-based plasticity was normalized by chemogenetic activation of PV-interneurons, highlighting a key role of SST->PV disynaptic inhibitory circuits.

Conclusions: Identification of the first molecular and circuit mechanisms of V1 plasticity regulation by SST-interneurons provides novel therapeutic targets for functional recovery.

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*Equal contribution

62 Resting-state functional connectivity predicting fMRI correlates of motor imagery

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Motor imagery (MI) can be defined as the mental simulation of an action without motor execution (ME) and is a powerful tool to study motor function in patients movement limitations and for motor rehabilitation. Resting-state functional connectivity (RSFC) networks are similar to those recruited during diversified tasks. This study aims to investigate whether fMRI-RSFC of brain regions involved in MI is predictive of MI-related activation and ability.

Healthy volunteers (N=31) performed ME and MI of self-paced ball squeezes, during 4 blocks of 30s, followed by a RS-fMRI scan at 1.5T. Seed-based RSFC maps of key MI regions of interest (ROIs) were calculated. Correspondence between RSFC and MI fMRI activity was evaluated by performing a voxelwise correlation analysis between the individual MI parameter estimates and each ROI RSFC map. MI was rated with questionnaires and isochrony index.

MI activation within the SMA and lateral premotor areas was predicted by RSFC with the pre-SMA, prefrontal (R) and inf parietal (R), and ventral premotor (L) ROIs. The strength of RSFC with sup parietal ROIs was predictive of activation in the brain regions correlating with the isochrony index. These results show that RSFC could be a tool to predict brain activation associated with MI ability, which could be used as an indicator of a patient's potential to benefit from MI practice during rehabilitation.

63 Experience-dependent conversion of transient spine into stable spine is gated by Lynx1

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Background: Experience is known to impact the formation of new spines and the elimination of existing stable spines. However, previous studies largely ignored an intermediate group of spines, which are newly formed yet exist prior to new experience. These spines usually retract within days, and rarely transform into stable spines. Here we aimed to identify the mechanisms that gate the conversion of these transient spines into stable spines to provide conceptually novel targets for restoring function. Specifically, we examined to what extent Lynx1, a brake for functional plasticity, impacts experience-dependent modulation of newly-formed-spine fate.

Methods: By chronic two-photon imaging in vivo, we examined spine turnover of apical dendrites of layer5 pyramidal neurons in adult visual cortex of Lynx1 knock-out mice mated with Thy1-GFP-Mline.

Results: In adult Lynx1 knock-out mice, visual deprivation elevated the survival rate of pre-existing young spines formed within 4 days prior to deprivation, but not in WT matched controls. This effect was specific to these pre-existing new spines but not observed in pre-existing stable spines, nor spines newly formed during visual deprivation.

Conclusions: Our study identified a new group of spines (new spines generated just prior to the time of new experience) as a key substrate for circuit plasticity, and Lynx1 as the first modulator of experience-dependent spine fate; providing a novel concept and a target for therapeutic intervention.

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64 Modulation of LRRK2 Kinase Activity by a Fragment of Its COR Domain

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Mutations in the Leucine-Rich Repeat Kinase (LRRK2) gene have been linked to an autosomal-dominant form of Parkinson's disease (PD). LRRK2 is a multi-domain protein that possesses both GTPase and kinase activity, and is known to form dimers in solution. These functions are altered by some of the pathogenic mutations, though it is unknown how this leads to the disease state. Additionally, the mechanism that connects these functions of LRRK2 is unclear. We study the COR domain, the sequential link between the two enzymatic domains to try to understand the regulatory mechanism of LRRK2. Recent studies in bacteria suggest that the COR domain is the interface for LRRK2 dimerization, which is necessary for kinase activity. Using co-IP and immunofluorescence, we confirm an interaction between the mammalian COR domain and full-length LRRK2. Interestingly, we find that the COR domain can modulate LRRK2 kinase activity. We identified a 48-residue fragment of COR that still possesses this modulatory function. Through enzymatic assays, binding studies, and structural modeling, we attempt to uncover the mechanism by which this modulation of LRRK2 kinase activity occurs. This will give us new insight as to how LRRK2 activity is regulated, which in turn may help us develop novel therapeutic strategies in the fight against PD.

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65 PRC2 controls neuronal subtype specification in the adult striatum

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During early brain development the polycomb repressive complex (PRC2) plays a crucial role in defining lineage and cell-type specificity by silencing genes that are specific to other lineages and neuronal cell types. PRC2 exerts its function by placing the H3K27me3 modification at the transcriptional start site of such genes. Continuous expression of core PRC2 complex components in adult neurons suggests a possible role of PRC2 in the maintenance of neuronal differentiated states. We found that loss of PRC2 in adult striatal neurons leads to the derepression of numerous developmental transcription factors that are normally enriched in other highly specialized neuronal cell types. Moreover, this upregulation precedes the downregulation of many medium spiny neuron specific genes, while having no effect on pan-neuronal gene expression. These gene changes are associated with distinct behavioral defects and are accompanied by slow and progressive neurodegeneration. We propose that, similar to its role in early lineage differentiation, the PRC2 complex is essential for preserving postnatal neuronal specialization and is vital to maintaining normal brain function.

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66 Neural Response to Positive Emotion are Associated with Impaired Attention in Depression

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Background: Patients with major depressive disorder (MDD) show impairments in attention and positive information processing. However, it is unclear what brain systems underlie this impaired attention in the context of positive emotion and to what degree attention improves following treatment. In the current study, we examined the brain basis of attention in the context of positive emotion using fMRI. We then examined changes in attention following ketamine treatment.

Methods: 12 subjects with MDD completed a positive emotion identification task involving human facial expressions during fMRI. First, we identified brain responses to happy faces. Subsequently, we examined correlations between clinical measures of attention using the HAMA scale and brain responses to happy faces. Finally, we examined patient reported changes in attention following ketamine.

Results: Neural responses within the posterior cingulate cortex (PCC) decreased in response to happy faces compared to rest. Greater attentional impairment was associated with lower response in the PCC to happy faces. We found that attention improved following treatment with ketamine ($t = 3.954$; $df = 11$; $p < .05$).

Conclusion: Results suggest that reduced PCC activity when processing positive emotion is associated with impaired attention, and that attentional impairment improves after receiving effective antidepressant treatment.

Funding: NIMH, Icahn School of Medicine at Mount Sinai

67 Predicting environmental perturbations of developmental neuroplasticity

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Background: Neurodevelopment is marked by periods of activity-dependent neuroplasticity wherein neural circuitry is optimized by the environment. If these critical periods are perturbed, optimization of function (i.e. visual acuity) can be permanently disrupted. A major clinical and scientific gap is knowledge of environmental insults that disrupt critical period biology. Historically, this knowledge has been limited by a lack of a comparable data shared between perturbagens and in vivo neuroplasticity and a lack of methods to systematically identify connections between the data.

Methods: To address this gap, we derived neuroplasticity signatures by computing differential expression of critical period or Lynx1-KO adult versus WT adult (n=3 C57Bl6, all groups). We computationally matched these transcriptional signatures of in vivo neuroplasticity to >500 public curated case-vs-control disease signatures. Disease enrichments were subset by environmental perturbagen status for further analysis.

Results: We found enrichments of gram-negative (but not gram-positive) bacterial infection signatures with neuroplasticity signatures. We are now testing these predictions in vivo to assess the transcriptional and functional impact on neuroplasticity by gram-negative bacterial infection via the lipopolysaccharide model.

Conclusions: Preclinical validation of this work will yield immediate testable hypotheses of clinical utility and shed light on the understudied impact of environmental perturbation on developmental neuroplasticity.

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68 Differential role of PDE2 in AMPAR-trafficking in D1 vs. D2 medium spiny neurons

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The number of post-synaptic AMPA-receptors (AMPARs) largely determines the strength and duration of synaptic transmission. Trafficking of GluA1-containing AMPARs from intracellular vesicles to the cell surface is regulated in part by PKA and PKG, cyclic nucleotide dependent kinases. Thus, the modulation of dendritic cAMP/cGMP levels determines the activity of PKA/PKG and is tightly coupled to GluA1-surface expression. Phosphodiesterase-4 (PDE4), an enzyme that degrades cAMP, controls dopamine-induced GluA1-membrane insertion. Here we asked whether additional PDEs expressed in striatal medium spiny neurons (MSNs) also regulate GluA1-membrane insertion. We combine live-cell imaging of cAMP/cGMP dynamics, along with GluA1-trafficking measurements and computational modeling of signaling to explore the contribution of each PDE to GluA1-trafficking in MSNs. We found that inhibiting PDE2, a highly expressed striatal PDE, increases GluA1-membrane insertion in D1-MSNs. Inhibiting PDE1, a dual-specificity cAMP/cGMP PDE, resulted in a counterintuitive decrease in dopamine-induced cAMP levels and GluA1-membrane insertion. This decrease was due to the allosteric activation of PDE2 by cGMP, as simultaneous inhibition of both PDE1 and PDE2, or expression of PDE2-mutants abolished the decrease in GluA1-membrane insertion. Intriguingly, inhibition of PDE2 in D2-MSNs promoted the removal of surface-AMPAR irrespective of stimulation of adenosine-2A agonists (Gs-GPCR) or D2R agonists (Gi-GPCR), whereas inhibition of PDE1 had no effect. These results reveal how the cell-specific interplay of PDE1 and PDE2 can lead to unanticipated, divergent regulation of dopamine-induced AMPAR-trafficking.

69 Trends and patterns in 15 years of functional MRI research in psychiatric disorders

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Background: The overall patterns of brain dysfunction within and across psychiatric disorders remain fuzzily understood. Systematically organising past research can identify true patterns, paradigm shifts and sources of bias, and will aid future study design.

Methods: We mapped coordinates of 542 task-related fMRI case-control studies in schizophrenia, bipolar disorder, major depression, anxiety disorders and obsessive compulsive disorder to atlas regions (JHU cortical and subcortical atlases). We investigated whether diagnostic category, task domain, direction of effect (controls >or< patients) and use of regions-of-interest influenced the anatomical pattern of results. Chi-squared tests were performed on cross-tables of number of studies reporting at least one coordinate in each atlas region.

Results: Only medial temporal lobe structures and the nucleus accumbens displayed strong effects of task ($p<0.0005$). Effects of diagnosis and contrast-direction were small or absent, with the most significant effect of diagnosis in the caudate ($p=0.0008$), and of contrast-direction in the nucleus accumbens ($p=0.0018$). Region-of-interest studies were more likely to report effects in frontal and temporal regions, with the most significant effect in the amygdala ($p<3*10-6$).

Discussion: Overall, locations of fMRI results are rather unspecific to traditional diagnostic categories. Task design may be important for studying specific subcortical structures, but less so for cortical regions. Region-of-interest studies have tilted the field towards the frontal and temporal lobes.

70 Selective inhibition of BETs as a potential therapeutic for neurodegenerative diseases

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The pro-inflammatory potential of microglia, which is suppressed under normal conditions, is quickly unleashed during brain damage or infection. Although microglial activation is initially protective, excessive or long-lasting activation can be deleterious to the healthy brain. Recently, several neurodegenerative disorders such as Alzheimer's disease have been associated with microglial dysregulation. Microglial activation is initiated by sensing danger signals through receptors followed by subsequent signaling cascades resulting in the assembly of chromatin complexes which promote transcription of key inflammatory genes. In the periphery, one family of epigenetic regulators necessary to this process are the bromodomain and extraterminal domain (BET) proteins which recognize acetylated histones and recruit factors to promote transcriptional elongation. We propose employing chemical inhibition of BETs as a potential therapeutic strategy for neurodegeneration. In peripheral macrophages stimulated with the bacterial component lipopolysaccharide (LPS), applying a BET inhibitor, iBET, suppresses the expression of inflammatory genes and prevents death by sepsis in vivo. Importantly, our studies have shown that BETs are also required for the inflammatory activity of microglia. Application of iBET to microglia stimulated by LPS in vitro prevents the transcription of key pro-inflammatory genes such as Il-6 and Irf9 based on gene expression analysis by microarray. Based on this evidence, we will apply iBET to an in vivo mouse model of microglial dysfunction to explore the utility of BET inhibitors as treatments for neurodegenerative diseases.

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71 Single-Neuron Information Processing and Supporting Circuit Motifs

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Little is known about the kinds of computations performed at the molecular level by signaling networks within individual neurons, and whether these computations can be preserved across different types of neural circuits. Recent research has begun to characterize the information transduction capacity of noisy biochemical signaling networks, and we are motivated by the information theory approaches taken in these studies. We developed a detailed biochemical integrate-and-fire model of an individual neuron; this is based on adrenergic and GABA receptors, as well as other receptors for drugs of abuse such as opiates, as inputs into the cAMP and calcium signaling networks, respectively, as they interface with a Hodgkins-Huxley model to yield an output firing pattern. We observe positive entropy change between stimulus and response signal distributions, which suggests measurable intraneuronal computation. Instances of this model can be linked into known neural circuit topologies to study the properties of their ensemble function and performance. We investigate which circuit motifs (e.g., feed-forward loops) propagate the input neuron's computational signal without introducing distortion, and which motifs act to suppress it, or admit competing signals. In serially connected feed-forward loops we observe robust preservation of signal, under varying input concentrations of norepinephrine and other modulating neurotransmitters. We compare our tested circuit topologies to simple neural circuits found in murine and human brain.

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72 The Parkinson's Disease Associated Mutation LRRK2-G2019S Impairs Synaptic Plasticity in Mouse Hippocampus

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Parkinson's disease (PD) is a major movement disorder characterized by the loss of the dopamine neurons and formation of Lewy bodies. Clinical and pathological evidence indicates that multiple brain regions are affected in PD in a spatiotemporal manner and associated with motor and a variety of non-motor symptoms, including mood, executive function and memory loss. The common PD-associated gene for leucine-rich repeat kinase (LRRK2) is highly expressed in brain regions that are involved with non-motor functions, including the neocortex and the hippocampus, but whether mutant LRRK2 contributes to neuronal dysfunction in these regions is unknown. Here, we used BAC transgenic mouse models of LRRK2 to explore potential non-motor mechanisms of PD. Through electrophysiological analysis of the Schaffer collateral-CA1 synapse in dorsal hippocampus, we find that overexpression of LRRK2-G2019S increases basal synaptic efficiency and disrupts long-term depression (LTD). Furthermore, these effects of G2019S are age-dependent and can be normalized by acute inhibition of LRRK2 kinase activity. In contrast, overexpression of wildtype LRRK2 has no effect under the same conditions, suggesting a specific phenotype for the G2019S mutation. These results identify a pathogenic function of LRRK2 in the hippocampus that may contribute to non-motor symptoms of PD.

Supported by: NIH Grant 1R01NS072359 (RBD, ZY).

73 Exploring key factors determining age at onset of Alzheimer's disease in APOE4 carriers using a cell-based lineage reprogramming approach

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Apolipoprotein E (APOE) is a risk factor for late-onset Alzheimer's disease (AD). Although homozygous APOE4/4 alleles increase AD risk by >10-fold, some elderly APOE4/4 carriers fail to develop dementia; the mechanism by which some individuals escape disease is unknown. Here, we hypothesize that disease onset of APOE4/4 carriers is affected by protective variants and/or environmental factors, especially those that impact the global epigenetic signature of aging. To test this, we will derive human induced pluripotent stem cells (hiPSCs) from APOE4/4 carriers, and then engineer isogenic APOE3/3 control hiPSCs using a genome editing tool; isogenic hiPSCs will be differentiated to astrocytes and neurons for molecular and functional characterization. We will also use a direct differentiation strategy, from APOE4/4 fibroblasts to neurons/ astrocytes, where epigenetic signatures of aging will be preserved. Using RNAseq and DNA methylation analysis, we will examine whether gene expression and epigenetic changes distinguish elderly APOE4/4 carriers from APOE4/4 AD cases. In a parallel study, we are examining whole genome sequence for genetic variants that influence age at onset in APOE4/4 carriers. Together, genetic, epigenetic and cell-based functional approaches will enable us to better understand how the age at onset of AD in APOE4/4 individuals can be modified.

JPB Foundation, ADRC

74 Identifying quiescent stem brain tumor stem cells with H2B-GFP labeling

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Glioblastoma multiforme (GBM) is the most malignant primary brain tumor, with only very limited therapy options. A sub-population of glioma stem cells (GSCs) has been described as the main source of GBM regrowth after therapy. The GSC population may be relatively quiescent in comparison to differentiated progeny. It is the aim of my studies to isolate and characterize quiescent GSCs.

Human GSC lines were transduced with lentiviral vectors for doxycycline inducible Histone2B-GFP (H2B-GFP) expression. The dilution of the H2B-GFP label allows following the division history of cells. Labeled GSC lines were intracranially transplanted into brains of SCID mice. Histological analyses of tumor cells at 2-8 weeks after transplantation revealed the quiescent cell populations, their spatial distribution and proliferation hierarchy. FACS of labeled cells will be used to purify quiescent GSC for culture assays and RNAseq.

The efficiency of H2B-GFP labeling was confirmed in vitro by doxycycline pulse/chase experiments. After intracranial transplantation, GSC grew as infiltrating tumor, preferentially spreading along the corpus callosum. About 10% of cells carry high nuclear GFP label, indicating slower division speed. Histological examination of GSCs and FACS experiments are ongoing.

My preliminary results indicate that the H2B-GFP labeling system permits identification of quiescent GSCs, providing a basis for identification of cellular and molecular features, as well as tumor-forming capabilities of GSC.

75 Light-regulation of TrKB Signaling

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Icahn School of Medicine at Mount Sinai, System Biology Center in NY/PROJ2

BDNF is a crucial neurotrophic factor shown to regulate neuronal survival, and synaptic plasticity. BDNF signaling is initiated by BDNF binging to its receptor TrkB, resulting in TrkB homodimerization, autophosphorylation and recruitment of proteins that activate downstream kinases such as ERK and AKT. Here we present novel light-mediated methods of regulating TrkB signaling that allow temporal and spatial control. TrkB receptor activation in the absence of BDNF was achieved by using blue-light activated plant photoreceptors, CRY2 and CIBN1 that had been genetically modified to promote dimerization. We also developed a light-inactivated TrkB, using MiniSOG, which is a genetically encoded blue-light singlet oxygen generator. For light-mediated TrkB activation, we expressed TrKB-CRY2-mCherry and TrKB-CIBN-GFP into HEK293T cells, which do not express endogenous TrkB receptors. Transfected cells exposed to blue-light showed an increased in phospho-TrkB, phospho-ERK, and phospho-CREB, suggesting light-mediated activation of TrkB activation. Controls maintained in the dark did not show any increased in signaling. For light-mediated TrkB inactivation, blue-light exposure of cells expressing TrkB-SOG resulted in a decreased in phospho-ERK, and phospho-TRKB after BDNF treatment, whereas controls maintained in dark conditions showed the expected increase in phospho-ERK. Transfected cells were also treated with EGF and exposed to light to show that inactivation of TrkB was pathway specific. Our preliminary data shows that light-mediated regulation of TrkB signaling provides an alternative approach to traditional pharmacological agents with superior spatiotemporal control.

76 Ash2L and p300 mediate histone H3 modifications at EGFR during its developmental silencing and re-expression in gliomas

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Glioma tumoral cells commonly share abnormalities in pathways that control proliferation, migration and differentiation of glial/neural progenitors; one such example is the epidermal growth factor receptor (EGFR) pathway. We hypothesized that EGFR silencing during glial differentiation and its aberrant re-expression in gliomas is partly mediated via epigenetic mechanisms at its promoter. To test this hypothesis, we have performed epigenetic analyses at the EGFR promoter, measuring both DNA methylation levels and histone H3 methylation/acetylation levels via chromatin immunoprecipitation (ChIP) using human tissues. Interestingly, we find a conserved DNA methylation pattern regardless of the EGFR levels. In contrast, ChIP analysis revealed enrichment of the activating modifications H3K27ac and H3K4me3 during fetal brain development when EGFR is highly expressed and their loss in adult white matter where EGFR is silenced. In the subventricular zone, where some glial cells continue to express EGFR, these modifications are moderately enriched. We also observe robust enrichment of H3K27ac/H3K4me3 in tumoral specimens. Furthermore, we find significant binding of the histone methyltransferase complex Ash2L and of the histone acetyltransferase p300 only in those samples showing enrichment of H3K4me3 and H3K27ac respectively.

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Aaron Topol

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Icahn School of Medicine at Mount Sinai

Schizophrenia (SZ) is a devastating, complex genetic psychiatric disorder, but converging evidence suggests that microRNA activity may contribute to disease onset. We previously reprogrammed fibroblasts from a small pilot cohort of four SZ patients into human induced pluripotent stem cells (hiPSCs), which were subsequently differentiated into neural progenitors cells (NPCs) and neurons, and observed altered gene expression, aberrant migration and diminished neuronal connectivity relative to controls. Three lines of evidence predicted a key role of miR-9 in SZ hiPSC NPCs. Nanostring nCounter analysis of the 800 most relevant human microRNAs (miRNAs) revealed miR-9, a key regulator of neurogenesis in neural stem cells, to be not only the most abundantly expressed miRNA in human hiPSC forebrain NPCs, but also to be one of the most decreased miRNAs in SZ hiPSC forebrain NPCs. A global regression model integrating genome-wide putative miRNA and transcription factor targets with RNAseq differential gene expression datasets revealed a significant change of miR-9 regulatory activity specifically in SZ hiPSC NPCs. Third, there was a strong correlation between miR-9 expression and miR-9 regulatory activity. We further found that retroviral overexpression of miR-9 is sufficient to ameliorate aberrant migration in SZ hiPSC forebrain NPCs. Stable long-term rescue does not seem to be mediated by known targets of miR-9 but instead by a complex interaction of indirect downstream events.

78 Trouble quieting the mind? Resting-state functional connectivity in reactive aggression

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Background: Individuals prone to reactive aggression can experience difficulty inhibiting aggressive responses in emotionally salient situations, yet little is known about their brain functioning when not challenged.

Methods: We acquired resting-state brain activity using functional MRI in reactive aggressive individuals (RA, n=12) and controls (n=12), who also completed personality questionnaires. The precuneus, a central node of the default-mode-network, was used in a seed-based resting-state functional connectivity analysis.

Results: Compared to controls, RA reported elevated Stress-Reactivity ($p<.001$), and reduced Self-Control ($p<.05$). While resting functional-connectivity within the default-mode-network did not differ between groups, only controls exhibited a conventional anti-correlation between the precuneus and a 'task-positive' region, the right inferior frontal gyrus (IFG), involved in detecting and allocating attention to salient events (cluster-corrected threshold: $p<.05$, ≥68 voxels). Across all subjects, the less negative the right-IFG functional connectivity to the precuneus, the higher the stress reactivity ($rs=.62$, $p=.004$), a result driven by group effect.

Conclusions: This trait x resting connectivity coupling suggests that proneness to stress-reactivity in RA could be related to a compromised ability to tamp down vigilance (precuneus) and attentiveness (IFG) at rest. Thus, failure to inhibit a task-positive region at rest (when it's not needed), may perhaps explain heightened readiness to over-react to salient stimuli in RA.

79 A neuron-specific STK24-protein isoform is associated with cognitive deficits and Alzheimer's disease

Vasiliki-Eirini Karagiorga, John Fullard, Georgios Voloudakis, Amanda C. Mitchell, Anastasios Georgakopoulos, Pavel Katsel, Stella G. Giakoumaki, Venu M. Pothula, Kristen Brennand, Panos Bitsios, Schahram Akbarian, Nikolaos K. Robakis, Vahram Haroutunian, Panos Roussos

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Background: Serine/threonine-protein kinase 24 (STK24) functions upstream of the mitogen-activated protein kinase cascade. The isoform a (STK24-a) is exclusively expressed in neurons. Previous Genome-wide Association Studies (GWAS) have reported association of STK24 variants with educational attainment and Alzheimer's disease (AD).

Methods-Results: We examined the association of STK24 risk variants with cognitive and molecular traits. The rs3783006 STK24 risk variant, lying within an enhancer that physically interacts with the promoter of the STK24-a isoform, is associated with:
(1) Worse cognitive performance in a sample of 1493 healthy individuals;
(2) Higher clinical dementia rating in a postmortem cohort of neuropathologically confirmed AD cases (n=426) and controls (n=229);
(3) Decreased protein levels of markers related to neuroprotection and synaptic function in postmortem brain tissue of AD cases (n=61) and controls (n=49);
(4) Lower STK24-a gene expression in the dorsolateral prefrontal cortex and superior temporal gyrus. Moreover, quantitative western blotting analysis in human brain tissue revealed that AD cases had lower STK24-a protein abundance.

Conclusions: Our findings suggest a potential neuroprotective role for the STK24-a protein isoform in the human brain, introducing it as a putative therapeutic target.

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80 Sex-Specific Effects of Adolescent Social Isolation on Cocaine-elicited and Anxiety-like Behavior In Adult Mice

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Adolescent stress results in long-term changes in behavior, suggesting that adolescence is another critical period of development. Adolescent social isolation (SI) increases preference for drugs of abuse in males. Few studies have investigated if there are sex differences in the response to adolescent stress. We identify changes in cocaine-elicited and anxiety-like behavior in males and females exposed to SI. Mice were isolated or group housed (GH) from postnatal day (P) 22 - P42 when isolated animals were rehoused until adulthood (~P70) to investigate the effects of SI on adult behavior, gene expression and neuronal physiology. SI reversed sex differences in cocaine CPP as well as anxiety behaviors. Additionally, SI reversed baseline sex differences in gene expression in the ventral tegmental area (VTA) and medial amygdala (meAMY). Interestingly, SI decreased the firing rate VTA dopamine neurons of both males and females when compared to their GH counterparts. These data suggest that the adolescent transition is a sensitive period for social stress in both sexes.

81 Dynamical Modeling of Neurite Outgrowth: Explaining How CB1 Receptor Stimulated changes in Multiple Subcellular processes trigger neurite outgrowth

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Department of Pharmacology and Systems Therapeutics

The outgrowth of neurite is a complex cell level process by which a neuron starts to acquire the morphological and functional capability. It is thought that many subcellular processes are involved in neurite outgrowth. A major question is how these subcellular processes act in a coordinated manner to produce this whole cell response. To identify the sub cellular processes associated with neurite outgrowth, Neuro 2A cells was stimulated the CB1 cannabinoid receptor agonist with HU210 for multiple time points (2h,4h,6h and 8h), followed by RNA-seq to identify HU201 triggered differentially expressed genes. The up regulated genes were subjected to Gene Ontology enrichment analysis to predict up regulated sub cellular processes that they belong to. Among the infered subcellular processes are vesicular transport, microtubule organization and elongation and membrane lipid metabolism. Based on these inferences, we built a dynamical multicompartment ODE model that integrate models of membrane production at the cell body, membrane delivery to the axonal tip via microtubule based vesicular transport and axonal microtubule growth. We predicted that such a large-scale model should simulate neurite-outgrowth and CB1 receptor stimulation of the processes. We find that we are able to simulate neurite outgrowth using the subcellular processes identified from the mRNA-Seq experiments and incorporating changes in the levels proteins encoded by upregulated genes leads to significant increases in the rate of neurite outgrowth. Details of the simulations will be presented.

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

Hongxing Zhang[1], Dipesh Chaudhury[1], Marshall Crumiller, Barbara Juarez[1], Allyson Friedman[1], Stacy Ku[1], Erin Calipari[1], Alexander Nectow, Ming-Hu Han[1, 2]

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Background: Ventral tegmental area (VTA) dopamine neurons play a key role in determining susceptibility versus resilience to social defeat stress. However, the neural circuit mechanisms that stabilize VTA dopamine neurons activity remain largely unknown. Locus coeruleus (LC) norepinephrine neurons send projections heavily to the VTA, and norepinephrine is implicated in regulating VTA dopamine neuron activity.
Method: In the chronic social defeat model, utilizing electrophysiological and optogenetic techniques, we investigated the functional role of LC-VTA circuit in mediating resilience to social defeat stress.

Results: In vitro recordings showed that LC-VTA neurons fired significantly higher in the resilient subgroup, while these neurons from susceptible mice had a normal firing, as compared to that of control mice. Consistently, in vivo recordings found that LC neurons of resilient animals exhibited higher firing and significantly increased phasic firing events as compared to control or susceptible mice. Furthermore, in susceptible mice, repeated optogenetic activation of LC-VTA neurons reversed social avoidance behavior, and induced homeostatic plasticity of VTA dopamine neurons projecting to nucleus accumbens, a neuronal activity-stabilizing balance between Ih and K+ channel currents seen in the resilient mice.

Conclusions: These studies suggest that LC-VTA projection is a novel neural circuit underlying natural resilience, and may provide a circuit target for depression treatment.

Funding: NIMH and NSFC

83 STAT3 regulates oligodendrocytes development in vivo

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To assess the functional role of STAT3 in oligodendrocytes development in vivo, we generated STAT3 conditional knock-out mice by crossing STAT3flox/flox mice with PDGFαR-CreER mice expressing inducible Cre recombinase (CreERTM) under control of mouse PDGFαR promoter. PDGFαR-CreER induction was performed by gavaging pregnant females with tamoxifen (10mg/20g) at embryonic day 12.5 (E12.5). Conditional ablation of STAT3 does not reduce the number of PDGFαR+ oligodendrocyte progenitors. However, these progenitors can't successfully differentiate into MBP+ mature oligodendrocytes. At E18.5, the majority of progenitors differentiate into highly branched oligodendrocytes with elaborate processes in control (PDGFαR-CreER; STAT3+/+) mice; while the progenitors remain undifferentiated with few simple processes in inducible knock-out (PDGFαR-CreER; STAT3flox/flox) mice. These results strongly suggest that STAT3 regulates the differentiation and maturation of oligodendrocytes, but not the initial specification.

84 Disruption of Cognitive Control in Cocaine Addiction: Evidence from a Resting State Connectome Analysis

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Icahn School of Medicine at Mount Sinai

Background: Cocaine addiction is characterized by a loss of control that is hypothesized to result from both altered motivational drive and impaired cognitive control.

Methods: We measured resting-state fMRI in cocaine users (n=36) and controls (n=35), deriving a whole-brain functional connectome per individual. The connectome was computed following standard procedures: parcellating each brain, calculating functional connectivity between all pairs of regions, and thresholding each connectome. This allowed to investigating functional connectivity defined as the number of connections between each region with all other brain regions (degree). Results presented are preliminary ($p<0.05$, uncorrected).

Results: Compared to controls, cocaine users showed increased functional connectivity in bilateral dorsal caudate, a region linked to compulsive behavior. Greater connectivity of the caudate correlated with increased severity of dependence (right: $r=0.53$; left: $r=0.42$). Functional connectivity was also increased in dlPFC, hippocampus, frontal operculum, and MTG, involved in working memory processes, memory and speech processing. Further, cocaine users showed reduced functional connectivity of prefrontal regions implicated in monitoring and cognitive control, such as dACC, IFG and vmPFC, and of SMA, precuneus and superior parietal lobe, supporting motivated attention.

Conclusions: The observed functional connectomes provide methodologically novel evidence for both potentially disinhibited motivational drive and impairment of prefrontal control in cocaine addiction during baseline resting state, supporting disruption of cognitive control in cocaine users.

Funding: 1R01DA023579 (Goldstein)

85 Gender differences in empathy: in terms of the self-other distinction

Zhiling Zou, Juan Kou, Jin Li

Empathy is ability to identify and understand others' subjective states. Women are always seen having higher empathy capacity than men. However, it is not clear yet what is the difference in the brain when they empathize. The current study aims to invested the gender differences of empathy in terms of self-other distinction with fMRI. 37 Chinese undergraduates (18 females) completed the emotional perspective taking task in the fMRI scanner. In each task trial, participants were instructed to watch a positive (or negative) picture and then rate "how good (or bad) will I feel if I were in this situation?"(self-condition) or "how good (or bad) will he/she feel in this situation? "(other-condition). The self-other distinction can be calculated as the difference of rating score in Other-condition vs. self-condition. Results showed that 1) compared to females, males had similar rating in other-condition but lower emotional rating in self-condition (only for negative stimuli); 2) males had higher neural activation in right precuneus in other-condition compared with self-condition for negative stimuli; 3) the BOLD signal of right precuneus was positively correlated to self-other distinction scores in males. The findings suggested that males show greater self-other distinction when emphasizing, which lead to lower empathy when facing negative stimuli.

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Sinai Neuroscience Outreach Program (SNOP)
(not to be judged competitively)

In celebration of Brain Awareness Week (BAW), the Sinai Neuroscience Outreach Program (SNOP), together with the Center for Excellence in Youth Education (CEYE) and the Friedman Brain Institute, hosted its 3rd annual Brain Awareness Fair on Thursday, March 19, 2015 at Mount Sinai Hospital. Over 50 volunteers, including students, postdocs, faculty, and staff from multiple Mount Sinai departments and centers shared their expertise and enthusiasm for brain health and brain research with local students, parents, and community members. The event attracted over 350 participants ranging in age from 2 - 86. With multiple hands-on activities and exhibits, participants were able to build their own pipe cleaner neuron models, design a brain hat, look at the human brain in 3-dimensions, examine all types of animal brains, and ask Mount Sinai's leading neuroscience experts questions about how our brains can think, feel, see, hear, smell, taste and much more.

GRADUATE PROGRAM INFORMATION

It has been a year of continued success and growth for the neuroscience graduate training program. In comparison with last year's admissions, this year there were increased numbers of applications to both the Graduate School and to the MSTP program, and in both cases such increases were accounted for almost entirely by those applying to neuroscience. This is noteworthy in a general climate of stable or even declining numbers of applications at other institutions. The metrics of those applying to Mount Sinai's neuroscience program this year were simply outstanding, further demonstrating that we are competing with the very best neuroscience programs in the country for an extremely talented and diverse student body. A special thanks to students and faculty alike who helped us in this year's admissions process!

Going forward, there are changes affecting the neuroscience curriculum starting in fall, 2015. First, the General Knowledge (GK) exam has been eliminated school-wide for all training areas. This decision came about, in part, in response to recommendations of the External Advisory Committee, which evaluated all aspects of Mount Sinai's Graduate Program this past summer. Neuroscience students typically took the GK exam--a stand-alone, 2-hr oral examination covering material from the Core course sequence--during the summer/fall between years 1 and 2. Its elimination will ensure a smoother and speedier transition from a focus on Core classes and rotations in year 1 to choosing a preceptor, developing a thesis proposal and carrying out dissertation research which commences in year 2. The written component of the thesis proposal exam is unchanged, and remains identical to the current NIH NRSA proposal guidelines with respect to format and page length. However, the oral examination of the thesis proposal will now include some testing of "general knowledge" of broader concepts and core knowledge related to the subject of the student's thesis research.

Second, there have been ongoing changes to the first-year curriculum for MSTP students, culminating in a new Core class designed specifically for MSTP students. This course will be taken by all MSTP students in year 1 of medical school, thus they will no longer be taking their training area-specific Core class along with PhD students.

Third, there is a continually expanding list of new Advanced course offerings that will be of interest to Neuroscience students (see (http://fusion.mssm.edu/gradschool/courses/course.cfm). A small sampling of these include Comparative Neuroscience (Patrick Hof and Mark Baxter), Advanced Topics in Reprogramming and Neuronal Differentiation (Kristen Brennand), Drug Discovery (Charles Mobbs), Neurodegeneration (Zhenyu Yue) and Introduction to Modern and Emerging Optical Methods (Graham Ellis-Davies) just to name a few. Students, please check regularly for these and many other Advanced Elective courses offered by other training areas that may be of interest to you; Faculty, please consider developing additional Advanced Elective courses in your own particular area of expertise or interest.

There are also some ideas that are in an active planning phase school-wide. First, consideration is being given to developing an Individualized Training Program for each incoming student. While the precise form this would take has not been decided, the idea would be to customize coursework and training based on an incoming student's past experience, perhaps allowing them to opt out of some modules or courses freeing up time to pursue additional Advanced Electives or other training opportunities. Second, alternative courses in Biostatistics and programming are being considered to augment or replace the current first-year Biostats course. Stay tuned for further developments as these ideas progress.

We are again pleased to report that a number of our current graduate students and postdoctoral fellows have successfully applied for fellowship support over the past year. Keep up the great work! It is a significant and prestigious achievement, particularly in this competitive funding climate, is a great help to your advisor, and also helps us to maintain funding of our NIH T32 training programs. It should certainly be a goal of every eligible student to apply for predoctoral grants or fellowships.

We currently have two T32 training grants, one supporting Year 1 and Year 2 Neuroscience students as they complete course work and begin thesis research (4 slots), which has been successfully renewed for 2014-2019. The other T32 supports graduate students (4 slots) and postdoctoral fellows (2 slots) carrying out mental health research. A new T32, submitted in May 2014 to NIA, scored well and is currently being considered for funding. One or more additional T32s are likely to be submitted this May 2015, targeted to NINDS and possibly other institutes, so we ask training faculty to please submit trainee information, biosketches, etc., when requested and in a timely manner, as we assemble these new training grant proposals. In tough financial times, we really need to expand NIH T32 support.

George Huntley and Stephen Salton

2015 UPCOMING EVENTS

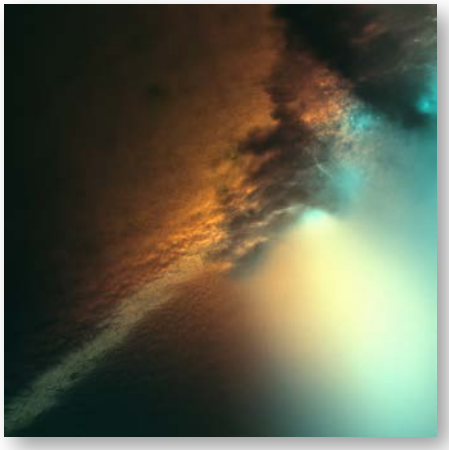

photo by Olivia Engmann

August

Grad School Classes Begin
August 17, 2015

September

6th Annual Postdoc Day
Sept. 18, 2015

October

Convocation
October 1, 2015

BIC 1st Annual Symposium
October 7, 2015

MD/PhD Retreat
October 2-4, 2015

Society for Neuroscience
October 17-21, Chicago

November

December

Grad School Winter Party
December 11, 2015

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