THE

2014

Friedman Brain Institute

and the NEUROSCIENCE TRAINING AREA

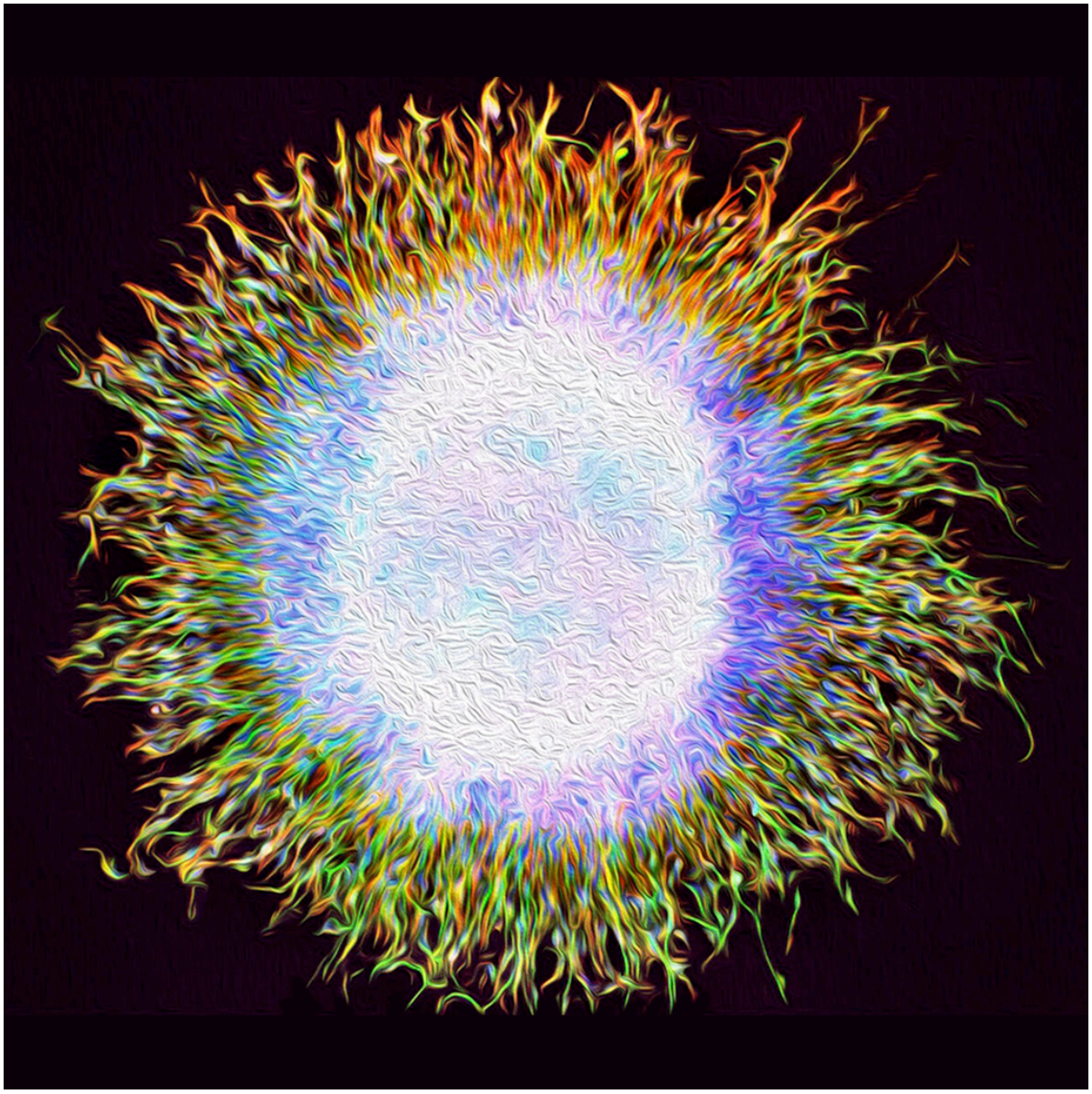

photo by Ngoc Tran

Icahn School of Medicine at **Mount Sinai**

SIXTH ANNUAL NEUROSCIENCE RETREAT

NEW YORK ACADEMY OF MEDICINE 1216 Fifth Avenue

Friedman Brain Institute
Leadership Team

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Paul Slesinger, PhD
Department of Neuroscience

6th Annual Neuroscience Retreat Committee

Retreat Organizers:
Rita Goldstein, PhD (Brain Imaging Center) and **Andrew Chess, PhD** (Genetics and Genomic Sciences and Neuroscience)

Retreat Administrators:
Marie Kopp, Celeste Reyes, Jenny Rivera and Veronica Szarejko

6th Annual Neuroscience Retreat

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

May 13, 2014

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6th Annual Neuroscience Retreat

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

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Neuroscience Retreat Schedule

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

NO FOOD OR DRINKS (OTHER THAN WATER) ARE ALLOWED IN AUDITORIUM

OPENING REMARKS AND ANNOUNCEMENTS (HOSACK HALL):

9:30am..... **Dr. Rita Goldstein** (Brain Imaging Center)

9:35am..... **Dr. Eric J. Nestler** (Friedman Brain Institute and Neuroscience)

10:05am..... **Dr. Stephen Salton** (Neuroscience)

10:15am..... **Keynote Address: Dr. Matthew Shapiro** (Neuroscience) *"Selective memory retrieval via interactions between the prefrontal cortex and the hippocampus"*

BREAK.....10:55am - 11:05am

SESSION 1

11:05am..... **Dr. Hirofumi Morishita** (Psychiatry, Neuroscience, and Ophthalmology), Chair I

11:10am..... **Mafalda Barbosa** (Psychiatry and Genetics and Genomic Sciences) "*Searching for genes implicated in the Rett-like phenotype spectrum using whole exome sequencing (WES)*"

11:25am..... **Hala Harony-Nicolas, PhD** (Psychiatry) "*A novel Shank3-deficient rat model to understand the neural basis of autism*"

11:40am..... **Bryan Denny, PhD** (Psychiatry) "*Examining emotional habituation to repeated negative stimuli in borderline personality disorder patients and healthy controls: Evidence for differential patterns of behavior, neural activity, and functional connectivity*"

11:55pm..... **Elizabeth Lucas, PhD** (Neuroscience) "*Experience-dependent inhibitory plasticity in the lateral amygdala mediates fear learning*"

12:10pm..... **Rosemary Bagot, PhD** (Neuroscience) "*Profiling plasticity in glutatmatergic afferents of the nucleus accumbens in an animal model of depression*"

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

SESSION 2

1:30pm..... **Dr. Nelly Alia-Klein** (Psychiatry and Neuroscience), Chair II

1:35pm..... **Anna Konova** (Psychiatry and Neuroscience) "*Extinguishing Drug Cue Associations in Addiction: Role of the VMPFC*"

1:50pm..... **Barbara Juarez** (Pharmacology and System Therapeutics) "*The role of midbrain dopamine neurons in mediating individual alcohol drinking behaviors*"

2:05pm..... **Henrietta Szutorisz, PhD** (Psychiatry) "*Adolescent THC exposure leads to reward-related behavioral abnormalities in second and third generation offspring*"

2:20pm..... **Nikolaos Daskalakis, MD, PhD** (Psychiatry) "*Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring*"

POSTER SESSION Library 3rd fl.

2:40pm..... Poster Session and Reception Begin

4:40pm..... Award Ceremony for Best Poster, Best Oral Presentation Award and First Place "Call for Images"

5:00pm..... Reception Ends

PLEASE REMEMBER TO RECYCLE YOUR NAME TAGS

Presenters

Searching for genes implicated in the Rett-like phenotype spectrum using whole exome sequencing (WES)

M. Barbosa[1], F. Lopes[2], A. Ameur[3], U. Gyllensten[3], P. Maciel[2], D. Pinto[1]

[1]Departments of Psychiatry, and Genetics and Genomic Sciences, ISMMS, USA;
[2]ICVS, Braga, Portugal; [3]Uppsala University, Sweden

Background: Rett syndrome is a rare neurodevelopmental disorder (NDD) but a common cause of severe intellectual disability in girls. Though Rett remains a clinical diagnosis, mutations in MECP2, CDKL5 and FOXG1 have been identified in Rett and Rett-like patients. Since a significant proportion of Rett-like patients are negative for alterations in these genes, we hypothesize that other genes can cause the disease.

Methods: 22 children and their parents were screened with 720K-arrays and WES. Rare nonsynonymous SNVs and frameshift-indels were selected for further follow-up: de novo, homozygous/compound heterozygous and maternally inherited X-linked variants. The functional impact of variants was predicted using in-silico tools, and gene prioritization considered biological function, genetic/protein interactions, brain expression and KO mice phenotype.

Results: Mutations in NDD genes not yet implicated in Rett were identified in STXBP1, SHROOM4,SLC35A2. Mutations in novel NDD candidate genes were also detected: ZBTB18, GABBR2,SMARCA1. Network analysis reveals that these genes interact by means of genetic/ protein interactions with each other and with the known Rett genes. Genotype-phenotype correlation allows for the delineation of a core phenotype as well as distinctive clinical features that could help guide/interpret genetic testing in future patients.

Conclusions: We expanded the phenotypic spectrum of previously known NDD genes to encompass Rett and identified new candidates for Rett-like phenotypes.

A novel Shank3-deficient rat model to understand the neural basis of autism

Hala Harony-Nicolas[1,2], Ozlem Bozdagi-Gunal[1,2], Rotem Gur[6], Nikolaos Daskalakis[1,], Shlomo Wagner[6], Mark Baxter[3], Joseph D. Buxbaum[1,2,3,4,5]

[1]Seaver Autism Center for Research and Treatment, [2] The Departments of Psychiatry, [3]Neuroscience, [4]Genetics and Genomics Sciences and the [5]Friedman Brain Institute and Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, NY, USA. [6]The Department of Neurobiology, The University of Haifa, Israel

Background: Mutations or deletions in the SHANK3 gene lead to a relatively more common monogenic forms of autism. The underlying mechanisms affected by Shank3 deficiency are not fully identified. We report the production and characterization of a first rat model for autism, the Shank3-deficient rat.

Methods: We are using electrophysiological, biochemical and genome wide transcriptional analyses to study the effect of the disruption in Shank3 on synaptic functioning and are applying behavioral analysis to relate changes to higher order processes.

Results: Shank3-deficient rats display deficits in attention and social recognition memory and alterations in synaptic plasticity in the hippocampus and in the hippocampal-mPFC circuitry. RNA sequencing, proteomic approach, and functional enrichment analysis, showed that decreased Shank3 levels affect distinct biological mechanisms. Shank3 perturbed signatures map to frontal and fetal developmental periods.

Conclusion: Shank3 deficiency alters behaviors relevant to autism and affects synaptic function and associated brain circuitry, which could lead to targets for novel therapeutics.

Funding: The Seaver Foundation, NIMH (MH093725, JDB), and by a gift from William G. Gibson and Paulina Rychenkova, PhD

Examining emotional habituation to repeated negative stimuli in borderline personality disorder patients and healthy controls: Evidence for differential patterns of behavior, neural activity, and functional connectivity

Bryan T. Denny[1], Jin Fan[1,2], Xun Liu[3], Stephanie Guerreri[1], Sarah Jo Mayson[1], Liza Rimsky[1], Antonia S. New[1,4], Marianne Goodman[1,4], Larry J. Siever[1,4], and Harold W. Koenigsberg[1,4]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai
[2]Department of Psychology, Queens College, City University of New York
[3]Institute of Psychology, Chinese Academy of Sciences
[4]James J Peters VA Medical Center

Background: Emotional habituation during repeated exposure to aversive stimuli is an adaptive process and represents a key component of many desensitization-based psychotherapies. Borderline personality disorder (BPD) patients are characterized by severe affective instability and have been shown to exhibit diminished habituation responses, though the neural mechanisms supporting this phenomenon remain unclear.

Method: We repeatedly presented negative images to 19 BPD patients and 25 healthy controls (HC's) and recorded behavioral and neural responses using functional magnetic resonance imaging (fMRI).

Results: HC's habituated behaviorally, whereas BPD's did not. Neurally, BPD patients showed exaggerated insula and amygdala activity to negative images overall relative to HC's. Further, repeated negative image presentation led to increased functional connectivity between insula and amygdala in HC's, but not BPD patients, and this functional connectivity was correlated with increasing behavioral habituation in both groups.

Conclusions: These results suggest potential neurobiological substrates for the diminished emotional habituation shown by BPD patients.

Funding: NIMH R01 MH077813 to HWK and the James J Peters VA Medical Center.

Experience-dependent inhibitory plasticity in the lateral amygdala mediates fear learning

Elizabeth K. Lucas and Roger L. Clem

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

Background: Plasticity in the lateral amygdala (LA) is required for the consolidation of emotional memories. Previous work has demonstrated enhanced excitatory signaling onto LA pyramidal cells after auditory fear conditioning. However, the contribution of inhibitory plasticity to fear memory consolidation is not well understood.

Methods: We used conventional and optogenetic whole-cell patch clamp electrophysiology to measure alterations in inhibition and excitation in LA pyramidal cells and interneurons after auditory fear conditioning.

Results: The frequency of spontaneous and miniature inhibitory postsynaptic currents (IPSCs) in LA pyramidal cells was reduced 24 hours after fear learning. Given that the parvalbumin (PV) subclass of interneurons exerts the most potent inhibitory control over pyramidal cells, we targeted PV cells as a source of the fear-induced IPSC reduction. Using cre-dependent optogenetics, we found a reduction in GABA release from PV cells onto LA pyramidal neurons in paired versus unpaired and naïve controls. These alterations were accompanied by a reduction of excitatory input onto PV cells, suggesting that both intrinsic and extrinsic factors attenuate PV cell activity to decrease LA inhibition.

Conclusions: Our data demonstrate that one mechanism by which emotional memory tips the excitatory:inhibitory balance towards enhanced glutamatergic signaling, and thus enhanced memory consolidation, is by experience-dependent downregulation of PV cell activity.

Funding: NIH Grant MH096678 (EKL) & NARSAD Young Investigator Award (RLC).

Profiling plasticity in glutatmatergic afferents of the nucleus accumbens in an animal model of depression

Rosemary Bagot[1], Ian Maze[2], Immanuel Purushothaman[1], Xiao Chuan Liu[1], Catherine Peña[1], Hannah Cates[1], Eileen Harrigan[1], Bin Zhang[3], Li Shen[1], Eric Nestler[1]

[1]Fishberg Department of Neuroscience, Icahn School of Medicine at Mount Sinai
[2]Laboratory of Chromatin Biology and Epigenetics, The Rockefeller University
[3]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

Background: Glutamate transmission in nucleus accumbens (NAc) is implicated in the pathophysiology of depression. The afferent source of this increased glutamate is not known. NAc medium spiny neurons (MSNs) receive glutamatergic projections from ventral hippocampus (vHIP), medial prefrontal cortex (mPFC) and basolateral amygdala (AMY).

Method: We employed optogenetics and next-generation RNA-sequencing to understand how synaptic and transcriptional plasticity in glutamatergic afferents of the nucleus accumbens drives adaptations in MSNs in a social defeat model of depression.

Results: Enhancement of vHIP inputs to NAc by stimulation of channelrhodopsin (ChR2)-expressing terminals in NAc increases susceptibility whereas the same stimulation of mPFC terminals induces resilience. Inter-region comparisons of global gene expression patterns after CSDS identified co-expression networks of transcripts that show contrasting regulation between mPFC and vHIP in mice resilient to CSDS

Conclusions: vHIP and mPFC projections to NAc exert opposing effects on susceptibility and resilience to CSDS. Network-based analysis of RNA-seq is uncovering the transcriptional signatures of susceptibility and resilience. Our results emphasize the importance of network-based approaches in understanding the complex pathophysiology of depression.

Funding: HDRF, NIH

Extinguishing Drug Cue Associations in Addiction: Role of the VMPFC

A.B. Konova, M.A. Parvaz, V. Bernstein, S.J. Moeller, R.Z. Goldstein

Dept. of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai

Background: Addicted individuals continue seeking drugs despite severe negative consequences, suggesting they may have diminished ability to form or maintain new associations for stimuli previously associated with drugs.

Method: 18 cocaine users and 15 healthy controls learned to associate a cue, the conditioned stimulus (CS), with a drug-related (CS+) or neutral (CS-) image. Extinction training immediately followed and involved repeated unpaired presentation of the CS. Retention of extinction learning was assessed a day later. Skin conductance responses (SCR) and fMRI were acquired throughout.

Results: Differential SCR (CS+>CS-), indexing the conditioned response, decreased over the learning phases ($F=3.78$, $P=0.07$) but did not differ between the groups ($P>0.56$). A similar linear pattern was observed neurally, such that response in the left insula/IFG (BA44) and bilateral VMPFC (BA24,11) increased with extinction learning across subjects. However, the slope of this increase in the VMPFC was greater in controls than in CUD, as indicated by a group × phase interaction. Furthermore, across subjects the success of extinction learning on day 1, as indexed by reduction in SCR, was correlated with the magnitude of VMPFC response on day 2 ($Rs=-0.41$, $P=0.04$).

Conclusions: Results support a role for the VMPFC in the retention of extinction learning for drug cues and highlight respective abnormalities in cocaine users that may contribute to an inability to discontinue drug-seeking.

Funding: NIDAR21DA02062

The role of midbrain dopamine neurons in mediating individual alcohol drinking behaviors

Barbara Juarez[1,2], A.K. Friedman[2], S.M. Ku[1,2], M. Crumiller[1], D. Chaudhury[2], E. Rose[1], J.J. Walsh[1,2], M.H. Han[1,2]

[1]Neuroscience Program, [2]Department of Pharmacology and Systems Therapeutics

Background: Alcohol consumption shows great variability across individuals. To understand the neurophysiological mechanisms that underlie this alcohol drinking variability, we used an inbred mouse model (C57BL/6J) in order to model individual alcohol consumption. We focused on neuroadaptions of the ventral tegmental area (VTA) dopamine (DA) reward circuit. The VTA sends functionally diverse projections to regions altered in reward, thus it is critical to investigate these differences.

Methods: We used a 2-bottle choice drinking paradigm to parse mice into alcohol drinking groups. We performed anesthetized in vivo and projection-specific in vitro electrophysiology to investigate the alterations of VTA DA neurons. We then utilized circuit-dissecting optogenetic tools in order to causally link observed alterations to individual drinking behaviors.

Results: Low alcohol drinking mice display increased in vivo VTA DA activity while high alcohol drinking mice maintain activity similar to EtOH-naïve mice. Optogenetically mimicking this increase in dopaminergic activity reduced high alcohol drinking behaviors. VTA-NAc neurons exhibited similar alterations as seen in our in vivo recordings. Increasing VTA-NAc DA firing in high alcohol drinking mice reduced alcohol preference for 3 hrs, but not 24 hrs.

Conclusions: Failure to engage the VTA DA reward circuit might underlie high alcohol drinking behaviors. Furthermore, there might be projection-specific roles underlying alcohol drinking behaviors.

Funding: T32MH087004

Adolescent THC exposure leads to reward-related behavioral abnormalities in second and third generation offspring

Henrietta Szutorisz, Yanhua Ren, Qammarah Martin, Joseph A. Landry, and Yasmin L. Hurd

Ichan School of Medicine at Mount Sinai, Departments of Psychiatry and Neuroscience

Background: Marijuana (Cannabis sativa) is now used to a greater extent than cigarettes by adolescents. While research efforts have been focused on the direct impact of marijuana, the potential multi-generational consequences remain elusive.

Method: To gain insight into transgenerational effects, we utilize an animal model to examine the consequences of the main psychoactive component of cannabis, delta 9-tetrahydrocannabinol (THC). Our previous studies have shown that parental THC treatment causes a spectrum of behavioral and neurobiological abnormalities in F1 offspring. To address whether subsequent generations are affected, we derived F2 and F3 offspring with paternal THC exposure history.

Results: The response of adult rats to natural reward was tested in palatable food self-administration and sucrose preference paradigms. F2 males with THC history had decreased work effort to self-administer palatable food and showed reduced sucrose intake in a two-bottle choice test. They also extinguished food-seeking behavior faster but had elevated reinstatement of food seeking in response to a previously reward-associated cue. F3 males showed increased food intake on a fixed ratio-1 schedule and increased motivation to obtain the reward in a progressive ratio paradigm. None of these abnormalities were observed in females.

Conclusion: These results suggest that cannabis use can lead to true transgenerational consequences.

Funding: NIH grants DA030359 and DA033660.

Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring

N. P. Daskalakis[1,2], M. J. Meaney[3], R. Yehuda[1,2]

[1] Icahn School of Medicine at Mount Sinai; [2]J.J.Peters Veterans Affairs Medical Center; [3]McGill University

Background: Differential effects of maternal and paternal PTSD have been observed in adult Holocaust survivor offspring in glucocorticoid receptor (GR) sensitivity and vulnerability to psychiatric disorder. This study examined the relative influences of maternal and paternal PTSD on blood cytosine methylation of the GR exon 1F (GR-1F) promoter, and its relationship to GR sensitivity, in 80 Holocaust offspring, with at least one survivor parent, and 15 Jewish controls.

Methods: Participants completed clinical interviews and self-report measures, and blood samples were collected for analysis of GR-1F promoter methylation and cortisol before/after low-dose dexamethasone.

Results: A significant interaction of maternal and paternal PTSD demonstrated that, in the absence of maternal PTSD, offspring with paternal PTSD showed higher GR-1F promoter methylation, whereas offspring with both maternal and paternal PTSD showed lower methylation. CpG site-specific effects of parental exposure, parental PTSD and offspring childhood trauma were also noted. Lower GR-1F promoter methylation was associated with greater cortisol suppression. Hierarchical-clustering analysis confirmed that maternal and paternal PTSD effects were differentially associated with clinical indicators.

Conclusions: For the first time, we demonstrate alterations of GR-1F promoter methylation in relation to parental PTSD. The moderation of paternal PTSD effects by maternal PTSD suggests differential mechanisms for the intergenerational transmission of trauma-related vulnerabilities based on the gender of the exposed parent.

Funding: NIMH-1RC1MH088101-01.

Abstracts

1 Dextromethorphan/Quinidine Combination as a Novel Antidepressant Strategy for Treatment-Resistant Depression

Gabriella M. Ahle[1], Sehrish Moughal Sayed[1], Erica Pazmino[1], Dan Iosifescu[1], Dennis S. Charney[1], James W. Murrough[1]

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

Background: The glutamate N-methyl-d-aspartate (NMDA) receptor has recently emerged as a novel therapeutic target for major depressive disorder (MDD). Recently, a combination of NMDA receptor antagonist dextromethorphan and CYP enzyme inhibitor quinidine (Nuedexta) has been approved by the FDA for treatment of pseudo bulbar affect. The current study tests the efficacy and tolerability of dextromethorphan/quinidine in patients with treatment-resistant depression (TRD).

Methods: The study is an open label 8-week trial of dextromethorphan/quinidine titrated to a maximum dose of 45/10 mg every 12 hours. The primary outcome is change in depression severity from baseline to end of treatment using the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes include self-reports of depression measured using the Quick Inventory of Depressive Symptomotology (QIDS-SR) and anxiety measured using the Hamilton Anxiety Scale (HAM-A).

Results: Of the three subjects who have completed the study thus far, MADRS scores at baseline were 27.67±0.58. Following eight weeks of treatment, MADRS scores decreased by 9 points to 18.67±11.9. QIDS-SR scores decreased by 5.34 points, from 14.67±3.06 to 9.33±6.11. HAM-A scores were reduced by 50% from 16±4.58 to 8±4.58. Thus far, dextromethorphan/quinidine has been well tolerated with no serious adverse events.

Conclusions: Preliminary findings suggest that the dextromethorphan/quinidine combination may be well tolerated and reduce symptoms in patients with T RD.

Funding: Avanir Pharmaceuticals, Inc

2 mPFC-BLA microcircuit involvement in fear conditioning

Maithe Arruda-Carvalho and Roger Clem

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

Background: Aversive memories are extraordinarily robust and long lasting, often leading to fear and anxiety disorders which prove resistant to treatment. Basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are critical regions for the acquisition and expression of fear memories. Particularly, the prelimbic (PL) subregion of mPFC is necessary for fear expression, whereas infralimbic (IL) mPFC is involved in fear inhibition. Although it is known that BLA and mPFC exhibit reciprocal connectivity, characterization of functional synaptic transmission in these pathways and its modulation by emotional learning is lacking.

Methods: PL or IL were targeted through stereotaxic infusion of AAV2-CaMKIIa-ChR2(H134R)-EYFP virus on C57BL/6J mice. Pathway specific synaptic responses were elicited in BLA principal neurons through illumination and recorded using whole cell patch clamp. Electrophysiology was performed in naïve or fear trained animals.

Results: Fear conditioning led to an increase in the excitatory:inhibitory ratio driven by prelimbic inputs, which was absent in the infralimbic pathway. T his change in the excitatory:inhibitory balance recruited by PL projections was mostly driven by an increase in excitation, accompanied by changes in the relative contribution of AMPA and NMDA receptors.

Conclusions: Fear conditioning selectively increases excitation in the PL-BLA pathway, possibly due to an increase in AMPA receptor conductance.

Funding: NARSAD Young Investigator Award (RLC), Human Frontiers Postdoctoral Fellowship (MAC) and seed funds from the Friedman Brain Institute and the Fishberg Department of Neuroscience (RLC).

3 Heterogeneity of microglia-neuron interactions in the adult brain

Pinar Ayata[1], Fan Zhang[1], Philip Feinberg[1], Melanie von Schimmelmann[1], Silas Mann[2], Annie Handler[2], Anne Schaefer[1]

[1]Laboratory of Brain Epigenetics, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY
[2]Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York

Background: Microglia are the resident macrophages of the mammalian brain and serve as the primary line of immune defense. While previously thought to exist in a dormant state until a pathological insult, recent studies have revealed that microglia are highly dynamic and are involved in the surveillance and maintenance of neuronal networks. These functional capacities of microglia have extended our understanding of microglia from a generic “immune sentinel” to a cell type that is intricately involved communication with neurons to ensure brain homeostasis.

Method: Given the heterogeneity of neuronal and glial subpopulations in the brain and of peripheral tissue macrophages, we speculated that microglia assume a specialized expression profile in order to accommodate the needs of a distinct microenvironments. Using translating ribosome affinity purification, we have established genetic profiles of microglial populations from various brain regions in vivo.

Results: The gene expression profiles revealed regional variance in the expression patterns of transcription factors, cell-adhesion molecules, ion channels and neurotransmitter receptors in microglia.

Conclusions: These findings suggest that microglia have very specific cellular identities needed to establish functional communication with distinct neuronal cell types. Functional examination of such regional markers will contribute substantially to the understanding of microglial involvement in brain homeostasis.

Funded by 2012 Director’s New Innovator Award National Institutes of Health, 2011 Research Award by Seaver Autism Center

4 Modeling Aberrant Chain Migration in Schizophrenia

K.G. Beaumont[1], K.J. Brennand[2,3], P. Slesinger[3] and M. Mrksich[1]

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Icahn School of Medicine at Mount Sinai, New York, New York 10029

Background: Schizophrenia (SCZ D) is an incapacitating psychiatric disorder affecting greater than 1% of the population and, while symptoms usually appear during adolescence, SCZ D is believed to be a neurodevelopment condition. One potential, yet unproven, hypothesis is that SCZ D arises, in part, due to abnormal neuronal migration and organization during development of the cerebral cortex.

Method: Recently, human cell-based models have been created by reprogramming skin samples from SCZ D patients into human induced pluripotent stem cells (hiPSCs), which are then differentiated into neural progenitor cells (NPCs) and neurons. These cells are an excellent model system for studying aberrant cell migration in SCZ D, however, cell migration is often a difficult phenomenon to study. We have developed a novel migration assay to address challenges in assaying migration, using engineered surfaces with self-assembled monolayers on gold.

Results: We show that chain migration is significantly lower in SCZ D NPCs than control NPCs and are currently investigating the potential role of Reelin in regulating this aberrant migration.

Conclusions: We can model aberrant chain migration in SCZ D using the unique combination of a novel engineered migration assay and hiPSCs derived from schizophrenic patients.

Funding: HHMI and NIH R21DA032986

5 Improving growth and maturation of hiPSC-derived neurons using engineered culture substrates

Michael Beaumont1, Kristin G. Beaumont[2], Milan Mrksich[2],
Kristen Brennand[1] and Paul Slesinger[1]

[1]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[2]International Institute for Nanotechnology, Northwestern University, Evanston, IL

Background: Currently, little is known about the functional properties of human neurons. Recent developments in hiPSC techniques provide a powerful method for establishing human neuron populations. We are developing a hiPSC-derived neuronal model for the study of drug addiction. One important aspect of this endeavor is to optimize growth conditions to establish mature, stable cultures. We are currently focusing on improving cell/matrix adhesion using controlled adsorption of matrix proteins.

Methods: Neurons from control (non-addicted) subjects are being evaluated to establish the basal electrical properties. To improve our in vitro model, we are using a novel technique for optimizing culture surfaces during neuronal differentiation. T his technique utilizes methyl-terminated self-assembled monolayers (SAMs) that permit strong protein adsorption and result in uniform substrate coverage, in contrast to the heterogeneous adsorption seen in standard protocols.

Results: Blanket-coated SAM surfaces exhibited uniform laminin coverage, in contrast to the heterogeneous patterns found on polyornithine controls. Over the course of a several week differentiation period, neurons grown on laminin-coated SAMs appear to progress much more quickly from immature, electrically inactive phenotypes to more mature phenotypes, compared to polyornithine/laminin.

Conclusions: Improving cell adhesion conditions in cultures of differentiating hiPSC-derived neurons appears to profoundly improve their growth, maturation and stability.

Funding: NIH 5T 32DA007135

6 Epigenetic Control of Synaptic Dysfunction Implicated in HIV-mediated Neurocognitive Impairment in Mice

Alejandra Borjabad[1], Wei Chao[1], Chao-Jiang Gu[1], Boe- Hyun Kim[1], Andrew Brooks[2], Jacinta Murray[3], Susan Morgello[3], and David J. Volsky[1]

[1]Molecular Virology, Infectious Diseases/Department of Medicine, ISMMS;
[2]Rutgers University; [3]Department ofNeurology, ISMMS

Background: HIV-infected people frequently manifest sub dementia neurocognitive impairments known as HAND or HIV-NCI. We developed a chimeric HIV, EcoHIV, which can infect mice. Here we show that HIV-infected mice are cognitively impaired and describe studies on NCI pathobiology in this system.

Methods: Mice were tested for NCI in a water maze and by fear conditioning, then for brain virus burdens and gene expression profiles by Affymetrix cDNA arrays. Mouse and human HAND transcriptomes were compared to identify similarities. Potential epigenetic modifications in infected mouse brain were tested by chromatin immunoprecipitation (ChIP). ChIP-sequencing was used to identify cellular promoters regulated by methylation.

Results: HIV-infected mice showed significant NCI in both behavioral tests. Behaviorally impaired mice and people with HAND shared a pattern of coordinated down-regulation of a large group of genes involved in synaptic plasticity, learning, and memory. Mouse brain microarray data showed high correlation with histone-3 hypermethylation on promoters of key genes associated with memory and learning including CaMKIIA, NGRN, and SYN. Treatment of mice with valproic acid mitigated NCI and epigenetic modulation of selected synaptic plasticity genes tested.

Conclusions: These findings establish EcoHIV-infected mice as a model for study of molecular pathophysiology of HIV induced neurocognitive disease.

Funding: DA017618; MH83627

7 Ablation of peripheral noradrenergic structures alters inflammatory status and response to chronic social defeat stress.

Dana Bregman[1], Georgia Hodes[1], Lena Khibnik[1], Hossein Aleyasin[1], Sam Golden[1], Madeline Pfau[1], Mitra Heshmati[1], Meghan Flanigan1[1], Scott Russo[1]

[1]The Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, 10029

Background: Susceptibility to chronic social defeat stress (CSDS) is associated with heightened peripheral inflammation, although the mechanisms underlying this response are undefined. In vitro studies of leukocytes suggest a role for noradrenergic transmission to hematopoietic niches. The sympathetic nervous system (SNS) provides noradrenergic innervation to these niches that may alter leukocyte populations and functionality in vivo.

Methods: Mice received either saline or 6-hydroxydopamine (6-OHDA), a drug that selectively ablates the peripheral SNS. Mice were then subjected to ten days of CSDS and evaluated in open field and social interaction (SI) tests. Leukocytes were counted following treatment but prior to CSDS.

Results: Immunohistochemical validation demonstrated that peripheral SNS structures in mice treated with 6-OHDA lost tyrosine hydroxylase (TH) reactivity, whereas the peripheral SNS of control mice remained intact. Central noradrenergic structures were unaffected in both control and treated mice. Treated mice showed decreased social avoidance compared to control mice. Pre-defeat leukocyte counts were significantly correlated with SI scores among control animals, but not among treated animals.

Conclusions: Destruction of the peripheral SNS prior to CSDS promotes behavioral resilience. These results suggest a role for the SNS in peripheral inflammation and stress vulnerability.

8 A systems biology approach to drug discovery in autism

Andrew Browne, Elodie Drapeau Ph.D., Hala Harony-Nicolas Ph.D., Joseph Buxbaum Ph.D.

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

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

Results: Three patient/sibling pairs are being reprogrammed to generate iPSCs and neuronal induction is being optimized with H9 cells. RNA sequencing of Shank3 WT and KO rats is being used as a parallel model for identifying candidate drugs based on anti-correlated expression.

Conclusions: Generation of iPSCs from PMS patients offers a powerful tool for disease characterization, drug identification, and screening. By identifying convergent results with parallel models of PMS and ASD, high confidence pathways can be identified that are common across patients.

Funding: NIH and Autism Speaks

9 Neuroserpin, a Proteolytic Brake, Limits Plasticity in Adult Visual Cortex

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Background: Reshaping of cortical connections by sensory experience declines with age. Permissive proteolytic activity regulated by a serine protease, tissue plasminogen activator (tPA), becomes equally restricted in adult brain. Understanding the mechanism for this loss of proteolytic activity is, therefore, a key link for improving function in adult brains.

Method: Using mouse visual cortex (V1) as a model, genetic and pharmacologic manipulations were combined with biochemical and functional analysis in vivo.

Results: We identified that an endogenous inhibitor of tPA, called Neuroserpin remains elevated in the adult V1 in mark contrast to the juvenile period when neuroserpin reduces in an experience-dependent manner. Strikingly, the removal of this proteolytic brake in the adult unmasked robust experience-dependent cortical plasticity, and synergistic reduction of perineuronal net, a plasticity brake enwrapping parvalbumin interneurons. At the upstream of Neuroserpin, an increase of another plasticity brake Lynx1 in the adult act as a gate to limit the experience-dependent Neuroserpin reduction and subsequent molecular and functional plasticity.

Conclusions: These results suggest a novel role of Neuroserpin as a brake for plasticity, and a proteolytic homeostasis as a key target for functional recovery in the adult brain disorders.

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10 RGS4 modulates sensory and affective components of chronic pain states

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Background: Regulator of G protein signalling 4 (RGS4), an intracellular modulator of several monoamine and opioid receptors, is expressed at high levels in pain-associated CNS regions, including the dorsal horn and medial prefrontal cortex (PFC). Here we investigated the role of RGS4 in the sensory and affective components of chronic inflammatory and neuropathic pain states.

Method: Two genetic mouse models were used, global RGS4 knockout, and viral mediated gene transfer for local RGS4 knockout in adult mPFC. We applied two models of inflammatory pain (formalin, or Complete Freund's adjuvant (CFA)) and the spared nerve injury model of neuropathic pain. We then used several behavioural paradigms to assess sensory symptoms (mechanical hypersensitivity and thermal hyperalgesia) and affective components (anxiety and depression like behaviours).

Results: RGS4 knockout mice demonstrated reduced nociceptive behaviours in the second phase of the formalin test. Although thermal nociception in the CFA model was unaffected by genotype, the analgesic efficacy of the delta opiate agonist SNC80 was increased in RGS4 KO. Knockout of RGS4 leads to increased anxiety and depression behaviours in both inflammatory and neuropathic pain models.

Conclusions: RGS4 plays a complex role in modulating the sensory and affective dimensions of chronic pain, and in analgesic responses to delta opioid receptor agonists.

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11 Genetic heterogeneity between subtypes of bipolar disorder in a large international cohort

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Background: Bipolar disorder (BD) is an episodic mood disorder encompassing manic and depressive states. Two main clinical subtypes are bipolar type 1 (BD1) characterized by manic episodes, and bipolar type 2 (BD2) characterized by hypomania and recurrent depressive episodes.

Method: We performed a genome-wide association scan on 6,413 bipolar disorder cases and 12,717 controls. Metaanalysis was performed with prior results from the Psychiatric Genomics Consortium Bipolar Group for a combined sample of 13,868 cases and 19,357 controls. We evaluated the role of structural variation in BD through CNV analyses. Lastly, we used risk score profiling and SNPbased heritability estimation to compare BD subtypes.

Results: We found a total of 8 genome-wide associated regions in the meta-analysis, including previously unreported risk locus on chromosome 10. CNV analyses showed modest enrichment of large, rare deletions in BD. SNP-based heritability estimations showed a significant difference in heritability between BD subtypes (BD1 $h2 = 0.35$,; BD2 $h2 = 0.23$; $p = 0.004$). Polygenic scoring analyses showed BD subtypes can be distinguished from one another using discovery datasets for different psychiatric disorders.

Conclusions: We report the largest GWAS for BD to date, revealing 8 genome-wide significant loci. Our CNV findings support previous findings of a decreased role of CNVs in BD compared to schizophrenia. Lastly, our polygenic scoring and heritability analyses provide the strongest evidence to date for molecular differences between clinical subtypes of BD.

12 Functional role of lateral habenula neurons projecting to ventral tegmental area in modulating susceptibility to social defeat stress.

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Background: We have recently shown a functional role of ventral tegmental area (VTA) dopamine (DA) neurons in encoding for the depressive (susceptible) phenotype in a chronic social defeat (CSD) model of depression (Chaudhury, Walsh et al., Nature 2013). However, the circuit mechanisms by which VTA DA neurons are modulated during the encoding of depression-related behaviours is unknown. The lateral habenula (LHb), a nucleus that functionally integrates signals between limbic forebrain and monoaminergic hindbrain regions, sends robust projections to the VTA. The LHb is known to encode for motivation-, reward- and depression-related behaviours.

Method: We used a combination of in vitro electrophysiology and optogenetics to investigate the role of LHb neurons projecting to VTA (LHb-VTA) in encoding for depression related behaviours.

Results: In vitro slice recordings of LHb-VTA show robust increases in activity in stress-susceptible, but not resilient, mice following exposure to CSD stress. Optical silencing of LHb-VTA neurons during a social interaction test, by activating halorhodopsin (NpHR), of previously stress susceptible mice rapidly induced a resilient phenotype. We are presently investigating the putative mechanism by which LHb inputs modulate the microcircuitry of the VTA.

Conclusion: These studies will provide further insight into the role of putative neural circuits modulating the brain reward circuits in encoding for stress susceptibility.

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13 Histone arginine methylation in the nucleus accumbens in response to repeated cocaine

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Histone methylation on Lys (K) residues has been linked to several neurological and psychiatric disorders, including drug addiction. In contrast to Lys methylation, the functional role of histone Arg (R) methylation in chromatin structure and gene transcription in brain remains underexplored. Histone Arg methylation is catalyzed by a family of enzymes called protein Arg methyltransferases (PRMTs).

First, we investigated the effects of a cocaine regimen (20 mg/kg, i.p., daily for 7 days) on PRMT expression in the NAc of mice. We observed that levels of PRMT6 protein and mRNA, which is responsible for repressive H3R2 asymmetric dimethylation (H3R2me2a), are decreased. To directly study the role of PRMT6 with cocaine, we selectively induced its overexpression (HSV-PRMT6) and knockdown (AAV-PRMT6miR) in the NAc and measured alterations in the rewarding properties of the drug using conditioned place preference (CPP). Then we ran ChIP-Seq to map H3R2me2a genome-wide binding profile after cocaine in NAc. Overlaps of H3R2me2a cocaine-induced ChIP-Seq differential binding sites with other histone marks revealed new target genes such as Src Kinase Signaling Inhibitor 1 (Srcin1/p140cap). To determine the behavioral relevance of Srcin1, we overexpressed Srcin1 (HSV-Scrin1) to study cocaine CPP and measure dendritic spines density on NAc medium spiny neurons (MSNs).

14 Nicotinic modulator Lypd6 regulates plasticity in adult visual cortex

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Background: The ability of the neocortex to adapt based on experience greatly declines after a developmental phase known as the critical period. Recent findings revealed that Lynx1, a protein that inhibits signaling through nicotinic acetylcholine receptors (nAChR), is a brake, limiting visual plasticity following the critical period via increased expression. However, the role of other Lynx family members is unknown. Another member of the Lynx family, Lypd6, has been shown potentiate calcium currents through nAChRs Here, we seek to elucidate the role of Lypd6 in visual plasticity.

Methods: Using mouse visual cortex (V1) as a model, genetic and pharmacologic manipulations were combined with biochemical and functional analysis *in vivo*.

Results: Lypd6 expression declines across critical period in visual cortex and is predominantly localized to lower layer somatostatin interneurons. Further, transgenic over-expression of Lypd6 leads to a persistence of visual plasticity in adult mice. Interestingly, thisthe transgenic mice Mice over-expressing Lypd6 have increased somatostatin-parvalbumin connectivity potentially underlying the phenotype.

Interestingly, viral-over-expression in somatostatin neurons is sufficient to induce adult plasticity.

Conclusions: These results suggest a novel role of LLypd6 in somatostiatin- interneurons as a positive regulator of cortical plasticity. modulates adult visual plasticity at least in part via expression in somatostatin interneurons.

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15 Complete exomic analysis of a Costa Rican autism cohort

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Background: Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders with high prevalence in the population, significant co-morbidity with intellectual disability (ID) and epilepsy, and largely unknown etiology. Whole-exome sequencing (WES) studies are accelerating the discovery of novel variants and genes in ASD.

Methods: We conducted a WES study on 192 trios of an autism cohort in the founder population of the Central Valley of Costa Rica (CVCR).

Results: We identified de novo loss-of-function single nucleotide variants (SNV) and INDELs (6.7% of patients), de novo missense SNV in known ASD/ID loci (6.2%), recessive (5.7%) and X-linked (3%) LoF SNV or INDELs, and de novo and inherited copy number variants (CNV, 7.8%).

Conclusions: By uncovering variation in mendelian disease loci, pinpointing prior candidate genes within CNVs, strengthening evidence on candidate loci and correlating molecular and clinical findings, our study enhances the clinical yield of WES applied to autism samples.

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16 Epigenetic mechanisms in chronic pain

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Background: Chronic pain is often accompanied by depression and anxiety. Tricyclic antidepressants (T CAs) alleviate some chronic pain and depression, but have a slow onset of action and present numerous adverse effects. Recent evidence links the epigenetic modulator histone deacetylase 5 (HDAC5) to depression and T CA efficacy (Renthal et al 2007, Tsankova et al 2006). We examine the influence of HDAC5 in inflammatory and neuropathic pain, as well as in responsiveness to T CAs under neuropathic pain conditions.

Methods: Genetic mouse models for constitutive HDAC5 deletion or conditional overexpression, to assess roles of HDAC5 in chronic pain, depression, and anxiety like behaviours. To determine the mechanism via which HDAC5 modulates T CA actions in specific brain regions we use western blot analysis, co-immunoprecipitation, and nuclear fractionation assays.

Results: Mice lacking HDAC5 show robust reductions in inflammatory pain symptoms but augmented anxiety like behaviours. While HDAC5 is not involved in the expression of neuropathic pain symptoms, it plays a critical role in the antiallodynic efficacy of the T CA Desipramine (DMI). We show that DMI promotes nuclear shuttling of HDAC5 and its gene silencing effects, and that prevention of HDAC5 actions enhances the efficacy of DMI and leads to an earlier onset of drug action.

Conclusions: HDAC5 plays a key role in the induction of inflammatory pain, but does not affect sensory symptoms of neuropathic pain.

17 Neural Responses to Positive Emotion are Associated with Perceived Stress in Patients with Major Depressive Disorder

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Background: Functional MRI (fMRI) analysis can help highlight neural circuitry involved in major depressive disorder (MDD). Patients with MDD underwent fMRI and completed self-reports of perceived stress in their lives in order to determine neural correlates of stress perception. One measure is the Perceived Stress Scale (PSS), a self-report measuring patient perception of stress.

Methods: 15 participants with MDD (ages 23 to 68, 7 female) completed a positive emotion identification task during fMRI. Using whole-brain general linear modeling and correlation analyses, we identified brain regions where the change in the Blood-Oxygenated-Level-Dependent (BOLD) signal during positive emotion perception is associated with perceived stress.

Results: Neural responses to positive emotion within the thalamus and cerebellum were negatively associated with perceived stress (whole brain FWE corrected, $p<0.05$). Higher neural activation in response to positive emotion correlated with less perceived stress. The thalamic cluster of interest extended into the precuneus, the dorsal cingulated gyrus, and the insula, with the most robust finding in the pulvinar thalamus (mean correlation = -0.59).

Conclusions: These results suggest that brain systems involved in processing positive emotion influence the subjective perception of stress.

Funding: National Institutes of Mental Health, Icahn School of Medicine at Mount Sinai

18 Neuronal Epigenome and Transcriptome Mapping in the Autism Brain and genetically engineered mice with targeted deletion of histone methyltransferase gene MLL1

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Background: Recent genome-sequencing studies in human neurodevelopmental and psychiatric disorders have uncovered mutations in genes that encodes different chromatin regulators such as MLL1, MLL2, MLL3. Epigenetic regulation of histone lysine methylation markings which define many TSS, enhancers and other noncoding regulatory sequences will be important in order to understand the functional significance of these regulatory noncoding sequences for the neurobiology of autism.

Method: H3K4me3 ChIPseq data for histone methylation landscapes on a genome-wide scale in neuronal nuclei and glia collected from ASD and non-diseased (postmortem) brain tissue and in genetically engineered mice with a conditional ablation of the H3K4-specific histone methyltransferase Mll1/Kmt2a in postnatal forebrain neurons that exhibit profound impairments in cognitive and memory functions is integrated with brain gray/white matter RNAseq data, non-human H3K4me3 ChIPseq data (macaque,chimp,mouse) and publicly available Brain midfrontal lobe SuperEnhancer data, Fantom5 brain enhancer data, NIH Roadmap Epigenomics to find cell type specific functional regions and human brain specific noncoding RNA then genetic variants affecting autism related gene levels are identified by constructing eQTL mapping for prefrontal cortex.

Results: Our preliminary work indicates that over 900 regions are differentially regulated in autism vs control brain cases. 94 % of 500 regulated distal regions are enriched in intronic and intergenic sequences. These sequences overlap with other functional regions such as Brain H3K27Ac, H3K4Me1 and carry eSNP that affect gene expression levels in prefrontal cortex. Some of them are predicted as novel new gene candidates based on expression level and H3K4Me3 level at TSS. Some of them are regulated in MLL1 knockout mice.

Conclusions: We are now testing whether MLL1 regulates our candidate H3K4 methylation sequences in neuronal epigenome and transciptome in MLL1 knockout mice to increase our predictive capability to identify functional enhancer and promoter H3K4me3 sequences that may play a key role in the pathophysiology of autism.

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19 Dysregulation of nELAVL RNA binding in Alzheimer's Disease brain

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Background: Neuronal ELAV-like (nELAVL) are RNA-binding proteins that play a role in controlling gene expression in synaptic plasticity. They have been linked to numerous neurological disorders including Alzheimer's disease (AD), yet their relationship to disease is unclear.

Method: To globally identify transcripts directly bound by nELAVL in human neurons, we generated a genome wide RNA binding map of nELAVL using HIT S-CLIP in human brain samples from control and AD subjects. HIT S-CLIP allows the identification of functional RNA-protein interactions in vivo by using UV-irradiation to covalently crosslink and then purify RNA-protein complexes.

Results: We identified 615 robust nELAVL targets in human brain, and investigated nELAVL-mediated regulation during AD progression. We found that in healthy versus diseased brains, nELAVL was differentially bound to 3'UT Rs and introns of critical neuronal transcripts, including AD-related genes. Unexpectedly, the most significant change of nELAVL binding in AD patient brain was evident on a class of noncoding RNAs, Y RNAs, which have been linked to misfolded RNA surveillance. nELAVL:Y RNP complexes were specifically remodeled during AD progression, and, in neuroblastoma cells, during acute UV stress.

Conclusion: We propose that during chronic neuronal stress, nELAVL/Y RNA association displaces other Y:RNP components and redistributes nELAVL binding, triggering a system of sensing RNA misfolding and inducing changes in mRNA regulation.

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20 The role of Tcf7l2 in regulating nicotine intake and protection from psychiatric-related deficits

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Background: Recent BAC-T RAP analysis has shown that the gene Tcf7l2 is highly enriched in the habenulo-interpeduncular system. T CF7L2 encodes a transcription factor activated by the evolutionarily conserved canonical Wnt signaling pathway. Wnt signaling is known to play a key role in guiding the innervation of IPN by MHb afferents during development, with the appropriate wiring of this pathway being particularly sensitive to any disruption in the signaling cascade. However, little is currently known about the role for Wnt signaling in the adult habenulo-interpeduncular system, or the role for Wnt in the adult CNS in general. Intriguingly, it is now well-established that lesions of the MHb/IPN can trigger schizophrenia-like behavioral deficits in rodents, and that close to 90% of human schizophrenia patients demonstrate calcification of, and presumably deficient activity in, postmortem MHb/IPN tissues. Based on the above observations, it is a possibility that T CF7L2, acting in the habenulointerpeduncular system, may regulate the motivational properties of nicotine and regulate the expression of psychiatric-related cognitive deficits, perhaps contributing to the remarkably high rates of tobacco addiction in those suffering from schizophrenia.

Methods: Knockout rat; nicotine IVSA; reversal learning; working memory

Results: Increased nicotine intake; reversal learning deficits

Conclusions: Nicotine use may precipitate psychiatric-related cognitive dysfunction and drug dependency in vulnerable individuals.

Funding: NIH

21 Striatal chromatin remodeling and gene expression impairments in human heroin abusers relate to history of drug use

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Background: In light of the new opioid epidemic, it is our goal to expand the limited knowledge about molecular underpinnings of heroin abuse by direct studies of the human brain, We previously revealed striatal dysregulation of genes related to glutamatergic neurotransmission, and our current experiments aimed to characterize associated epigenetic regulatory mechanisms..

Methods: We used a homogeneous postmortem collection of human heroin abusers as well as a rat heroin self-administration model to explore gene expression in the striatum (microarray, Nanostring, qPCR) directly related to glutamatergic neurotransmission, and to dissect related epigenetic mechanisms (Western blot, ChIP).

Results: We observed marked striatal transcriptional and epigenetic perturbations in human heroin abusers. Heroin induced a striking dysregulation of chromatin remodeling enzymes and genes involved in glutamatergic neurotransmission and lead to significant hyperacetylation of specific histone H3 lysine residues (K23, K27) as well as impairments of H3.3 nucleosomal incorporation over the gene body of implicated glutamatergic genes. Furthermore, the observed molecular changes were strongly and differentially influenced by drug use history and acute heroin toxicology. Importantly, we reproduce the heroin-induced epigenetic perturbations in our rat model, opening an avenue for further mechanistic studies of translational relevance.

Conclusions: Overall, the data suggest that epigenetic perturbations and the resulting more open chromatin configuration might be intimately involved in the regulation of heroin-induced striatal synaptic plasticity.

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22 White Matter Alterations in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is associated with multiple functional brain differences, including abnormalities of the insula, striatum, thalamus, and orbitofrontal cortex. Despite fairly consistent functional findings, structural differences that may underlie these changes are poorly understood. Tract-based-spatial-statistics (TBSS) are a powerful tool for probing the integrity of white matter (WM) tracts by assessing fractional anisotropy (FA). This investigation utilized TBSS to examine WM in OCD patients and controls.

Methods: Fifteen adults with OCD and 17 matched controls underwent diffusion-weighted MRI at 3T. FSL software was used for data preprocessing via the Diffusion Toolbox and analysis via the TBSS package. Group comparisons used the General Linear Model and Randomize functions (5000 iterations/contrast), thresholded at pFWEcorrected<0.05.

Results: Relative to controls, subjects with OCD exhibited decreased FA in the bilateral body of the corpus callosum and left corona radiata near the insula, external capsule, and posterior internal capsule between the thalamus and striatum. No regions of increased FA were found in OCD subjects.

Conclusions: OCD patients had decreased FA along several major WM tracts, including those running between cerebral hemispheres and through the mid-insula and internal capsule adjacent to the striatum and thalamus. Intriguingly, deep brain stimulation of the ventral striatum/internal capsule is an effective treatment for refractory OCD. These findings suggest that in addition to functional abnormalities, anatomical connectivity alterations may contribute to OCD and serve as potential treatment targets.

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23 Role of TET1 and 5-hydroxymethylcytosine in cocaine action

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Background: TET proteins oxidize 5-methylcytosine to 5-hydroxymethylcytosine (5hmC), which can further leads to unmethylated cytosine. Although 5hmC is most enriched in brain, the influence of 5hmC and TET in neuropsychiatric disorders remains elusive.

Methods & Results: We demonstrate that cocaine administration decreased TET1 expression in nucleus accumbens (NAc), a key brain reward structure, in both mice and humans. Mouse behavioral assays after viral-mediated TET1 overexpression or knockdown indicated that TET1 negatively regulates behavioral responses to cocaine. Through genome-wide 5hmC sequencing, we recognized robust regulations of 5hmC at both enhancer regions and coding regions. By superimposing with RNAseq transcription dynamics, we found these 5hmC alterations enrich both at genes that show steady expression regulation and genes poised for future induction. In addition, these genes are clustered in groups that have pivotal roles in drug addiction. Through oxidative bisulfite sequencing, we validated these 5hmC changes. Though deemed as a transient mark, we found some 5hmC alterations last up to a month after cocaine exposure.

Conclusions: Our study reveals a novel epigenetic mechanism of cocaine action.

Funding: NIDA

24 A novel protocol for characterizing long non-coding RNAs in autism spectrum disorders (ASD) and related disorders

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Introduction: Long non-coding RNAs (lncRNAs) have so far been implicated in gene transcriptional regulation, and have been suggested to play a role in ASD and other neurodevelopmental disorders (NDDs). Making use of a curated list of lncRNA genes released by GENCODE, we are developing a novel protocol to sequence full-length lncRNAs as a first step towards incorporating lncRNA expression profiles into the analysis of gene regulatory networks underlying these disorders.

Methods: As proof-of-principle, we have designed a lncRNASeq custom-capture protocol for the purpose of uncovering gene structure details of lncRNAs in the vicinity of ~1000 protein-coding genes implicated in NDDs. We are designing capture probes targeting lncRNA exons and generating full-length cDNA libraries using total RNA extracted from a neuroblastoma cell line. The cDNA libraries are hybridized to our capture probes to select for lncRNAs of interest and subsequently sequenced on the PacBio RS platform.

Results: The sequencing results from this protocol will serve as a proof-of-principle for the identification and characterization of lncRNAs genome-wide or around any gene of interest.

Conclusions: Once our protocol has been tested successfully on cell lines, we will use it to profile lncRNA expression in brain tissue from ASD cases and controls.

Funding: Graduate scholarship from the Seaver Foundation.

25 Enhancing Depression Mechanisms in Midbrain Dopamine Neurons Achieves Homeostatic Resilience

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Background: Therapeutic efficacy is typically achieved by reversing pathogenic mechanisms. We demonstrate a novel antidepressant effect that is achieved by enhancing depression-causing mechanisms in ventral tegmental area (VTA) dopamine neurons.

Method: Utilizing social defeat, in vitro electrophysiology, pharmacological, viral and optogenetic approaches we explored the projection-specific role of VTA dopamine neurons in resilience to social stress-induced depression.

Results: In a chronic social defeat stress model of depression, depressed (susceptible) mice display hyperactivity of VTA dopamine neurons, a pathogenic mechanism induced by an up-regulation of a hyperpolarization-activated current (Ih). Mice resilient to social defeat stress, however, exhibit a stable normal firing of these dopamine neurons. Unexpectedly, we found that resilient mice had an even larger Ih, which was observed in parallel with increased potassium (K+) channel currents. We demonstrated that experimentally enhancing the firing-increasing Ih or optogenetically increasing the hyperactivity of VTA dopamine neurons in susceptible mice, completely reversed depression-related behaviors, an antidepressant effect achieved through resilience-like, projection-specific homeostatic plasticity.

Conclusions: These results unravel a novel therapeutic path of promoting natural resilience for depression treatment.

26 A role of Regulators of G protein signaling in the Nucleus Accumbens in opiate addiction and analgesia.

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Background: Regulator of G Protein Signaling 9-2 (RGS9-2) is a multifunctional signal transduction protein highly expressed in the striatum. RGS9-2 plays a major role in modulation of several GPCR responses in the striatum, and has been shown to negatively modulate dopaminergic and opioidergic transmission. We recently identified RGS9-2 complexes in the striatum associated with acute and chronic actions of different μ-opioid receptor agonists.

Method: By using viral mediated gene transfer approaches and optogenetic studies we explored the brain specific actions of this molecule in a series of behavioral paradigms for opiate reward and analgesia.

Results: Our studies reveal that RGS9-2 actions in the nucleus accumbens (NAc) negatively regulate rewarding actions of morphine and they also affect physical dependence development. In addition, RGS9-2 plays a key role in μ-opioid derived analgesia and tolerance in paradigms of acute and chronic pain, in an agonist-specific way. Furthermore, optogenetic activation of NAc D1-receptor enriched neurons leads to increased levels of RGS9-2 and accelerates the development of analgesic tolerance.

Conclusions: These findings point to RGS9-2 complexes in the NAc as novel targets for treatment of addiction and reveal the influence of RGS9-2 in the NAc in morphine analgesia and tolerance.

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27 G-protein independent activation of a mutant G protein gated inwardly rectifying (GIRK) channel

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Background: Alcohol is a widely used drug, yet the understanding of its targets and mechanisms remains incomplete. Among its targets are GIRK channels, which are directly activated by alcohol, independent of their typical G-protein mediated pathway. Currently, however, the molecular mechanism underlying alcohol activation of GIRK remains unknown. Here, we study purified mutant GIRK2 channels in a defined reconstituted system that allows a precise analysis of how alcohol alters channel gating.

Methods: We have engineered a mutant GIRK2 channel that allows for chemically covalent alcohol “tagging” via modulation with methanethiosulfonate (MT S) reagents at a single cysteine residue. Protein for this channel has been purified in a yeast expression system, reconstituted into liposomes, and its function measured using a high throughput potassium flux assay.

Results: The purified mutant channel is selectively activated using MT S-hydroxyethyl (MT S-HE), which mimics the addition of a high affinity alcohol at a previously identified critical locus. T his activation is sensitive to block by Ba2+ and is several fold larger than the basal GIRK current, in the absence of the Gβγ subunit.

Conclusion: Activation of a mutant GIRK2 channel via chemical modification demonstrates conclusively a G-protein independent method of channel activation via modulation with MT S-HE. Future studies will elucidate the detailed mechanism of G-protein independent activation.

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28 Thalamus and Mediodorsal Nucleus Morphometry in Schizotypal Personality Disorder (SPD): Same or Different than Schizophrenia (Sz)?

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Background: Thalamic structural abnormalities are documented in Sz patients, but the extent these are shared by individuals with SPD has not been widely examined. This is a volumetric comparison among individuals with SPD, Sz, and HCs of the thalamus and the mediodorsal nucleus (MDN), a thalamic nucleus implicated in Sz with important prefrontal cortical connections.

Method: SPD individuals (n=24), patients with Sz (n=50) and HCs (n=44) ages 18-50 who received structural MRI were selected from a larger sample by balancing groups for age and sex. Thalamic and MDN volumes were compared between-groups using mixed-model ANOVA. Significant interactions were followed-up with Fisher's LSD.

Results: SPD and Sz thalamus and MDN absolute volume were significantly smaller than HC, but not significantly different from each other (thalamus:$F[2,115])=6.96, p<0.01$; MDN:$F[2,115]=28.26, p<0.001$). Relative to thalamic volume, SPD and Sz MDN volumes were smaller than HC ($F[2,115])=18.02, p<0.01$). There was a significant diagnostic-groupxhemisphere interaction, with Sz demonstrating hemispheric asymmetry ($F[2,115]=4.44, p<0.05$); a post-hoc hemisphere difference-score comparison was significant ($F[2,115]=4.44, p<0.05$), with Sz difference greater than SPD.

Conclusions: SPD showed less marked thalamic and MDN volume abnormalities compared to Sz. Clinical correlates will be presented.

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29 Modeling anterior segment manifestations of ciliopathies

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Background: Primary cilia are microtubule based organelles present on the surface of most mammalian cell types. Defects in ciliary proteins result in developmental abnormalities and multiple ciliopathies. Complete ablation of cilia in mice leads to midgestation lethality.

Method: To understand the role of primary cilia during eye development we generated conditional KO mice Wnt1Cre;IFT 88fl/fl in which the IFT 88 gene, required for assembly and maintenance of the primary cilium, is excised in all mesenchymal cells originating from neural crest cells.

Results: We have confirmed complete ablation of primary cilia in the stroma and corneal endothelial cells. In contrast, we found normal cilia in the corneal epithelium that arises from different embryological origin. Although mutant mice die at birth the analyses of embryos at late gestation revealed significant reduction of the anterior chamber with occasional fusion of the endothelium to the lens epithelium and a thinner stromal ECM. Although migration of neural crest cells appears normal, reduction or absence of the iridocorneal angle starts at E17.5. T his morphological anomaly in the peripheral region of the eye mesenchyme together with craniofacial defects is reminiscence of the human Axenfel-Rieger's syndrome. The expression of regulatory genes involved in these processes and molecular interplays mediated by cilia during eye development are under investigation.

Conclusions: These mice allow the study of anterior segment digenesis in ciliopathies and more broadly represent an accessible paradigm to address the role of primary cilia in tissue morphogenesis.

30 Behavioral and neurobiological correlates for predicting resilience and susceptibility to social defeat

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Background: Depression is a neuropsychological disorder affecting millions of people. Research in other areas of neuropsychological disorders, such as schizophrenia, has begun developing methods for predicting and preventing disease. However, there is no means for predicting susceptibility to depression.

Methods: Social defeat is a highly validated mouse model of depression. We used acute and chronic social defeat stress for elucidating the neurocircuitry involved in establishment and maintenance of divergent behavioral phenotypes. Furthermore, we developed non-invasive behavioral paradigms to quantify activity in cortical regions prior to defeat and correlate this activity to neurobiological mechanisms involved in establishment and maintenance of post-defeat behavioral phenotype. To observe the neurobiological correlate of this behavior, we analyzed cFos expression in various cortical and subcortical regions. To investigate circuit-specific variations in resilience and susceptibility, we used a GFP virus to isolate amygdala-projecting prefrontal neurons that are active during the establishment of behavioral response to social defeat.

Results: We found that performance on a prefrontal-dependent task was correlated with resilience while performance on a hippocampal-dependent task was correlated with susceptibility. Moreover, resilient animals have higher correlative activation between prefrontal and temporal regions. Further, we found that amygdala-projecting prefrontal neurons of resilient animals have higher densities of mushroom spines compared to susceptible animals.

Conclusion: Together, these results suggest that resilient animals have pre-existing higher prefrontal-temporal connectivity that can be predicted via behavioral tests.

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31 HIV Persistence and Development of Neurocognitive Disease in Immunocompetent Mice Infected with Chimeric HIV

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Background: HIV-infected people on antiretroviral therapy (ART) frequently manifest sub-dementia neurocognitive impairments (HIV-NCI) despite virus suppression and restored immunity. We constructed chimeric HIV, EcoHIV, which can infect mice but does not cause immunodeficiency. We studied HIV persistence and the development of NCI in infected mice.

Methods: We determined HIV integration and expression in various tissues, presence of infectious virus, and sensitivity to ART, up to 18 months after EcoHIV infection of immunocompetent mice. Virological metrics in mice were compared to those in patients on suppressive ART. NCI was tested in water maze and fear conditioning.

Results: EcoHIV-infected mice remain immunocompetent and maintain HIV in stable, low-productive, and ART insensitive reservoirs of integrated DNA with potential to reactivate. The HIV metrics in chronically infected mice were similar to those in blood lymphocytes of patients on cART with CD4 count $\geq 400/mm^3$. Macrophages, the presumed cellular vectors of HIV brain disease, were the primary virus reservoirs in infected mice. EcoHIV was present in brain at low levels but infected mice manifested significant NCI in water maze and fear conditioning tests.

Conclusions: Infection of conventional mice with chimeric HIV mimics the physiological conditions for development of NCI in HIV-infected humans on cART.

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32 Inhibitors of the nuclear export protein chromosomal region maintenance 1 (CRM1) ameliorate axonal damage in multiple sclerosis

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Background: Axonal damage is a prominent feature underlying the pathogenesis of nervous system destruction in neurodegenerative diseases including Alzheimer's, Parkinson's, and multiple sclerosis (MS). Our objective is to further elucidate the mechanisms underlying axonal damage in MS.

Methods: To further explore how nuclear export results in axonal damage, we used experimental autoimmune encephalomyelitis (EAE), a disease model of MS which displays an ascending paralysis and axonal damage. A second model of axonal damage using models of kainic-acid induced neurodegeneration was used to confirm the neuroprotective effects.

Results: We have previously shown that HDAC1 is translocated from the nucleus to the axoplasm in models of MS. We found that blood-brain barrier permeable inhibitors (KPT compounds) of CRM1 are able to reverse clinical symptoms in EAE. KPTtreated EAE mice regained motor function and this correlated with both decreased inflammatory lesions in the spinal cord and fewer markers of damaged axons. In vitro and ex vivo data with kainic-acid induced neurodegeneration point towards neuroprotective effects of KPT inhibitors.

Conclusion: Our data suggest that inhibiting nuclear export through CRM1 activity has therapeutic benefit for ameliorating axonal damage in models of MS by both modulating the immune system and protecting CNS axons from damage.

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33 Regulation of the nuclear structure during oligodendrocyte differentiation

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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 OLG nuclei from other cell types in the brain. Nuclear envelope (NE) proteins are known to modulate nuclear structure and therefore we hypothesized that they play 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; Immunoprecipitation; Western blot; Confocal imaging.

Results: We show that as differentiation progresses, there are changes in the expression of NE components, such as decreased levels of Emd, Lmnb1 and Lbr, and increased levels of Sun1, Syne1 and Lmna. Down-regulation of these proteins in cultured cells decreases the levels of heterochromatic markers (H3K9me3, H3K27me3, HP1a), suggesting a role in oligodendrocyte nuclear reorganization. In vivo studies support these results, since oligodendrocyte nuclei in mice carrying mutations in Lmna show decreased levels of heterochromatin and are clinically characterized by a hypomyelinating phenotype.

Conclusions: Nuclear lamina is important for the proper function of myelin and changes in the nuclear structure during oligodendrocytes differentiation involve multiple protein complexes of chromatin modifying enzymes and nuclear envelope proteins that mediate the formation of heterochromatin at nuclear periphery.

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34 Excitation/inhibition balance in the nucleus accumbens microcircuit underlies stress resilience or susceptibility

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Background: Dysregulation of the mesolimbic reward circuit is a cardinal feature of mood and stress disorders. Previously, we observed an increase in excitatory synapses in the nucleus accumbens (NAc) of mice that are susceptible to stress and we hypothesize that there may be an overall shift in the balance of excitation to inhibition that leads to the development of depression-like behavioral responses to stress

Methods: We investigated shifts in excitation/inhibition balance on NAc medium spiny neurons (MSNs) following repeated social defeat stress, a mouse model of depression. Following repeated social defeat stress, we performed patch electrophysiology or immunohistochemistry on NAc slice from susceptible and resilient mice in D2-GFP MSNs.

Results: We find a concurrent decrease in spontaneous inhibitory postsynaptic currents restricted to the indirect pathway in susceptible mice, with an overall elevation of excitation to inhibition ratio in dopamine receptor D2-expressing MSNs compared to control and stress resilient mice. On the other hand, we observe increased inhibition of direct pathway MSNs in resilient mice after stress. Susceptible mice have an overall decrease in vesicular GABA transporter (vGAT) protein, which is not due to decreased inhibition by parvalbumin-positive interneurons but may be caused by changes to other interneuron subtypes within the NAc.

Conclusions: We are currently using Cre-dependent miRNA-mediated knockdown of neuroligin-2 in vivo to manipulate inhibitory synapses within the NAc microcircuit and test their contribution to stress susceptibility or resilience in a cell-type specific manner.

35 Relationships between interleukin-6 (IL-6), depression and ketamine: Preliminary evidence

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Background: Interleukin-6 (IL-6) is a multifunctional cytokine and inflammatory marker that is a potential biomarker for stress-related psychiatric disorders. Animal studies have indicated a role for IL-6 in the etiology of stress related disorders; however, more research needs to be done on the relationship between IL-6, depression and treatment in humans.

Methods: Blood samples were taken from participants and serum was isolated. A high sensitivity ELISA with signal amplification (eBioscience) was used to measure circulating levels of IL-6. Serum samples from 26 MDD patients pretreatment and 21 healthy controls were analyzed at baseline and a second sample was isolated from a subset of patients 24 hours after treatment with ketamine.

Results: IL-6 levels were found to be higher in MDD patients compared to healthy controls and were modulated by ketamine.

Conclusion: The current results suggest that IL-6 is a significant inflammatory biomarker in MDD. Furthermore, initial evidence indicates that ketamine rapidly lowers IL-6 levels. Future research investigating the relationship between IL-6 levels, stress-related psychiatric disorders and treatment outcomes is warranted.

Funding: Icahn School of Medicine at Mount Sinai.

36 Cognitive-Emotional Training for Depression

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Background: Neurobehavioral therapies (NBTs) are interventions designed to target and change neurobiological mechanisms underlying psychological disorders, capitalizing on brain plasticity. We reporThere a proof-of-concept study of a novel cognitive-emotional training designed to enhance cognitive control for emotional processing and target components of the neural networks implicated in Major Depressive Disorder (MDD).

Methods: Twenty-one participants with current MDD completed eight cognitive training sessions over four weeks. Participants were randomly assigned to a cognitive emotional training paradigm (Emotional Faces Memory Task (EFMT)) or an active control condition (CT). Assessments of MDD symptoms, attention, working memory, and negative affective bias in cognitive processing were administered at baseline and after 4 weeks of treatment.

Results: Participants in the EFMT group (n=11) exhibited a greater reduction in MDD symptoms compared to the CT group (n=10), $F(1, 19) = 5.605$, $p = .029$. Six of 11 (55%) EFMT participants achieved clinical response (≥ 50% reduction in symptoms from baseline). EFMT participants also exhibited improvements in negative affective bias whereas the CT participants did not. Both groups exhibited similar, small improvements in attention and working memory.

Conclusions: Cognitive-emotional training may be an efficacious intervention for MDD. Future studies are needed to fully understand the effectiveness and neural mechanisms of these training strategies.

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37 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 in CNS neurons. Recent studies suggest that germline VGF deficient mice show pro-depressive phenotypes, that hippocampal VGF expression is reduced by depression paradigms, while intrahippocampal VGF C-terminal peptide infusions have antidepressant efficacy.

Methods: We utilized germline VGF knockout mice and VGF conditional knockout mice to further explore the global and region-specific roles of VGF in depression-related behaviors and antidepressant efficacy. Chronic social defeat stress/social interaction tests, sucrose preference test and forced swim test were used to measure depression-related behaviors.

Results: We show that both germline VGF knockout mice and dorsal hippocampus-specific VGF knockout mice show increased chronic social defeat stress-induced social avoidance and attenuated responses to chemical antidepressant (imipramine) treatment in the forced swim test.

Conclusions: This pro-depressive phenotype and impaired response to antidepressant treatment in germline VGF knockout mice and dorsal hippocampus-specific VGF knockout mice provide direct evidence for global and regionspecific role(s) of VGF in depression and in mediating antidepressant efficacy.

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38 Role of mTOR signaling in the dorsal striatum in cocaine self-administration

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Background: The loss of control over drug intake that defines human cocaine addiction emerges after prolonged drug consumption. When animals self-administer cocaine for extended periods of time each day, drug use escalates over several weeks. Previous research has shown that the regulation of protein translation through microRNAs in the dorsal striatum plays a critical role in escalation of cocaine intake in rats. In this project, we investigated the role of mTOR, an important regulator of cap-dependent protein translation, in the dorsal striatum in cocaine self-administration.

Methods & Results: Extended access self-administration of cocaine produced a down regulation of mTOR protein levels in the dorsal striatum of rats. Interestingly, knockdown of mTOR levels with a lenti- shmTOR construct precipitated increased cocaine self-administration under restricted access conditions, while leaving responding for food pellets unaffected. Knockdown of mTOR produced an upward shift in the dose response curve, just like extended access self-administration, indicating enhanced reinforcing effects of cocaine with unchanged dose-sensitivity. Preliminary pharmacological experiments with infusions of the mTOR inhibitors rapamycin and pp242 in the dorsal striatum prior to self-administration suggested that rapamycin may reduce cocaine self-administration, while neither drug affected food responding.

Conclusion: Thus, these preliminary results suggest that mTOR inhibition in the dorsal striatum through rapamycin and shmTOR may paradoxically have opposite effects on cocaine self-administration.

39 Human caspase-4 modulates microglia and contributes to cognitive deficits in a mouse model of Alzheimer's disease

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Background: Recent genetic and causal gene network studies indicated that mediators of innate immune signaling, such as CR1, MS4A, TYROBP and TREM2 play a causal role in the onset of Alzheimer's disease (AD). We have shown previously that human caspase-4 is upregulated in the AD brains.

Method: In the current study, we have developed a novel caspase-4 transgenic mouse, and investigated the pathogenic mechanisms of caspase-4 by integrating multiple disciplines including transcriptomics, biochemistry, stereology, behavior, and electrophysiology.

Results: Caspase-4 is predominantly expressed in microglia, upregulated in brains of AD subjects, and mouse model of AD, and shows highly correlated expression with AD risk genes. Assessment of spatial learning performance using Barnes maze task revealed deficits in reversal learning. Long-term potentiation was significantly impaired in the hippocampus of CASP4/APP/PS1 mice.

Conclusions: Our analyses indicates that caspase-4 contributes to AD through pathogenic alteration of microglia.

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40 Role of Sema7A in development of cortical inhibitory circuits during the critical period

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Background: Early sensory experience exerts profound control over developing cortical circuits during an early 'critical period' (CP) of heightened cortical plasticity. In mouse visual cortex (V1), neurons are normally dominated by the contralateral eye (CE). Brief moncular deprivation (MD) of the CE during the CP shifts ocular dominance (OD) of V1 neurons to the open (ipsilateral) eye. Both BDNF and the onset of GABA inhibition are important for initiating the CP, but pathways linking these molecules to GABA maturation are unknown.

Methods: Sema7A is an atypical member of the Semaphorin family of guidance cues that mediates axon growth. We found that expression of Sema7A was highly enriched on GABA neurons.

Results: In Sema7A KO mice, whole-cell recordings and immunocytochemistry suggest that development of GABA circuits are delayed and excitatory/inhibitory balance is altered. Accordingly, Sema7A KO mice are insensitive to MD during the CP. Furthermore, we find that Sema7A is regulated by BDNF. In humans, microdeletions in 15q24, which include SEMA7A, lead to autism and visual perceptual abnormalities.

Conclusions: Thus, these data suggest that Sema7A is a critical molecular mediator of BDNF-dependent GABA circuit maturation during the CP, deficits in which may lead to autism and related cognitive and perceptual abnormalities.

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41 Infectious HIV Model of Synaptodendritic Damage in Mouse Primary Brain Cell Cultures

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Background: Antiretroviral therapy reduced the prevalence of HIV-1 dementia but not of HIV-1-associated neurocognitive impairments (HIV-NCI). In contrast to dementia, the cellular dysfunctions of HIV-NCI are poorly understood but they may include synaptodendritic dysfunction rather that neuronal apoptosis. Here we describe a mouse cell culture model of HIV infection for study of molecular basis of HIV-NCI.

Methods: Murine primary macrophages and mixed brain cell cultures were infected with a mouse-tropic chimeric HIV, EcoHIV. The viral characteristics and cellular effects of this infection were determined including HIV tropism to mouse cells, neuronal morphology, dendritic arborization, neuronal marker expression, and neuronal survival. Murine leukemia virus (MLV) served as control.

Results: Macrophages were susceptible to EcoHIV but not to MLV as determined by virus expression, inhibition, and progeny virus infectivity assays. In brain cell cultures, EcoHIV infected primarily microglia; MLV was only found in astrocytes. EcoHIV-infected brain cell cultures showed negligible apoptosis but exhibited 42% decline in the number of dendrites, thickening of axons, and reduction in synaptophysin with no change in NeuN.

Conclusions: The similarity of the HIV-1 infection phenotypes in human and mouse CNS cells and synaptodendritic damage shown here suggest that this culture/infection system may serve as a model for study of cellular changes underlying HIV-NCI.

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42 Deficiency of Sorcs1, a gene responsible for sexually dimorphic insulin resistance in humans, is associated with dimorphic behavioral deficits

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Background: Insulin resistance and Type 2 diabetes mellitus (T2DM) increase the risk for Alzheimer's disease (AD), and SORCS1 is genetically linked to both T2D and AD. We have previously shown that endogenous murine Aβ40 and 42 levels are increased in the brains of female Sorcs1 deficient mice.

Method: 12 month-old male and female Sorcs1 +/+, +/- and -/- mice had anxiety-like behavior and memory assessed in the elevated plus maze (EPM) and novel object recognition (NOR) tests.

Results: 12-month old female but not male Sorcs1 +/- and -/- deficient mice displayed less anxiety-like behavior in the EPM compared to their Sorcs1+/+ littermates. Furthermore, female Sorcs1 +/- and -/- deficient mice displayed significant memory deficits in NOR unlike their Sorcs1 +/+ littermates that displayed intact memory. In contrast, all male Sorcs1 +/+, +/- and -/- mice displayed intact memory.

Conclusion: The sexual dimorphism in behavioral deficits of Sorcs1 deficient mice is interesting given that the genetic linkage to SORCS1 is stronger for women in both T2D and AD.

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43 Hypocretin modulation of VTA DA and GABA neurons in Social Defeat Stress

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Background: Depression is a chronic illness characterized by heterogeneity of syndrome and complex etiology. Our lab has shown that in a social defeat mouse model of depression, hyperactivity of ventral tegmental area (VTA) dopamine (DA) neurons mediate depression-like behaviors. The activity of the VTA is regulated by a number of neural substrates. The lateral hypothalamus (LH) sends hypocretin (hcrt) projections to the VTA that modulate both DAergic and GABAergic cells. Abnormalities in hypocretin (hcrt)-mediated physiological functions have been shown to induce depression related symptoms, including sleep dysfunction, exacerbated stress responses, anxiety and disrupted reward processing.

Method: To study the role of hcrt in the VTA, we use molecular and electrophysiological techniques.
Results: Following chronic social defeat stress (CSDS), there is a trending increase of hcrt receptor-2 (hcrtR-2) expression in the VTA of both resilient and susceptible mice. Interestingly, using slice electrophysiology, I found that hcrt increased the firing activity of few DA cells, but increased the firing of most GABA cells in the VTA.

Conclusions: These findings may help characterize hcrt action and signaling in the heterogeneous and opposing population of cells and its differential projections in the VTA. Further studies are necessary to demonstrate hcrt modulation of VTA pathogenic mechanisms underlying depressive-like behaviors.

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44 Physiological Role of PADI2 in Oligodendrocyte Development

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Background: In the central nervous system (CNS), peptidyl arginine deiminase 2 (PADI2) is the most abundant enzyme responsible for the conversion of arginine into citrulline, a stable post-translational modification traditionally detected in cytosolic proteins. High levels PADI2 and citrullinated myelin basic protein were detected in the brain of MS patients and correlated with increased protein antigenicity. However, PADI2 is a common target of Olig2 and Olig1 in differentiating oligodendrocytes and recent studies have reported its nuclear localization and citrullination of histones, thereby suggesting a role in transcriptional regulation of oligodendrocyte differentiation.

Method: RT-qPCR, immunocytochemistry, Western blot, primary CNS cell cultures, ESC differentiation.

Results: In the present study, we show that PADI2 is expressed by oligodendrocytes and astrocytes, but not cortical neurons in primary CNS culture. More importantly, PADI2 is up-regulated at transcript and protein levels during oligodendrocyte differentiation both in vitro and in vivo, supporting its role in oligodendrocyte differentiation. Increased PADI2 levels were accompanied by increased histone H3 citrullination during oligodendrocyte differentiation. Meanwhile, increased protein citrullination was observed in differentiating oligodendrocytes stimulated by extracellular ATP.

Conclusion: Proteins citrullination including histone citrullination may constitute an unrevealed regulatory mechanism for oligodendrocyte differentiation. Further studies utilizing comprehensive analysis of proteomics, chromatin immunoprecipitation coupled with deep sequencing (ChIP-seq) and mouse genetics are in progress to provide more insight into the physiological role of PADI2 in oligodendrocyte development.

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45 Autophagy Status in a Huntington's Disease Mouse Model

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Background: Huntington's disease (HD) is one of the polyglutamine (polyQ) disease family, which is a devastating neurodegenerative disorder. Huntingtin protein (Htt) with polyQ expansion leads to accelerated protein aggregation. PolyQ-Htt can be degraded by autophagy and enhanced autophagic degradation is expected to be beneficial. However, the status of autophagy in HD brain remains unclear.

Methods: Q175 knock-in HD mouse model was utilized to characterize autophagic activity in HD. Transgenic GFP-LC3 reporter was expressed in Q175 mice to monitor autophagosomes.

Results: Examination of autophagy-related proteins showed transient and moderate changes of their levels in the cortex and striatum of Q175 mice. Analysis of the GFP-LC3 distribution showed a similar pattern in the striatum of Q175 and wild-type mice. Interestingly, there was a reduction in the activity of Atg14L-linked Vps34, which is a catalytic subunit of class III phosphatidylinositol-3-phosphate kinase, in the brains of Q175 compared to wild-type. Furthermore, p62/SQSTM1 is redistributed to the nucleus and colocalized with polyQ-Htt in the striatum of Q175 mice.

Conclusion: There is a temporospatial alteration in the levels of autophagy-related proteins and a significant reduction of Vps34 kinase efficiency in Q175 model. The nuclear co-sequestration of p62 and Q175-Htt may result in an impairment of selective autophagy in the cytosol that precipitates the Q175-Htt aggregation.

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46 Examining the role of VGF-derived C-terminal peptides in hippocampal-dependent memory formation

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Background: Expression of VGF (nonacronymic), a secreted neuropeptide precursor, is regulated by hippocampal-dependent learning, exercise, and the BDNF signaling pathway. VGF germline knockout mice exhibit impaired memory performance and a pro-depressive phenotype similar to BDNF knockout mouse models. Previous work in our lab has shown that VGF-derived C-terminal peptide enhances excitatory postsynaptic potential in hippocampal slices, an effect that requires precursor BDNF processing and BDNF-TrkB signaling.

Methods: Using conditional gene knockout approaches and functional blockade of secreted VGF-derived peptides, we investigated the role that VGF C-terminal peptide plays in hippocampal-dependent fear memory formation, and its effect on memory-associated gene expression and protein modification.

Results: We demonstrate that hippocampal VGF function is critical for memory formation through its action on the BDNF-TrkB signaling pathway.

Conclusions: Our results reveal a critical role of VGF C-terminal peptide as a potential modulator of BDNF secretion and/or processing in the hippocampus during memory consolidation, and provide mechanistic insight into the regulation of memory-associated synaptic plasticity

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47 Chromatin landscape defined by repressive histone methylation during oligodendrocyte differentiation

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Background: Oligodendrocyte progenitor differentiation is characterized by the up-regulation of myelin genes and the gradual loss of membrane excitability, but the genetic mechanism underlying these switches are unclear.

Method: Using genome-wide chromatin profiling of oligodendrocyte progenitors (OPC) and immature oligodendrocytes (iOL), and focusing on two major repressive marks on lysine K9 (H3K9me3) and K27 (H3K27me3) of histone H3.

Results: We define a role of K9 in down-regulating neuronal genes and electrical excitability. In contrast, K27 is relatively stable during this transition, but regulated neuronal migration genes. The levels and activity of the respective K9 methyltransferase (K9HMT) is induced by stimuli of OPC differentiation and silencing the K9HMT enzymes (but not K27HMT) functionally alters their electrical properties.

Conclusions: The K9 methylation of histone H3 serves a critical and causal role in the transition of electrically active progenitors to electrically silent oligodendrocytes.

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48 Role of NRBF2 in modulating Class III-PI3K/autophagy activity and memory in mice

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Background: Autophagy is a conserved lysosomal degradation pathway for recycle of intracellular content and energy. Autophagy is required for neuronal survival, and its dysfunction is implicated in neurodegeneration. PI3K-III complex is essential in controlling autophagy and endocytosis. In the previous study, we have identified a new component of PI3K-III complex: Nuclear receptor-binding factor 2 (NRBF2).

Method: To understand the physiological role of NRBF2 in autophagy regulation and central nervous system, we generated NRBF2 KO mice. Through a combination of biochemical, cell biological and behavioral experiments, we dissected the role of NRBF2 in regulating PI3K-III complex and autophagy activity, and examined the effect of loss of NRBF2 on memory in mutant mice.

Results: In the NRBF2 KO mice brain, both total and Atg14Llinked VPS34 kinase activity is dramatically impaired, concomitant with disassembly of PI3K-III complex. NRBF2 KO mice survive normally but display defects in spatial and fear memory. p62/SQST M1, the substrate of autophagy, is accumulated in the brain and forms clustered granular extracellular structure specifically in the hippocampus of NRBF2 KO mice. The granular structures are immunopositive for Reelin, an interneuron-derived matrix protein associated with synaptic function, ageing and Alzheimer's disease.

Conclusions: Our study identified NRBF2 as a novel physiological autophagy regulator through modulating PI3KIII complex assembly and activity. NRBF2 and PI3K-III may participate in the cellular pathways in interneurons that control memory.

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49 E2F1 and c-Myc Coregulate Cell Cycle Genes and Chromatin Components during the Transition of Oligodendrocyte Progenitors from Proliferation to Differentiation

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Background: Cell cycle exit is an obligatory step for the differentiation of oligodendrocyte progenitor cells (OPC) into myelinating cells. The decision of OPCs to divide or exit the cell cycle relies on important key transcriptional regulators.

Method: Using bioinformatics analysis of existing datasets, we identified E2F1 and c-Myc as key transcriptional regulators of this transition and confirmed direct binding of E2F1 and c- Myc to identified target genes using chromatin immunoprecipitation.

Results: The expression of both E2F1 and c-Myc was elevated in proliferating OPCs, where they bound to the promoter of genes involved in cell cycle regulation (i.e. Cdc2) and chromatin components or modulators (i.e. Hmgn1, H2Az, Uhrf1). Conversely, the expression of E2F1, c-Myc and their regulated target genes decreases upon differentiation. Increased expression of E2F1 gene targets was also detected in mouse gliomas (that were induced by retroviral transformation of OPCs) compared with normal brain. Conversely, E2F1 silencing in glioma cell lines decreases the expression of its target genes and restores myelin gene expression. Silencing of c-Myc was associated with decreased histone acetylation at target gene promoters, increased histone methylation and premature nuclear peripheral chromatin compaction.

Conclusions: We conclude that both E2F1 and c-Myc are important modulators of the transition between proliferation and differentiation of OPCs.

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50 Autophagy protein Beclin1 controls neuronal viability through multiple membrane trafficking pathways and tau phosphorylation

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Background: Beclin1 is an essential autophagy protein and binds and stimulates the VPS34/PI(3)K lipid kinase complex, which produces PI(3)P and helps form double-membrane autophagosomes. Beclin1 has been implicated in some nonautophagy cellular processes including phagocytosis; it is also a tumor suppressor. In the mammalian brain, Beclin1 has been linked to multiple neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's Disease.

Method: To characterize Beclin1 function in the brain we made multiple Beclin1 transgenic mice including overexpressed GFP-tagged Beclin1, conditional knock-outs in the cerebellum and hippocampus, and Beclin1 heterozygotes. We made a Beclin1 deficient MEFs and performed a microarray on Beclin1 heterozygote brain regions.

Results: Deletion of Beclin1 in the cerebellum and hippocampus led to rapid cell loss (earlier than deletion of other autophagy proteins). Ultra-structural examination of knock-out brain regions revealed aberrant membrane structures, abnormal endosomes/lysosomes and mislocalized phospholipid. Beclin1 deficient MEFs showed decreased PI(3)P levels, VPS34 activity, and endocytosis. Also, reduced expression of Beclin1 increased levels of phosphorylated Tau in brain regions, providing a novel link to AD. A microarray study of Beclin1 heterozygous mice uncovered tau kinase signaling and mitochondrial genes among the top hits.

Conclusions: Beclin1 is essential for membrane trafficking, neuronal viability and its loss leads to toxic tau pathology; it is a potential drug target for tauopathies and other diseases.

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51 A metabolic-cognitive brain interface with implications for compulsive behavior and obesity susceptibility

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Background: Appetitive drive is modulated by complex interactions between central and peripheral mechanisms. Glucose is a major player in energy metabolism and a critical regulator of feeding and reinforcement learning. Glucose-sensing hypothalamic agouti-related peptide (AgRP) neurons mediate appetitive drive, energy metabolism, and obesity. Striatopallidal medium spiny neurons (MSNs) regulate approach and avoidance behaviors, reinforcement learning, and are implicated in obesity, compulsivity, addiction and other psychiatric diseases.

Methods: We used advanced molecular techniques coupled with transgenic mouse models and novel neuromodulatory and behavioral neuroimaging methodologies to demonstrate anatomical and functional connectivity between hypothalamic AgRP and nucleus accumbens shell (NAcSh) striatopallidal MSNs relevant to feeding, reinforcement learning, and glucose metabolism. We also examined NAcSh striatopallidal MSNs in behavioral and metabolic aspects related to obesity vulnerability in obesity-prone and resistant rats.

Results: We show that NAcSh striatopallidal MSNs regulate AgRP-mediated feeding. We also characterize a novel role for these neurons in the regulation of peripheral glucose metabolism and postingestive reinforcement learning, and show that impairment of this regulatory system contributes to compulsive overeating and obesity vulnerability.

Conclusions: Striatopallidal MSNs comprise a metabolic cognitive interface whose abnormalities are associated with compulsivity, obesity, and certain psychiatric diseases. Our results suggest that impairment of this brain interface underlies susceptibility to compulsive behaviors and metabolic abnormalities associated with metabolic and psychiatric disease.

52 Predicting cross-task behavioral variables from fMRI data using k-support norm

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Background: Sparsity regularization allows handling the curse of dimensionality, a problem commonly found in fMRI data.

Method: We compare LASSO (l1 regularization) and the recently introduced k-support norm on their ability to predict real valued variables from brain fMRI data for cocaine addiction, in a principled model selection setting. In the context of those two regularization methods, we compare two loss functions: squared loss and absolute loss.

Results: With the squared loss function, k-support norm outperforms LASSO in predicting real valued behavioral variables measured in an inhibitory control task given fMRI data from a different task, designed to capture emotionally-salient reward. The absolute loss function leads to significantly better predictive performance for both methods in almost all cases and the k-support norm leads to more interpretable and more stable solutions often by an order of magnitude.

Conclusions: Our results support the use of the k-support norm for fMRI analysis and the generalizability of the I-RISA model of cocaine addiction.

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53 The Genome in Three Dimensions: A New Frontier in Human Brain Research

Amanda C. Mitchell, Schahram Akbarian

Background: Less than 1.5% of the human genome encodes protein. However, vast portions of the human genome are transcriptionally and epigenetically regulated. Many noncoding regulatory DNA elements are thought to regulate the spatial organization of interphase chromosomes. Chromosomal 'loopings', for example, are pivotal for the orderly process of gene expression. They enable distal regulatory enhancer or silencer elements to interact directly with proximal promoter and transcription start sites potentially bypassing many kilobases of interspersed linear genomic sequence. To date very little is known about the regulation of these supranucleosomal structures in brain nuclei.

Methods: We introduce chromosome conformation capture (3C) for brain and compare higher-order chromatin structures at the chromosome 6p22.2-22.1 schizophrenia and bipolar disorder risk locus and neurodevelopmental risk genes (DPP10, MCPH1) in adult prefrontal cortex and various cell culture systems, including neurons derived from reprogrammed skin cells.

Results: We show that chromosome conformation capture, a widely used approach to study higher-order chromatin, is applicable to tissue collected postmortem, thereby informing about genome organization in the human brain. We show that an intergenic schizophrenia associated SNPs located at H3K4me1 and H3K27ac marks physically associates with a cluster of histone variants.

Discussion: We predict that the exploration of three-dimensional genome architectures and function will open up new frontiers in human brain research and psychiatric genetics and provide novel insights into the epigenetic risk architectures of regulatory noncoding DNA.

54 Regulator of G protein Signaling 4 (RGS4) is an important modulator of antidepressant drug actions and stress responses

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Background: The signal transduction protein RGS4 modulates GPCR function via interactions with Galpha subunits. RGS4 is expressed in brain regions implicated in mood and addiction, and modulates the function of monoamine and opioid receptors.

Method: We used genetic mouse models and viral mediated gene transfer combined with behavioral and biochemical assays to investigate the role of RGS4 in acute and chronic stress responses. Moreover, we studied the role of RGS4 in the Nucleus Accumbens (NAc) or Medial Prefrontal Cortex (mPFC) in the efficacy of fast acting (ketamine) and typical (monoamine targeting) antidepressants in models of depression and neuropathic pain.

Results: We show distinct roles of mPFC RGS4 in acute versus chronic stress. Prevention of RGS4 actions leads to anxiety and depression-like phenotype. Blockade of RGS4 actions in the NAc leads to a treatment-resistance phenotype, as mice fail to respond to standard doses of monoamine targeting antidepressants. On the contrary, reduction of RGS4 levels in the mPFC enhances responses to ketamine.

Conclusions: Our findings point to RGS4 as a key modulator of anxiety and depression and a possible target to enhance the actions of drugs used for the treatment of depression and neuropathic pain.

55 Structural insignts into the crosstalk mechanism between 5-HT2A and mGlu2 receptors acting as a GPCR heteromer in schizophrenia

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Background:5-HT2A and mGlu2 receptors are Gprotein-coupled receptors (GPCRs) linked to schizophrenia, and to the mechanism of action of atypical antipsychotic drugs (e.g., clozapine), and the new class of potential antipsychotic drugs acting as agonists of mGlu2/3 receptors (e.g., LY379268). GPCRs have been thought to function as monomers. Nevertheless, evidences corroborates the existence of GPCR homo-, hetero-dimers that differentially alter Gprotein-dependent signaling.

Method: Fura2Imaging

Results: Our findings suggest that the Gq/11-coupled 5-HT2A receptor and the Gi/o-coupled mGlu2 receptor form a GPCR heteromeric complex. Here, we analyze the mGlu2 receptor ability to crosstalk and activate Gq/11 protein-dependent signaling through the 5-HT2A-mGlu2 heteromeric receptor. We show that expression of 5-HT2A and mGlu2 as a GPCR heteromer is necessary to induce Gq/11 protein-dependent signaling by LY379268. We demonstrate that although co-expression of mGlu2 receptor together with a mutant 5-HT2A receptor defective in G protein activation abolishes LY379268-induced Gq/11 protein-dependent signaling, an mGlu2 receptor that activates G proteins is also required to encode this signaling outcome

Conclusions: We show that the signaling crosstalk between the components of the 5-HT2A-mGlu2 heteromeric receptor is dysregulated in postmortem frontal cortex of schizophrenic subjects. These findings may provide a route for the development of drugs for the treatment of schizophrenia.

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56 Neural correlates of inference and imagination in OCD

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Background: Obsessive-compulsive disorder (OCD) is characterized by excessive absorption with imagined negative events. T his absorption may be explained by inferential confusion, a process whereby individuals obscure the distinction between imagination and reality. Associations between brain, inferential confusion and negative event imagination in OCD have not yet been examined.

Methods: Preliminary fMRI data were obtained while 12 healthy individuals (HC) and 13 patients imagined personal positive and negative scenarios (IM task). Whole-brain analysis within OCD examined associations between neural activity during IM and scores on the Inferential Confusion Questionnaire and Short Imaginal Processes Inventory –Fear-of-Failure subscale.

Results: Patients scored significantly higher than HC on both scales. Within OCD, higher scale scores correlated with greater brain activity during IM in various regions, including the insula, amygdala, and parahippocampus. Overall, activation in these regions did not differ between OCD and HC during IM.

Conclusions: Higher scores on measures of inferential confusion and negative imagination suggest these processes are of interest to OCD. Patients with these traits more strongly engage regions associated with emotion and memory during imagination. These findings have implications for the formation and persistence of obsessions in OCD.

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57 Characterization of Thap1 (DYT6) protein

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Departments: [1]Neurology, [2]Genetics, [3]Pediatrics

Background: Mutations of THAP1 (THanatos-associated domain-containing Apoptosis-associated Protein 1), a zinc-finger transcription and pro-apoptotic factor, cause early onset torsion dystonia, type 6.

Methods: We used 3 commercially available ⊠Thap1 antibodies, western blotting, immunoprecipitation, oligonucleotide column chromatography, shRNA knockdown, viral and plasmid-mediated over-expression, primary neuronal culture, mass spectrometry and RT-qPCR to characterize Thap1 mRNA and protein in mouse brain and periphery at different ages and in nucleus and cytoplasm.

Results: One polyclonal and two monoclonal antibodies recognize a 32kDa species with a half-life of two hours, following over-expression of Thap1 in HEK cells and primary striatal cultures. The same species is endogenously expressed at low levels in nuclear extracts from adult and embryonic neuronal tissues. All 3 antibodies recognize multiple, different Thap1-like imunoreactive (LI) species at 30 and 50kDa, only two of which are altered by over-expression, knockdown, or cycloheximide. These higher MW Thap1-LI species vary between tissues and ages. The affinity of the 50kDa species for the Thap1 DNA binding sequence is enhanced by treatment of nuclear extract with phosphatase.

Conclusions: Authentic Thap1 is present at 32kDa and 50kDa, and likely undergoes multiple post-translational modifications that vary by cell type and age. The antibodies currently in use by multiple laboratories recognize authentic Thap1 and multiple other non-specific protein species, compromising the interpretation of published results obtained with these antibodies.

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58 Protracted abstinence influences the 'Tug of War' between pleasant and cocaine-related cues in addicted individuals: evidence from a longitudinal ERP study.

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Background: Attention-bias towards drug-related and away from pleasant stimuli characterizes drug addiction. With protracted abstinence, treatment-seeking individuals with cocaine use disorders (tsCUD) show recovery of emotional functioning, but it remains unclear how longer-term abstinence affects drug-related attention-bias. We hypothesized that 6-month abstinent tsCUD would show increased reactivity to pleasant stimuli compared to baseline, shifting attention-bias away from cocaine-related cues.

Methods: Event-related potentials (ERPs) were acquired in 19 tsCUD and 8 controls while viewing pleasant, unpleasant, neutral and cocaine-related pictures at baseline and at 6-month of abstinence. The late positive potentials (LPP) component of the ERP was scored to index the motivated attention to these stimuli.

Results: A mixed ANOVA yielded a significant session (baseline, follow-up) by picture contrast (pleasant-neutral, unpleasant-neutral, drug-neutral, drug-pleasant) by group (tsCUD and controls) interaction. Specifically, at follow-up compared with baseline, there was a significant increase in LPP amplitude in response to pleasant (relative to neutral) pictures and a significant decrease in response to drug relative to pleasant pictures.

Conclusion: Results show that longer-term abstinence is associated with increased salience of pleasant and decreased salience of drug stimuli. These findings highlight the utility of ERP components as clinically relevant biomarkers with a potential for more ubiquitous use.

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59 Early life development of susceptibility to depression

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Background: Adverse experiences during childhood enhance the risk of psychiatric disorders and poorer physical health in adulthood. However, little is known about the effects of stress interactions from early life and adulthood on gene expression and neuron firing patterns in the mesolimbic dopamine system.

Methods: Mice were standard reared or exposed to early life stress (ELS), reared normally during adolescence, and then half of each group underwent chronic social defeat stress in adulthood. Susceptibility to depression-like behaviors was tested, physiological recordings were captured in the ventral tegmental area (VTA), and RNA sequencing was performed on nucleus accumbens (NAc) and VTA brain samples.

Results: Stress in the postnatal period significantly enhanced susceptibility to social defeat stress in adulthood. Social avoidance, open field exploration, forced swim, and sucrose preference behavior were all impaired by ELS with defeat. RNA-sequencing revealed distinct patterns of gene expression in VTA and NAc subsequent to ELS and social defeat. Stress likewise altered physiological responses in
VTA dopamine neurons.

Conclusions: We have developed a paradigm in mice whereby early life experiences alter susceptibility to depression and are accompanied by broad changes within brain reward circuitry. These methods will allow us to examine critical periods for intervention early in development.

Funding: This work is supported by the NIH and HDRF.

60 Sex differences in stress regulation of genome-wide transcriptional profiles in the mouse nucleus accumbens

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Background: Adult women are twice as likely as men to develop major depression, although the precise molecular mechanisms underlying sexual dimorphism in depression susceptibility are unknown. We have developed a stress paradigm—subchronic variable stress (SCVS)—to mimic these sex differences in mice. Female mice subjected to SCVS exhibit depression-like behavior after 6 days of stress exposure, whereas male mice exhibit this behavior only after chronic stress exposure (28 days, but not 6 days, of SCVS).

Methods: We profiled sex differences in gene expression and transcriptional regulation in the mouse nucleus accumbens (NAc), an essential structure in the processing of reward and motivation, using next generation mRNA and small RNA sequencing. All sequencing was performed on NAc tissue from intact male and female mice subjected to SCVS. We performed bioinformatic analysis to determine differential expression patterns and predict microRNA (miR) targets.

Results: We find very little overlap in stress-regulated mRNA and miR profiles between male and female mice. miR target analysis revealed sex differences in regulation of molecular pathways related to stress vulnerability.

Conclusions: Our results demonstrate that male and female mice initiate fundamentally different transcriptional responses to stress that correlate with behavioral phenotype.

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61 Impulsivity, Anger and Poor Self-Control in Intermittent Explosive Disorder Associated with Reduced Thalamo-Cortical Structural Integrity

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Background: Reactive aggression, reflected on a continuum of severity culminating with recurrent bouts of anger in intermittent explosive disorder (IED), is a risk factor for multiple public health problems. Data on potential executive dysfunction and underlying neural morphological integrity in IED are limited. We explored the interplay between trait anger, impulsivity, self-control, and gray matter volume (GMV) of associated regions.

Methods: 30 male volunteers [high-aggression (HA) = 15, comprised of IED and subthreshold-IED; matched low-aggression (LA) = 15] completed trait anger, impulsivity, and self-control questionnaires. Of these, 21 (11 HA; 10 LA) were MRI scanned to assess GMV integrity.

Results: Compared to LA, HA showed 1. elevated impulsivity and poor self-control driven by IED ($p<.001$); 2. reduced GMV in the right inferior frontal gyrus ($t(19) = 5.568$, $p <.001$) negatively correlated with attentional impulsivity ($r=-.448$, $p=.048$); and 3. reduced left thalamus GMV ($t(19)=4.157$, $p<.001$) negatively correlated with trait anger reactivity ($r=-.540$, $p=.011$).

Conclusions: Individuals with IED reported elevated anger reactivity, motor and attentional impulsivity, and trait poorer self-control, separating them from subthreshold-IED. These trait differences, coupled with inferior frontal gyrus and thalamic structural abnormalities provide neurobiological correlates of IED and the higher-order typology of reactive aggression.

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62 Developmental THC exposure differentially impacts heroin self-administration in adult rats based on individual behavioral trait

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Background: The risks of substance abuse, its consequences and treatment differ by multiple factors including inherent individual differences. Of the behavioral traits, impulsivity has been widely implicated in addiction vulnerability. Our research into the effects of adolescent THC exposure on subsequent heroin intake behavior had suggested potential impact of individual differences related to impulsivity. The current study investigated the impact of trait impulsivity on heroin addiction vulnerability and potential common molecular mechanisms between impulsivity and addiction vulnerability.

Method: Heroin self-administration behaviors were studied in spontaneously hypertensive rats (SHR) with adolescent THC exposure, using Wistar-Kyoto (WKY) rats as control. Gene expression profiles in nucleus accumbens (NAc) were studied by a customized PCR array. Role of Crem on behavior was studied by intra-NAc core infusion of HSV-Crem.

Results: Enhanced heroin self-administration and impulsive behavior were observed in SHR. Adolescent THC intended to increase heroin intake as well as impulsive action in SHR. In WKY, adolescent THC decreased heroin intake without affecting impulsive action. Decreased Crem expression in the NAc core was a characteristic feature of drug-naive SHR. Over-expression of Crem in SHR NAc core decreased impulsive action.

Conclusions: Adolescent THC exposure differently regulate heroin SA in animals depending on behavioral trait. NAc core Crem deficit contributes to impulsivity, which may contribute to their heroin vulnerability.

Funding: DA030359

63 Interneuron transplantation into the N Accumbens or D. Striatum limits the rewarding effects of cocaine in mice undergoing place preference testing

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Background: The medial ganglionic eminence (MGE) is a transient structure in the developing brain that gives rise to the majority of cortical interneurons. Numerous reports have appeared over the past several years reporting that MGE transplantation into the adult brain can induce plasticity in a variety of animal models of disease. From epilepsy to Parkinson's disease and neuropathic pain, MGE transplantation modifies behavioral endpoints used in each model to assess therapeutic efficacy. However, little evidence has been gathered to provide a mechanistic interpretation of MGE-induced plasticity.

Method: We studied the effect of transplanted fetal MGE cells in cocaine action, based on the notion that the molecular, cellular, and circuit mechanisms that underlie cocaine's behavioral effects are well known. We transplanted MGE cells into the nucleus accumbens or the ventral tegmental area, two brain regions important in cocaine action, and studied their influence on conditioned place preference (CPP) to cocaine, which provides an indirect measure of cocaine reward.

Results: We found that MGE transplantation into either region significantly reduced CPP scores.
Conclusions: We are now studying how MGE transplantation affects the predicted molecular (immunohistochemistry, RNA-seq), electrophysiological, and epigenetic (qChIP, ChIP-seq) changes that typically occur in these mice after repeated cocaine administration.

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64 Automatic Fitness Function Selection for Compartmental Pyramidal Neuron Model Optimization

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Background: During normal aging, layer 3 pyramidal neurons of the rhesus monkey prefrontal cortex exhibit significant morphological changes, as well as higher action potential firing rates in vitro. Computational modeling of individual neurons can provide insight into the ionic mechanisms underlying the increased excitability. A unique database of electrophysiological recordings and morphologic reconstructions constrains the models.

Method: We propose a general method using Latin hypercube sampling and principal component analysis to select fitness functions and weight them relative to one another. We use these in a differential evolution (DE) optimization to tune ionic mechanisms. DE is conducted on the Neuroscience Gateway.

Results: We demonstrate the method with a compartment model comprising a simplified pyramidal neuron morphology and three ion channels, optimized to data from representative young and aged neurons. Compared to a manual approach involving iterative generation of fitness functions, our novel method produces better fitting models using a tenth of the computation time.

Conclusions: T his method will be used to generate morphologically detailed models of 20+ young and aged PFC neurons, predicting which ionic mechanisms underlie age-related physiological changes.

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65 Mouse “Models” of DYT6/THAP1 Dystonia

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Departments: [1]Pediatrics, [2]Neurology, [3]Genetics

Background: Dysfunction of the basal ganglia and cerebellum are implicated in early onset torsión dystonia, characterized by painful, involuntary muscle twisting. Mutations in THAP1, encoding a transcription and pro-apoptotic factor, result in autosomal-dominant, partially penetrant, DYT6. Mutations are largely point mutations in the DNA-binding domain (DBD), but some produce a very premature stop codón.

Methods: We created three THAP1/DYT6 mouse “models”:1) constitutive knockin (KI) of the C54Y causative mutation in the DBD; 2) constitutive knockout (KO); and 3) transgenic mouse expressing Thap1C54Y in striatal output and cerebellar Purkinje neurons.

Results: KI/KI, KO/KO and KI/KO embryos are early embryonic lethal. Heterozygote and transgenic brains are grossly normal, but there is hypocellularity of the deep cerebellar nuclei. Up to 12+ months of age, none of the mice display a spontaneous movement disorder. The KI/+ mouse has abnormalities on multiple assays of motor function, including beam walking, rotarod, gait pattern, and pole test. Downstream transcriptional targets of Thap1are differentially regulated in KI/+ relative to KO/+, and there are regional variations in regulation. Norepinephrine is markedly elevated in the striatum of the KI/+ mouse, and response to propranolol is genotype-dependent.

Conclusions: 1) Thap1C54Y is unable to rescue early embryonic lethality of THAP1-null mice. 2) Pathophysiology of THAP1 mutations may not be restricted to loss-of-function. 3) A THAP1 mutation is associated with monoaminergic dysfunction.

Funding: NIH, BSDPF

66 Regulation of Dendritic Spine Turnover in Adult Visual Cortex by Lynx1

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Background: The rate of synapse turnover decreases as a function of age to consolidate synaptic networks. A clinically central issue is that this in turn limits the potential of adult plasticity to recover from brain disorders and injuries. Identification of the specific mechanisms that regulate developmental decline in spine turnover would provide promising targets to unmask the potential of adult plasticity for interventions. We hypothesized that the robust spine turnover in adult brain is masked by the increased expression of Lynx1, an endogenous nicotinic brake, recently identified to limit experience-dependent plasticity in the adult visual cortex.

Method: To test this, the spine turnover rate in adult visual cortex of Lynx1 knock-out (KO) mice was measured by chronic in vivo imaging using two photon microscopy. The dendritic spines from layer 2/3 and 5 pyramidal neurons were sparsely labeled by mating Lynx1KO mice with Thy1-GFP M line mice. Cranial windows were implanted over the visual cortex for chronic imaging.

Results: We found the overall increase in both gain and loss of spines in the Lynx1KO mice compared to WT mice.

Conclusions: This result suggests that the adult cortex does have a potential for robust synapse turnover, but it is effectively masked by the increased expression of Lynx1.

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67 Identification of a novel gene causing Essential Tremor (ET)

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[1]Neurology and [3]Friedman Brain Institute, ISMMS [2]Neurology, Hospital Universitario Donostia

Background: ET is one of the most common neurological diseases in adult life whose prevalence increasing steadily with age. The main motor symptom of ET is an 8- to 12-Hz postural or kinetic tremor of the arms. Although large families and at least three loci have been described, conventional cloning techniques have failed to identify the genetic causes of ET.

Methods: Whole exome sequencing was used for causative gene identification in a family featuring classic ET. In-vitro analyses in transfected HEK-293 cells were performed, where cells were stimulated with several neurotrophins that bind to the wild-type protein and qPCR and western-blot were used for mRNA relative quantification and protein expression, respectively.

Results: As a result, three novel disease-segregating mutations absent in normal population were identified. Two were predicted to be pathogenic and subsequent testing of additional ET cases for the best candidate failed to identify any additional mutation carrier. However, mutant and wild type cells showed significant differences in mRNA expression ($p= 0.0002$), which were higher when cells were treated with neurotrophic factors.

Conclusion: Our disease-segregating candidate is likely to be responsible for ET since its protein expression decreases significantly under the treatment of neurotrophic factors. T his decrease in protein levels is expected to cause reduced levels of neuronal apoptosis and consequent increase in toxic species, likely causing neurodegeneration.

Funding: NINDS (R21NS082881, R01NS079388)

68 Integrating Multi-scale Data to Identify Common Networks Involved in Sleep and Stress

Joseph Scarpa[1], Peng Jiang[2], Karrie Fitzpatrick[2], Martha H. Vitaterna[2], Bojan Losic[1], Fred W. Turek[2], and Andrew Kasarskis[1]

[1]Icahn Institute for Genomics and Multiscale Biology, [2]Northwestern University

Background: Clinical and experimental literature have rapidly converged to demonstrate that sleep and circadian dysfunction play an integral role in the onset and maintenance of a broad spectrum of chronic diseases, including neurological and psychiatric disorders. This work investigates molecular networks that drive both sleep and stress traits in order to elucidate novel disease mechanisms, propose novel therapeutic targets, and probe molecular relationships between sleep and stress that were not previously recognized or understood.

Method: Utilizing three genetically segregating mouse populations, we model the spectrum of stress susceptibility in natural populations and its effect on sleep-wake traits. We use WGCNA to identify stress- and sleep-associated gene modules. By integrating genetic, gene expression, and module information, we build Bayesian networks to identify novel gene regulatory sub-networks and key causal regulators common to both stress and sleep phenotypes.

Results: We link sleep and stress traits through a variety of common molecular subnetworks, including modules enriched with immune, mitochondrial, and chromatin-modifying GO categories. We also identify neurodegenerative key drivers in subnetworks linking sleep and stress.

Conclusions: Our computational strategy identifies sleep and stress traits with common tractable subnetworks and offers a novel strategy for identifying pathological mechanisms of CNS disease.

Funding: Defense Advanced Research Projects Agency and Icahn Institute funds.

69 Modulating LRRK2 Kinase Activity by Targeting Dimerization

Adam Schaffner, Xianting Li, Yacob Gomez, James Powell, Iban Ubarretxena, Zhenyu Yue

ISMMS Graduate School, Department of Neurology

Background: Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) are the most common cause of familial Parkinson's Disease. Although the LRRK2 pathway to pathology is poorly understood, it is believed that enhanced kinase activity, conferred by genetic variants, plays an important role and exists as a drug target. To guide kinase inhibitor design, it is necessary to understand how LRRK2 kinase activity is regulated.

Methods: Evidence suggests that dimerization is required for LRRK2 kinase activity. Utilizing Co-IP, immunohistochemistry, and EM-3D reconstruction, our lab explores the dimerization interface of LRRK2. Using kinase assays and domain mapping we want to understand how to disrupt the dimerization interface and see how this affects LRRK2 kinase activity.

Results: Our studies indicate that the COR domain is the dimerization interface of LRRK2. The COR domain can self interact and co-localizes with LRRK2 in cells. 3D reconstruction of LRRK2 further validates this idea. In addition, we show the N-terminal half of the COR domain, when added exogenously to LRRK2, can reduce kinase activity.

Conclusions: By regulating dimerization, the COR domain acts as a key player in LRRK2 function. Because the Nterminal region of the COR domain can modulate LRRK2 activity, presumably by disrupting dimerization, it has the potential to develop into a kinase inhibitor that targets LRRK2 allosterically.

Funding: NIH, MJFF, NINDS

70 Shared Inhibitory Dysregulation and Possible Remediation in Intermittent Explosive Disorder and Cocaine Addiction

SJ Moeller[1], MI Froböse[2], **KE Schneider[1]**, AB Konova[1,3], M Misyrlis[1,3], MA Parvaz[1], RZ Goldstein[1], and N Alia-Klein[1]

[1]Icahn School of Medicine at Mount Sinai; [2]Donders Institute; 3Stony Brook University

Background: Intermittent explosive disorder (IED) is an understudied impulse control disorder marked by episodic reactive aggression. Using a Stroop fMRI task, we investigated whether IED participants have poor PFC-mediated error-related processing. We further investigated whether such PFC deficits in IED (A) parallel those seen in cocaine use disorder (CUD), similarly characterized by dysfunctional PFC circuitry; and (B) could be fortified with methylphenidate.

Methods: We compared 11 IED, 21 CUD, and 17 controls on Stroop error>correct fMRI activity. Subsequently, in a double-blind placebo-controlled design, we administered oral methylphenidate (20 mg) during fMRI Stroop in 4 IED and 4 controls. We extracted and analyzed the fMRI signal from the same regions as our main sample.

Results: In our main sample, IED (and CUD) had error>correct hyperactivations in the anterior cingulate cortex and dorsolateral PFC relative to controls ($p<0.05$ corrected). In our preliminary sample, inspection of the extracted fMRI signal means indicated that methylphenidate decreased hyperactivations in these same regions in IED, consistent with our previous study in CUD.

Conclusions: IED and CUD had comparably hyperactive neural response to errors, suggesting a common neural endophenotype of compromised self-control. Because methylphenidate reduces aggression in youth and modulates PFC-mediated inefficiencies in multiple self-control disorders, this medication merits further investigation in IED.

Funding: R01MH090134

71 ngs.plot: Quick Mining and Visualization of Next-Generation Sequencing Data by Integrating Genomic Databases

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Background: Understanding the relationship between the millions of functional DNA elements and their protein regulators, and how they work in conjunction to manifest various phenotypes is the key to advance our understanding of the human genome. Next-generation sequencing technology is now widely used to probe into these protein-DNA interactions and to profile gene expression at genome scale. As the cost of DNA sequencing keeps dropping, the interpretation of the massive amount of data generated poses a big challenge.

Method & Result: We have developed ngs.plot – a standalone program to visualize enrichment patterns at functionally important regions based on the next-generation sequencing data. Benchmark shows that ngs.plot is not only efficient but also scalable. We use a few examples to demonstrate that ngs.plot is easy to use and yet still very powerful to generate figures that are publication ready.

Conclusions: We conclude that ngs.plot is a very useful tool to fill the gap between data and information in this era of big sequencing data.

72

Mll1/Kmt2a is Essential for Maintenance of Neuronal Histone Methylation and Prefrontal Cognition

Mira Jakovcevski[1]*, Hongyu Ruan[2]*, **Erica Y. Shen**[3]*, Aslihan Dincer[3]*, Xincai Ji[1], Qi Ma[2], Cyril J. Peter[3], Cong L. Lin[3], Iris Cheung[1], Rahul Bharadwaj[1], Amanda C. Mitchell[3], Gilles E. Martin[1], Patricia Ernst[4], Wei-Dong Yao[2], and Schahram Akbarian[1,3]

[1]Brudnick Neuropsychiatric Research Institute [2]Harvard Medical School
[3]Icahn School of Medicine at Mount Sinai [4]Geisel School of Medicine at Dartmouth

Background: MLL1/KMT2A encodes a histone H3K4 methyltransferase linked to neurodevelopmental diseases associated with intellectual disability and autism. Mll1 regulates neural stem cell survival and neurogenesis but whether it plays an essential role in postmitotic neurons, with regard to epigenome maintenance, synaptic function, and behaviors, remains unknown.

Method: Electrophysiological recording, behavioral testing, microarray, chip-sequencing, chromosomal capture, ChIP-PCR

Results: Conditional Mll1 deletion in postnatal forebrain neurons is associated with reduced brain size, increased pre-weanling lethality and impairments to an array of cognitive and memory functions. Widespread, genome-scale changes in neuronal mono- and trimethyl-H3K4 methylation were associated with dysregulated expression of > 1000 cortical transcripts, including Grin3a, Foxp2, Meis2, Satb2 and other genes important for synaptic connectivity and complex behaviors. Electrophysiological recordings from medial prefrontal layer V pyramidal neurons, a processor of top-down information and major output relay of the cortex, demonstrated severely impaired synaptic facilitation and temporal summation, two forms of short-term plasticity critical for working memory.

Conclusions: Mll1 is essential for the maintenance of neuronal H3K4 methylation at regulatory sequences critical for synaptic signaling and cognition

Funding: NIH grants P50MH096890

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PRC2 regulates neuronal subtype specification in the adult striatum

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Background: 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, comprised of the histone methylatransferase Ezh1/2, exerts its suppressive function by placing the H3K27me3 modification at the transcriptional start site of genes. Continuous expression of core PRC2 complex components in adult neurons, and a global increase in H3K27me3 with age, suggests a possible role of PRC2 in the maintenance of neuronal differentiated states.

Results: We found that loss of PRC2 in terminally differentiated and functionally specialized striatal neurons leads to the de-repression 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. The transcriptional de-differentiation is associated with distinct behavioral defects and is accompanied by slow and progressive neurodegeneration.

Conclusions: We propose that, similar to its role in early lineage differentiation, the PRC2 complex is essential for preserving neuronal specialization and is vital to maintaining normal brain function.

Funded by 2012 Director's New Innovator Award National Institutes of Health, 2011 Research Award by Seaver Autism Center

74 Computational drug repurposing to modulate neuroplasticity

Milo Smith, Hirofumi Morishita, Joel Dudley

Departments of Psychiatry and Genetics & Genomics

Background: The decline in neuroplasticity across development can hinder recovery from disorder that emerges in youth (e.g. amblyopia) or with age (e.g. stroke). As well, neuroplasticity may play a role in mental disorder (e.g. bipolar). However, there have been no systematic attempts to repurpose drugs to modulate neuroplasticity for disorder.

Method: Transcriptome-guided drug repurposing is a creative new approach to drug discovery that has been used to unearth superior treatment for irritable bowel disease (Dudley et al. Sci Trans Med 2011). For the first time, we are applying this process in brain to identify drugs to modulate neuroplasticity.

Results: Our preliminary work indicates that leveraging transcriptome data can predict neuroplasticity-enhancing drugs to treat disorder. Amblyopia, a model of developmental neuroplasticity, can be reversed if a molecular brake of plasticity, Lynx1, is deleted (Morishita et al. Science 2010). We matched a unique Lynx1 network to small molecule transcriptomes, and this blinded process rediscovered drugs known to enhance plasticity to reverse amblyopia (valproic acid and fluoxetine), as well as predicted novel pro plasticity candidates.

Conclusions: We are now increasing our predictive capability by computing hyperplastic Lynx1-KO and juvenile transcriptome networks. We will test our candidate compounds for their ability to enhance plasticity to reverse amblyopia. If successful, our approach will be a template to discover treatments for other disorders that may benefit from modulation of neuroplasticity.

75 Plasticity in the hippocampus of LRRK2 mutant mice

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[1]Department of Neurology, [2]Department of Pharmacology & Systems Therapeutics
Icahn School of Medicine at Mount Sinai

Background: Parkinson's disease (PD) is a major movement disorder characterized pathologically by the loss of the dopamine neurons and formation of Lewy bodies. In addition to motor abnormalities, PD patients display a variety of non-motor symptoms including executive function and memory loss. Identification of genetic mutations for PD provides tremendous opportunity to understand the molecular basis of PD pathogenesis. The PARK8 gene encoding leucine-rich repeat kinase (LRRK2) is of special interest, because it is associated with the most common mutations linked to PD. Interestingly, LRRK2 expression is high in multiple brain regions including cortex, striatum, and the hippocampus, suggesting that PD-associated mutations in this protein might contribute to non-motor deficits in cognitive function.

Method: We used BAC transgenic mice in which either LRRK2 wildtype protein or LRRK2-G2019S mutant protein is overexpressed to a similar level, and studied long-term plasticity at the hippocampal CA3-CA1 synapse (synaptically-induced LTP and LTD) and hippocampus-dependent forms of learning and memory (novel object/location recognition).

Results: We found increased input-output curves and decreased LTD in hippocampus of LRRK2-G2019S mutant mice which were rescued by LRRK2 kinase inhibition. Performance in the object location recognition task showed a trend toward decreased performance.

Conclusions: Our results show that the LRRK2-G2019S mutation is associated with altered synaptic plasticity and behavior in learning and memory tasks, and suggest that LRRK2 plays an important role in hippocampal function

Funding: NIH - 5 R01-NS072359 to ZY and RDB

76 Cerebrospinal fluid ceramides from multiple sclerosis patients impair neuronal bioenergetics

O.G. Vidaurre,[1] **et al.**, A.E. Miller,[1] N.J. Haughey,[2] F.D. Lublin,[1] P. Casaccia[1]

[1]Mount Sinai departments: Neuroscience; Corinne Goldsmith Dickinson Center for MS; Bioinformatics; Neurology; Radiology; Psychiatry. [2] Department of Neurology, Johns Hopkins Hospital, Baltimore, MD.

Background: Axonal damage in MS is a prominent cause of disability and yet its pathogenesis is incompletely understood. Previous studies suggest that diffusible factors present in the CSF might contribute to MS pathology.

Methods: Bioenergetic profiles of rat neurons exposed to CSF from MS patients or controls were measured using Seahorse Analyzer and correlated with levels of ceramides and neurofilament light chain in the CSF. Unbiased transcriptomic analysis was used to identify transcriptional changes in the cultures. The main findings were validated using an independent source of CSF.

Results: Acute exposure to CSF from MS patients induced oxidative stress and decreased expression of neuroprotective genes while increasing expression of genes involved in lipid signaling and oxidative stress. Protracted exposure of neurons to stress led to neurotoxicity and bioenergetics failure after CSF incubation and positively correlated with the levels of neurofilament light chain. A lipidomic analysis showed increased levels of ceramide C16:0 and C24:0 in the MS-CSF. Micelles composed of these ceramides was sufficient to recapitulate the bioenergetic dysfunction and oxidative damage induced by MS-CSF on the neurons.

Conclusions: C16:0 and C24:0 ceramides are enriched in the CSF of MS patients and are sufficient to induce neuronal mitochondrial dysfunction and axonal damage.

Funding: NIH-R01-NS69835

77 Septo-Habenular Regulation of Nicotine Intake

George Voren, Dr. Paul Kenny

Icahn School of Medicine at Mount Sinai, Pharmacology

Background: The medial habenula (MHb) projects almost exclusively to the interpeduncular nucleus (IPN) via the fascicular retroflexus. This major descending projection serves to connect the limbic forebrain and midbrain monoaminergic centers. Recently, our laboratory has shown that the MHb-IPN system, which densely expresses nicotinic acetylcholine receptors, plays an important role in regulating aversive properties of nicotine that limit consumption of the drug. The MHb receives prominent cholinergic/glutamatergic input almost exclusively from the triangular nucleus of the septum (TNS) and glutamatergic antagonism within the MHb has been shown to increase nicotine intake in rats. The role of the TNS-Mhb pathway in regulating nicotine intake has not been explored. We hypothesis that the TNS plays a role in regulating nicotine consumption.

Method: - First, characterize alterations in the activity of TNS neurons, accomplished using single-unit in vivo electrophysiological recordings, in rats as they intravenously self-administer nicotine infusions across a broad range of doses.
-Test functional significance of the TNS-MHb pathway in regulating nicotine intake by expressing DREADD receptors selectively in the TNS-MHb pathway in rats, and examine how modulating activity of these neurons effects nicotine intake.

Results: Preliminary data suggests TNS neuronal activity is highly sensitive to nicotine. Inhibiting the TNS results in intrasession changes in nicotine consumption as measured by nicotine intravenous self-administration.

Conclusions: The TNS is responsive to nicotine and seems to play a role in regulating nicotine intake by modulating MHb-IPN activity.

Funding: NIH

78 Functional Role of Locus Coeruleus Norepinephrine Neurons Projecting to Ventral Tegmental Area in Mediating Social Defeat Stress

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

[1]Department of Pharmacology and Systems Therapeutics [2]Department of Neuroscience

Background: Ventral tegmental area (VTA) dopamine neurons play a key role in determining susceptibility versus resilience to stress in the social defeat model of depression. However, the neural circuit mechanisms modulating VTA dopamine neurons activity in this model remain largely unknown. Here, we focus on locus coeruleus (LC) norepinephrine neurons projecting to the VTA (LC-VTA), as norepinephrine is implicated in the regulation of VTA dopamine neuron activity.

Method: In the chronic social defeat model, utilizing in vitro/vivo electrophysiological and optogenetic techniques, we investigated the functional role of LC-VTA circuit in mediating social defeat stress.

Results: In vitro recordings showed that surprisingly, LCVTA 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 showed that LC neurons of resilient animals exhibited higher firing and significantly increased phasic firing events as compared to control and susceptible mice. Furthermore, chronic, but not acute, optogenetic activation of LC-VTA neurons in susceptible mice reversed social avoidance behavior.

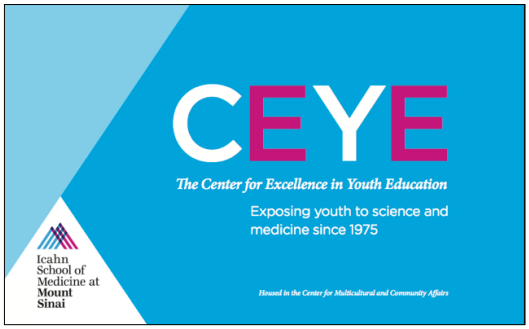
Conclusions: These studies suggest that activation of LCVTA projection promotes the resilient phenotype, which unravels a novel neural circuit that underlies natural resilience, and may provide a useful circuit target for depression treatment.

Funding: NIMH and NNSF

79 The Center for Excellence in Youth Education: A Model for Education Pipeline Programming for Students Underrepresented in the STEM Career Fields.

(not to be judged competitively)

Alyson Davis, MSW



Despite the socio-economic gains experienced by ethnic and racial minorities over the past forty years in the United States, significant barriers to higher education and professional training persist for certain racial/ethnic minority groups, limited English speaking populations, and economically disadvantaged students. Since 1975, the Center for Excellence in Youth Education (CEYE) has maintained and nurtured a mission to encourage and increase the presence of these historically under-represented groups in science, technology, engineering, math (STEM careers) and licensed professions. The CEYE, housed in the Center for Multicultural and Community Affairs (CMCA) at the Icahn School of Medicine (ISMMS), is one of the longest sustaining and well-developed pipeline programs in the nation. CEYE's educational portfolio of science enrichment programs for grades 7 through collegiate level builds on the existing expertise and infrastructure of the ISMMS to provide underrepresented students with challenging learning experiences. These experiences bolster student preparation and performance in science, language arts, mathematics and technology in a context where they can explore a wide spectrum of careers in medicine, research, nursing, and allied health, as well as extend their reach to college and these career fields. Presented is an overview of the CEYE educational program model developed over a 40-year period of successful programming, and includes our framework of program design and implementation, the development and utilization of Dyad Pedagogy, description of program impact, and a listing of critical success factors and lessons learned.

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Student Poster from CEYE
(not to be judged competitively)

Juan Casteneda
High School for Math, Science and Engineering

The study performed in the Haller Lab utilized Danio rerio as a model system to study renal disease and proteinuria. Novel genes were examined to identify their role in glomerular barrier filtration function, especially the endothelial surface layer or the glycocalyx. The aim of this study is to examine the relevance of Galectin-9 (Gal-9) in the pathophysiology of proteinuria. Zebrafish embryos were injected with Gal-9 morpholino to knock down the gene expression. The development of the renal phenotype in these embryos was classified based on the severity for edema. FABP Green fluorescent assay of the eye vasculature was conducted to monitor proteinuria as a result of possible renal damage. Electron microscopy and confocal microscopy were performed to study changes in the glomerular filtration barrier and the general vascular system. The different methods demonstrated that the knock down of Gal-9 gene results in the development of renal phenotype due to disruption of glomerular endothelial cells and that Gal-9 is essential to maintain the integrity of the glomerular filtration barrier.

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SNOP: Coordinated, multi-institutional Brain Awareness Week activities in New York City
(not to be judged competitively)

Sinai Neuroscience Outreach Program

The Sinai Neuroscience Outreach Program (SNOP) promotes neuroscience education at all levels and to foster an interest in brain research. SNOP collaborates with local New York City schools to educate students in grades K-12 by imparting basic fundamentals through discussion-based lessons and hands-on activities. SNOP programming is run by volunteers from within the Mount Sinai community, including students, fellows, faculty, and staff. SNOP had many goals for the 2013-2014 academic year. The 2013-2014 Executive Board had a 100% increase in members compared with the prior year, and 4 new positions were created. The 2014 Brain Fair had a 50% increase in volunteers, a 200% increase in attendees, and a 50% increase in the number of activities offered compared to the prior year. In 2013-2014, SNOP had a 350% increase in lessons taught and a 25% increase in students taught compared to the prior year. To date, SNOP has taught 999 students and 81 lessons. In Spring 2014, SNOP partnered with the New York Academy of Sciences Afterschool STEM Mentoring program. 11 SNOP volunteers will receive the credential of New York Academy of Sciences Teaching Fellow for completing 12 hours of training and 12 hours of teaching in one semester.

Informational Booths

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PosterPost
(not to be judged competitively)

Where does your poster go after you present it? Back in the poster tube, carelessly thrown in the corner of your lab and eventually tossed out. Not for long! Blanca Andino, Madhu Rengasamy, and Neha Uppal are bringing a twist to the trend of open-access journals and pre-print servers by creating PosterPost. PosterPost is a website that allows scientists at Mount Sinai to share their pre-published data in the form of conference posters. Not only does PosterPost allow you to show off your hard work, you will be able to receive useful feedback from the Mount Sinai community. Visit gradschool.mssm.edu/posterpost to get more information about who we are, how we started, and what our mission is -- and to sign up today!

Mount Sinai Innovation Partners

Visit with Mount Sinai Innovation Partners!

Mount Sinai Innovation Partners (MSIP), Mount Sinai's intellectual property protection and commercialization office, will have a booth setup in the first floor lobby area throughout the day. Lisa Placanica, PhD, Business Development Director, along with other MSIP members, will be present to answer your questions regarding protection, development and commercialization of your research/technology.

MSIP is responsible for the full spectrum of commercialization activities required to bring Mount Sinai's inventions to life. These activities include evaluating, patenting, marketing, and licensing new technologies, while also negotiating agreements for sponsored research, material transfer, and confidentiality.

2014 UPCOMING EVENTS

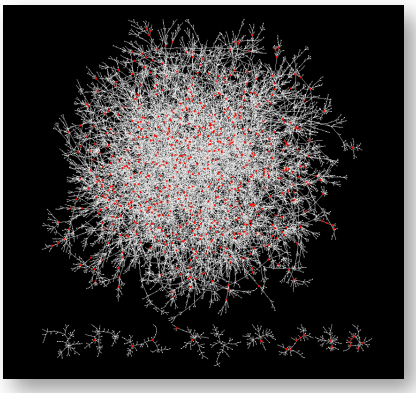

photo by Joseph Scarpa

August

Grad School Classes Begin
August 18, 2014

September

MD/PhD Retreat
September 5th-7th, 2014

5th Annual Postdoc Day
Sept. 26, 2014

MSSM Commencement
Sept. 29, 2014

October

BIC 1st Annual Symposium
October 28, 2014

November

Society for Neuroscience
November 15-19, Washington, DC

December

Grad School Winter Party
Date: TBD

Graduate Program information

For the 2014-2015 academic year, the neuroscience curriculum will undergo a few minor changes in content, and it is slated to undergo a major change in organization and scheduling, allowing the entire Neuroscience core curriculum (Cores 1-4) to be completed in Year 1 of graduate school. This year-long introductory course, called Principles of Neural Science, Behavior and Brain Pathophysiology, is comprised of four units: Molecular and Cellular Neurobiology (Unit 1, Fall), Systems Neuroscience (Unit 2, Spring 1), Neural Basis of Behavioral Plasticity (Unit 3, Spring 2), and Molecular Pathogenesis of Neurological and Psychiatric Disorders (Unit 4, Spring 2). The latter two courses will be interleaved with one another during the Spring 2 semester. Students in the Neuroscience PhD program will also be required to take Topics in Clinical Neuroscience, co-directed by Hirofumi Morishita and James Murrough, which is team-taught by a diverse set of clinical research faculty and physicians, JC in Neurobiology, co-directed by Dara Dickstein and Anne Schaefer, which is our student WIP/journal club, and Biostatistics. With the recent opening of the Hess Center and relocation of a number of Neuroscience labs, efforts are being made to teach these courses at both Hess and IMI.

No major programmatic changes have taken place. The Neuroscience-specific formats of the Qualifying Exam (Basic Neuroscience Knowledge Exam with no written document) and the Thesis Proposal Exam (written document that conforms to the current NIH NRSA proposal instructions with respect to format and page length), remain in place. We anticipate, that with the completion of the Neuroscience Introductory Core Course in graduate school Year 1, the Qualifying Exam can then be taken earlier, in late summer Year 1 or early fall of Year 2.

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 (which is why the format of the Neuroscience Thesis Proposal conforms to the NRSA proposal guidelines).

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 predoc slots starting 6/2014) and postdoctoral fellows (2 slots) carrying out mental health research. Two new T32s are being submitted this May, targeted to NIA and NINDS, 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. Lastly, we had an exceptional group of students matriculate into the program in 2013, and look forward to welcoming a terrific pool of new graduate students matriculating this fall. Our graduate program competes with the best neuroscience programs in the country for an extremely talented and diverse student body.

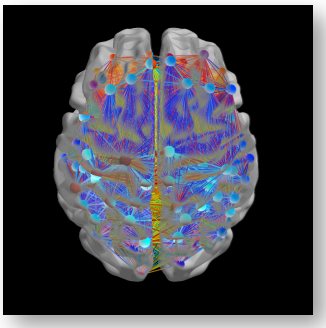

photo by Stefan Fuertinger

George Huntley and Stephen Salton

NOTES