THE

2013

Friedman Brain Institute

and the NEUROSCIENCE TRAINING AREA

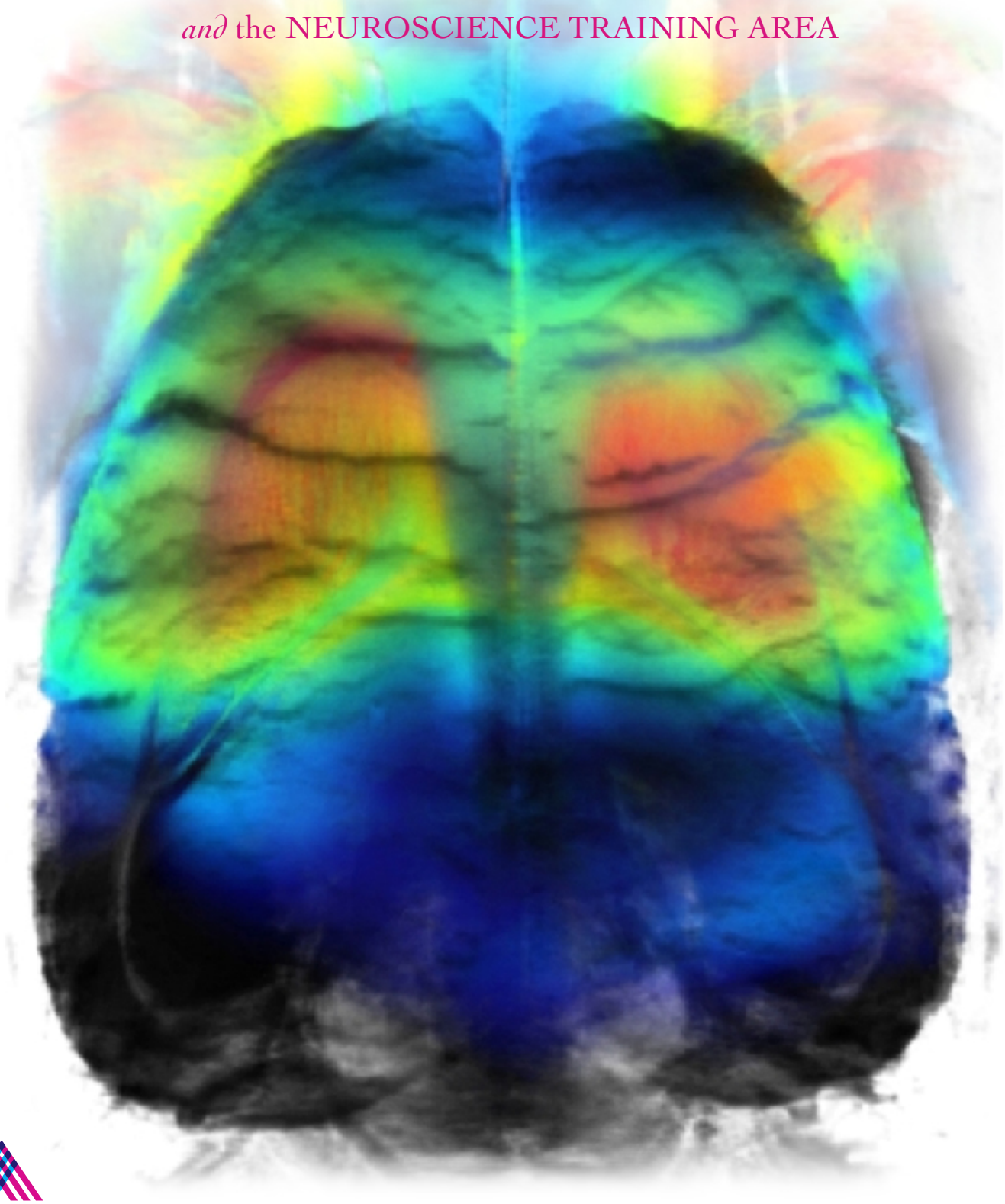

photo by Michael Michaelides

Icahn School of Medicine at **Mount Sinai**

FIFTH ANNUAL NEUROSCIENCE RETREAT

NEW YORK ACADEMY OF MEDICINE 1216 Fifth Avenue

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Retreat Administrators:

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5th Annual Neuroscience Retreat

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

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5th Annual Neuroscience Retreat

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

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Abstracts (Posters)

Neuroscience Retreat Schedule

April 26, 2013

9:00am..... Breakfast (President's Hall, 1st fl.)

OPENING REMARKS AND ANNOUNCEMENTS (HOSACK HALL):

9:30am.....Andrew Chess (Developmental and Regenerative Biology and Neuroscience)

9:35am.....Eric Nestler (Neuroscience)

10:05am.....Stephen Salton / George Huntley (Neuroscience)

10:15am.....Lauren Friedman (President, Sinai Neuroscience Outreach Program "SNOP")

10:20am.....Keynote Address: Dr. Daniela Schiller (Psychiatry) *"A map for social navigation in the human brain"*

SESSION 1

11:00am..... Roger Clem (Neuroscience) Chair I

11:15am..... Heather Berlin (Psychiatry) *"Neuroimaging of Olfaction in Obsessive-Compulsive Disorder"*

11:30am..... Noreen Bukhari (Psychiatry) *"Mechanism Regulating Adult Brain Plasticity by a Cholinergic Brake Lynx1"*

11:45am..... Georgia Hodes (Neuroscience) *"Individual differences in peripheral inflammatory signaling functionally contribute to social defeat stress"*

12:00pm..... Chiara Mariottini (Pharmacology & System Therapeutics) *"Role of Wilm's tumor 1 in synaptic plasticity and memory"*

LUNCH..... 12:15pm - 1:25pm, Room 20, 2nd fl.

SESSION 2

1:30pm..... Emily Stern (Psychiatry), Chair II

1:45pm.....Geoffrey Smith, (Director, Center for Technology, Innovation and Entrepreneurship)

2:00pm..... Michael Michaelides (Pharmacology & System Therapeutics) *"DREAMM: In vivo and quantitative cell type-specific functional whole-brain circuit mapping in freely-moving animals"*

2:15pm..... Jeremy Olson (Neuroscience) *"A New Chromophore For Two-Color Control of Cell Signaling"*

2:30pm..... Christian Williams (Neuroscience/Psychiatry) *"Modeling spatial navigation in the human brain"*

2:45pm..... Melanie von Schimmelmann (Neuroscience) *"PRC2 governs adult neuron specification and function"*

POSTER SESSION Library 3rd fl.

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

5:00pm.....Best Poster and Best Oral Presentation Award: Selected by a jury of FBI faculty

5:30pm.....Reception Ends

PLEASE REMEMBER TO RECYCLE YOUR NAME TAGS

Presenters

Neuroimaging of Olfaction in Obsessive-Compulsive Disorder

Heather Berlin, PhD, MPH, Cheuk Tang, PhD, Johnny Ng, PhD, Wayne Goodman, MD

Obsessive-compulsive disorder (OCD) is a common psychiatric illness. Neuroimaging studies show that OCD patients have greater activation of their right insula to disgusting images compared to healthy controls (HCs). OCD patients may be more sensitive to unpleasant stimuli regardless of the sensory modality, which may trigger their obsessions and compulsions. We investigated the function of the olfactory system in response to pleasant (banana, vanilla, chocolate) and unpleasant (garbage, feces, urine) odors in OCD patients (N=7) compared to HCs (N=8) using fMRI and our specially developed olfactometer. Unscented air was the control stimulus. Subjects rated stimuli on intensity and valence and completed questionnaires measuring odor identification, OCD symptoms, disgust sensitivity, and emotion. Compared to HCs, in response to unpleasant (vs. pleasant) odors OCD patients had increased activation of their right anterior insular, left posterior insular, and anterior cingulate cortex/superior cingulate; and decreased activation of their left lateral orbitofrontal cortex, left dorsolateral prefrontal cortex, and putamen (bilateral). Similar to results in the visual domain, people with OCD appear to be more "neurally sensitive" to unpleasant odors. Their decreased activation in prefrontal regions in response to unpleasant odors implies that they have less cognitive/top-down control over their increased unpleasant feelings (indicated by increased insula and cingulate activation). This first study to examine olfaction in OCD using fMRI further elucidates the neural underpinnings of OCD, which may contribute to the development of better treatments.

Mechanism Regulating Adult Brain Plasticity by a Cholinergic Brake Lynx1

Noreen Bukhari[1,2,3], Poromendro Burman[1,2,3], Ayan Hussein[1,2,3], Michael Demars[1,2,3], Scott Russo [2], Stella Tsirka[4], Hirofumi Morishita[1,2,3]

Dep. of [1]Psychiatry, [2] Neuroscience, and [3] Ophthalmology, Icahn School of Medicine at Mount Sinai, [4]Dep. of Pharmacological Sciences, Stony Brook University

Experience-dependent cortical plasticity waxes and wanes with age. Recently Lynx1 protein, an endogenous inhibitor of nicotinic acetylcholine receptors, was identified as a novel "molecular brake" which increases in the adult visual cortex. Strikingly, removal of this brake restores visual function of amblyopic mice. However, it is unknown if the mechanism of plasticity unmasked by removal of Lynx1 is comparable to juvenile mechanism. Elucidating a unified mechanism between juvenile and adult plasticity would promote better understanding of the potential for functional recovery in adult brain disorders. We found that removal of Lynx1 unmasks the molecular, structural and functional mechanism similar to juvenile brain. Interestingly, unlike its juvenile counterpart, we also discovered that the adult visual cortex is regulated by two additional brakes including a novel second molecular brake downstream of Lynx1. Therefore, in contrast to the existing paradigms, we propose that juvenile and adult brain operate through the same plasticity mechanism but the adult brain is additionally regulated by three-tiered brakes beginning with Lynx1 to maintain stability of mature cortical networks. The identified key regulatory steps may provide novel therapeutic targets for optimal functional recovery in adult brain disorders.

*Funded by the NINDS5T32NS551147-5 (N.B.), MCHDI/ Knights Templar Eye Foundation/ Whitehall Foundation/ March of Dimes (H.M.).

Individual differences in peripheral inflammatory signaling functionally contribute to social defeat stress.

Georgia E. Hodes, Madeline Pfau, Sam A. Golden, Daniel J. Christoffel, Mitra Heshmati, Marylene Leboeuf, Miriam Merad, Scott J. Russo

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

Interleukin-6 (IL-6) is increased in the blood of subjects with depression and may reflect hyperactivity of the peripheral immune system. We utilized repeated social defeat stress (RSDS), to examine the functional relevance of peripheral IL-6. A time-course analysis of peripheral IL-6 indicated that susceptible mice exhibit heightened IL-6 levels following their first defeat, which remain elevated 48 hours after defeat cessation. To examine if IL-6 levels contributed to individual differences in stress sensitivity, peripheral mononuclear cells (PBMCs) were isolated before defeat and stimulated with lipopolysaccharide (LPS) to examine immune response. PBMCs from animals who later showed a susceptible phenotype had an exaggerated release of IL-6 following the LPS stimulation. To test the functional relevance of the peripheral immune response to depression-associated behavior in vivo we blocked susceptibility to RSDS by systemically injecting an antibody that neutralized IL-6 in the periphery. Additionally, IL-6 knock out mice also displayed resilient behavior. Removal of the peripheral immune system by irradiation followed by bone marrow transplants from susceptible mice induced social avoidance following a sub-threshold microdefeat. Together these studies indicate that innate differences in the inflammatory response to stress underlie the development of depression-like behavior in the social defeat model.

Role of Wilm's tumor 1 in synaptic plasticity and memory

Mariottini C[1], Seco J[1], Munari L[1], Stern S[2], Gao V2, Alberini C[2], Blitzer R[1], Iyengar R[1]

[1] Dept. of Pharmacology, MSSM
[2] Center for Neural Science, NYU

To characterize the transcriptional program engaged by LTP and memory formation, we monitored the activation of multiple transcription factors (TFs) in rat hippocampal slices in which LTP had been induced by strong HFS. Among activated TFs, Wilm's Tumor 1 (WT1) was of interest due to its dual roles in transcription and mRNA targeting. Expression of WT1 in dendrites of CA1 pyramidal neurons increased after LTP induction, and after inhibitory avoidance (IA) training in rats, suggesting that WT1 contributes to LTP and memory consolidation. LTP induction by normally ineffective weak HFS was enabled by knockdown of hippocampal WT1 in rats (oligoantisense injection) or expression of dominant-negative (dn) WT1 in mouse forebrain; slices from WT1 dn/+ mice showed greater enhancement than WT1 dn/dn littermates. Moreover, retention of IA in rats was enhanced by WT1 knockdown in rats, and WT1 dn/dn mice showed improved contextual fear memory compared with WT1 dn/+ or wildtype littermates. WT dn/dn mice showed normal open field activity and novel object recognition / location performance. These data suggest that WT1 deficiencies could interfere with the ability to selectively remember significant (strong) versus insignificant (weak) events, and reduce behavioral flexibility by disrupting the ability to extinguish previous associations when contingencies change, with possible implications for autism spectrum disorder.

Support: NIH grants GM54508, GM071558.

DREAMM: In vivo and quantitative cell type-specific functional whole-brain circuit mapping in freely-moving animals

Michael Michaelides[1], Sarah Ann Anderson[1], Michael Krashes[2], Daniel Urban[3], John Neumaier[4], Gene-Jack Wang5, Bradford Lowell[2], Bryan Roth[3], Nora Volkow[5], Yasmin Hurd[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Beth Israel Deaconness Medical Center/Harvard University, [3]University of North Carolina, [4]University of Washington, [5]National Institute on Drug Abuse

Mapping functional connectivity of discrete, overlapping cells in the intact brain during behavior is crucial for advancing our understanding of brain function in normal and disease states. We developed an imaging technology (DREAMM) that allows quantitative, whole-brain mapping of cell-type specific functional circuits in freely-moving rats and mice. In rats, we documented DREAMM's ability to map whole-brain functional anatomy after transient, remote Gi-mediated activation of prodynorphin (Pdyn)- and proenkephalin (Penk)-expressing neurons of the nucleus accumbens shell. In mice, DREAMM was used to map functional anatomy after remote Gq-mediated activation of serotonin transporter (Slc6a4)-expressing dorsal raphe neurons and agouti-related peptide (AgRP)-expressing arcuate hypothalamic neurons. DREAMM revealed distinct network activation in response to each neuronal manipulation, which was congruent with anatomical projections of each cell-type and regional c-Fos activation. DREAMM responses were also consistent with behavior during the imaging period, as differences in motor and stress-related behaviors resulting from neuronal manipulations coincided with activation of motor and stress-related brain circuitry. DREAMM enables quantitative assessment of global cell-type specific neuronal circuits in freely-moving animals, which will be an important reverse-engineering strategy to decipher neuronal networks associated with normal and pathologic behavior.

A New Chromophore For Two-Color Control of Cell Signaling

Jeremy P. Olson[1], Matthew Banghatt[2], Hyung-Bae Kwon[2], Kevin T. Takasaki[2], Chiayu Q. Chiu[3], Michael J. Higley[3], Bernardo L. Sabatini[2], and Graham C.R. Ellis-Davies[1]

[1]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, [2]Department of Neuroscience, Howard Hughes Medical Institute, [3]Department of Neurobiology, Harvard Medical School

We have developed a caging chromophore, diethylaminocoumarin 450 (DEAC450), that absorbs blue light strongly and violet light 10-fold more weakly in the one-photon domain (350 nm vs. 470 nm) and 720 nm light 60-fold more weakly than 900 nm light in the two-photon domain. The absorption minimum is in the range (340-360 nm or 720 nm) that is traditionally used for photolysis of many widely used nitroaromatic caged compounds. Two-Color uncaging experiments have been performed in the one-photon domain. DEAC450-caged cAMP and CDNI-GABA were co-applied to cholinergic striatal interneurons, and the caged compounds were photolyzed to modulate the neuronal firing rate in a bi-directional way. In the two-photon domain, a proof of concept experiment was performed where DEAC450-caged Glu was uncaged at 900 nm at a spine head on pyramidal neurons in acutely isolated brain slices. The postsynaptic responses evoked were similar to spontaneous postsynaptic excitatory miniature currents. We are currently exploring further applications of this chromophore through the development of DEAC450-caged GABA and DEAC450-caged DA. We are also exploring various two-color experiments (one and two-photon) that were previously unachievable before development of this chromophore.

This work is supported by the NIH (GM053395 and NS069720).

Modeling spatial navigation in the human brain

Christian H Williams, Rita M Tavares, Daniela Schiller

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

How does the brain represent our location in space? In rodents, grid cells in the entorhinal cortex and place cells in the hippocampus encode the animal's position. In humans, angle-based fMRI models have provided evidence for the existence of similar grid cells, also in the entorhinal cortex. We hypothesized that the human brain represents location on a 3-D coordinate system, and that the vector between one's starting position and one's current position can be used to predict activation in areas associated with spatial navigation. To examine this we designed a virtual environment task where participants navigated a 3-D arena while undergoing functional MRI. Throughout the scan we recorded the participant's position along the X, Y, and Z axes. We then converted those cartesian coordinates into polar coordinates, which include a vector and the angles between that vector and each axis. We used a cosine function on the resulting angles to create predictors for BOLD signal analysis and found correlations with neural activation in the hippocampus and entorhinal cortex. These results suggest that the hippocampus and entorhinal cortex constitute a spatial navigation system that encodes the current location based on the angles and the distance measured from one's previous position.

PRC2 governs adult neuron specification and function

Melanie von Schimmelmann[1], Philip Feinberg[1], Silas Mann[2], Annie Handler[2], Scott Dewell[3], Anne Schaefer[1]

[1]Laboratory of Brain Epigenetics, Department of Neuroscience, Icahn School of Medicine at Mount Sinai

[2]Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University

[3]Genomics Resource Center, The Rockefeller University

The Polycomb Repressive Complex 2 (PRC2) plays a key role in controlling the expression of genes during early brain development. PRC2 function is executed by one of its catalytic methyltransferase components Ezh2 or Ezh1 that use histone H3K27 trimethyation to suppress the expression of neuronal and non-neuronal genes in a lineage-specific fashion. After completion of development, neurons continue to express Ezh1/2 and display high levels of H3K27 methylation at various gene loci. The preservation of PRC2 function in the adult brain suggests a possible role in maintenance of neuronal differentiated states. We hypothesize that in the adult brain, PRC2 switches its function from regulation of differentiation to regulation of neuronal specialization. In support of this model, we found that PRC2 deficiency in adult neurons abrogates the brain region-specific pattern of neuronal gene expression. These gene changes are associated with distinct behavioral defects and are accompanied by slow neurodegeneration. We propose that, similar to its role in early lineage differentiation, the PRC2 complex acts to preserve postnatal specialization of individual neurons and is essential for maintaining the neuron-specific patterns of gene expression required for highly specialized functions.

Abstracts

1 Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease.

Azeb Tadesse Argaw[1,2,3], Linnea Asp[1,2,3], Jingya Zhang[1,2,3], Kristina Navrazhina[1,2,3], Trinh Pham[1,2,3], John Mariani[1,2,3], Sean Mahase[1,2,3], Dipankar Dutta[1,2,3], Jeremy Seto[1,2,3], Elisabeth Kramer[1,2,3], Napoleone Ferrara [4], Michael Sofroniew[5] and Gareth John[1,2,3,6]

[1]CGD Center for MS, [2] Friedman Brain Institute and [3] Neurology, Icahn School of Medicine at Mount Sinai, New York. [4] Genentech, San Francisco. [5] Neurobiology, UCLA, Los Angeles, CA.

In inflammatory CNS conditions such as multiple sclerosis (MS), current options to treat clinical relapse are limited, and more selective agents are needed. Disruption of the blood-brain barrier (BBB) is an early feature of lesion formation that correlates with clinical exacerbation, and predisposes to edema, excitotoxicity, and entry of serum proteins and inflammatory cells. Here, we identify astrocytic expression of the angiogenic factor VEGF-A as a key driver of BBB permeability in vivo. In GfapCre:Vegfafl/fl mice, BBB breakdown, lymphocyte infiltration and neuropathology were restricted in inflammatory and demyelinating lesions, and paralysis was reduced in experimental autoimmune encephalomyelitis (EAE), a model of MS. Knockdown studies in CNS endothelium revealed activation of the downstream effector, endothelial nitric oxide synthase (eNOS) as a principal mechanism underlying effects of VEGF-A on the BBB. Systemic administration of the selective eNOS inhibitor cavtratin abrogated VEGF-A-induced BBB disruption and pathology in vivo, and cavtratin therapy protected against neurologic deficit in mice with EAE. Collectively, these data identify blockade of VEGF-A signaling as a protective strategy to treat inflammatory CNS disease.

Funding: NINDS, National MS Society, Beker Foundation, Noto Foundation.

2 Krüppel-like factor-6 is required for oligodendrocyte maturation and CNS myelination.

Linnéa Asp[1,2,3], Elisabeth Kramer[1,2,3], Xiomara Pedre[1,2,4], Dipankar Dutta[1,2,3], Young-Min Lee[5], Jia Liu[1,2,4], Jingya Zhang[1,2,3], César Berrios[1,2,3], Azeb Tadesse Argaw[1,2,3], Elena Zaslavsky2,3,6, Yuko Hara[2,4], David Braun[2,3,6], John Mariani[1,2,3], Trinh Pham[1,2,3], Sam Horng[1,2,3], Q. Richard Lu[7], Goutham Narla[8], Cedric Raine[9], Matilde Inglese[1,2,3], Patrizia Casaccia[1,2,4], Scott Friedman5 and Gareth John[1,2,3,9]

[1]CGD Center for MS, [2]Friedman Brain Institute, [3]Neurology, [4]Neuroscience, [5]Medicine and [6]Systems Biology, Icahn School of Medicine at Mount Sinai, New York [7]Developmental Biology, UT Southwestern, Dallas [8]Medicine, Case Western Reserve University, Cleveland, [9] Pathology, Albert Einstein College of Medicine, Bronx.

Successful CNS myelination requires oligodendrocyte progenitor (OPC) cell cycle withdrawal followed by maturation, but the mechanism coordinating this switch is incompletely characterized. Here, we show that this transition depends upon the Krüppel-like transcription factor, Klf6. Oligodendrocyte-selective Klf6 inactivation in mice produced tremor, ataxia, and death before three weeks of age, resulting from severe and selective oligodendrocyte loss and CNS myelination failure. Microarray analyses confirmed specific loss of oligodendrocyte transcripts in the Olig1Cre:Klf6fl/fl CNS, and revealed novel oligodendrocyte-expressed genes. ChIP in OPC cultures validated candidate Klf6-regulated effectors; Klf6 silencing resulted in their dysregulation and in OPC apoptosis upon cell cycle exit. In Olig1Cre:Klf6fl/fl embryos, OPCs were specified and migrated normally, but failed to express Klf6-induced genes and died at the onset of differentiation. Collectively, these data identify Klf6 as a key regulator of the oligodendrocyte proliferation-maturation transition, and show that it is necessary for CNS myelination. Funding: NINDS, National MS Society, Beker Foundation, Noto Foundation.

3 Extreme genetic heterogeneity among rare copy number variation in autism spectrum disorders

Mafalda Barbosa[1], Andreas Chiocchetti[2], Franziska Degenhardt[3], Regina Waltes [2], Sven Cichon[3], Christine Freitag [2], Dalila Pinto[1]

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[2] Dept. Child & Adolescent Psychiatry, Univ Frankfurt and [3]Life&Brain, Bonn, Germany

The etiology for ASD has only been identified in 10-20% of cases screened thus far. A cohort of 716 ASD German patients and their relatives (total of 2114 subjects) was assessed using the ADIR and ADOS diagnostic tools, and genotyped on the Illumina OmniExpress 730K-SNP-array. For CNV analysis, we used 4 calling algorithms: PennCNV, QuantiSNP, GNOSIS, CNVPartition. A total 1967 samples passed stringent quality control, 673 being probands. Of these, 394 were from trios, 42 quads and 20 large families. A matched control group of 1320 phenotyped subjects was also included in the study. A variety of de novo CNVs were detected in cases, from large aberrations (e.g. novel 13q14.2 5Mb-deletion) to rare pathogenic CNVs (e.g. Potocki-Lupski 17q12-dup-syndr). Interestingly, inherited CNVs along with second genomic hits were seen in six subjects (e.g. maternal NRXN1 intragenic deletion and de novo 22q11.2-duplication), giving support to a multi-hit hypothesis. Also, we found CNVs that often present a remarkably variable neurobehavioral phenotype such as the 3q29-deletion, which can present as intellectual disability, ASD, psychosis, anxiety, hyperactivity and/or aggressiveness. Further experimental validation and network modelling of genes intersected or disrupted by CNVs, are planned.

M.B. is supported by a scholarship (SFRH/BDINT/51549/2011) from Gulbenkian Foundation and Portuguese Foundation for Science and Technology

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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Schizophrenia (SCZD) is an incapacitating psychiatric disorder affecting greater than 1% of the population and, while symptoms usually appear during adolescence, SCZD is believed to be a neurodevelopmental condition. One potential, yet unproven, hypothesis is that SCZD arises, in part, due to abnormal neuronal migration and organization during development of the cerebral cortex. Recently, human cell-based models have been created by reprogramming skin samples from SCZD 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 SCZD, however, cell migration is often a difficult phenomenon to study, due to quantification challenges and cell heterogeneity. Using a newly developed assay, we show that chain migration (which is an important migration modality in NPCs) is indeed significantly lower in SCZD NPCs than control NPCs. Future work will investigate the mechanism driving this aberrant migration.

Thanks to Howard Hughes Medical Institute and the National Institute on Drug Abuse for funding.

5 Development of a hiPSC-derived model of dopamine activity in methamphetamine addiction

Michael Beaumont[1], Kristen Brennand[1], Martin Paulus[2] and Paul Slesinger[1]

[1]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[2]Department of Psychiatry, University of California, San Diego, La Jolla, CA

Dopamine neurons are integral to the reward pathway in the mesolimbic system that is directly affected by drugs of addiction. Currently, little is known about the activity of human dopamine neurons and recent advances in the generation of human induced pluripotent stem cells (hiPSCs) from fibroblasts provide a powerful method of creating models of human neuron populations. We are studying hiPSC-derived neurons as a model of human dopamine activity. Initially, fibroblasts from control (non-addicted) subjects are being evaluated to establish the basal electrical properties of their hiPSC-derived neurons. Neural progenitors from control iPSCs are differentiated in growth conditions favoring cultures enriched for dopamine neurons (20-30%). Immunostaining reveals expression of pan-neuronal (βIII-tubulin) and dopamine-specific (tyrosine hydroxylase, TH) markers. Over a 5-week differentiation period, neurons progress from immature, electrically inactive phenotypes to more mature phenotypes expressing sharp, fast, voltage-sensitive currents and evoked action potentials. Spontaneous firing activity, phasic synaptic currents, burst currents and hallmarks of dopamine neurons (e.g. Ih) are also seen. The next phase of this study will include neurons derived from fibroblasts collected from subjects participating in a methamphetamine addiction study at UCSD. Neurons from control and addiction-prone subjects will be exposed to methamphetamine to investigate any potential differences in dopamine function.

6 Diffusional Kurtosis Imaging study of experimental models of demyelination and remyelination

César A. Berríos-Otero[1], Lazar Fleysher[2], Jingya Zhang[1], Els Fieremans[4], Gareth John[1], and Matilde Inglese[1,2,3]

[1]Department of Neurology, [2]Radiology and [3]Neuroscience, Icahn School of Medicine at Mount Sinai, NY, NY.
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Advanced MRI techniques such as diffusion tensor MRI (DTI) can provide more pathologically specific markers than conventional MRI. DTI measures the micron-scale displacement of water molecules within densely packed axons and is particularly sensitive to diffuse microscopic injury in white matter (WM). Diffusion kurtosis imaging (DKI) is a recently developed diffusion MRI method to probe non-Gaussian diffusion properties, which provides conventional DTI parameters and additionally enables the quantification of diffusional non-Gaussianity through the estimation of the mean kurtosis (MK), a marker of tissue architecture complexity. MK in particular has been found to be sensitive to the type of microstructural variations that occur in gray matter injury. Furthermore, a recently introduced diffusion model of WM suitable for DKI analysis, has allowed for quantifying the intra- and extra-axonal diffusivities, the axonal water fraction, and the tortuosity of the extra-axonal space. These WM-parameters may be more specific, than standard DKI-parameters, to particular pathological processes. Here we report our initial findings investigating changes in these parameters and in corresponding histological features in normal and AdIl-1 or lysolecithin injected rodents as models of demyelination and spontaneous remyelination in GM and WM, respectively.

7 Novel familial Alzheimer's disease presenilin 1 mutation with complete loss of catalytic activity

Hannah Brautigam[1], Dara L. Dickstein[1], Patrick R. Hof[1], Sam Gandy[2,4,6], Michelle E. Ehrlich[2,3]

[1]Departments of Neuroscience, [2]Neurology, [3]Pediatrics, and [4]Psychiatry, Icahn School of Medicine at Mount Sinai and [5]James J. Peters VA Medical Center

A familial Alzheimer's disease (FAD)-linked presenilin 1 (PS1) missense mutation, L271V, results in a point mutant and a misspliced protein lacking exon 8 (PS1Δ8). The pathogenesis of PS1Δ8 is controversial because complete loss of γ-secretase function is unusual, and violates current concepts about γ-secretase structure. In mice, complete loss of PS1 and PS2 expression is embryonic lethal. A PS1Δ8 transgene expressed under control of the Thy1 promoter failed to correct the Notch-deficient embryonic PS1 KO phenotype. We also determined that PS1Δ8 was unlikely to be pathogenic in causing amyloid plaques, since human APP X PS1Δ8 mice failed to form plaques. Another mutant PS1 cross, PS1Δ9 x human APP, does form amyloid plaques as expected. Despite its unlikely role in cerebral amyloidogeneis, we propose that the current most likely model is that PS1Δ8 forms a heterodimer with endogenous PS1 and thereby modulates γ-secretase of substrates. In cell culture, we can demonstrate that wildtype PS1 and PS1Δ8 do interact and co-immunoprecipitate. Studying PS1Δ8 may provide a more accurate picture of γ-secretase structure and function, which, in turn, may improve design of γ-secretase modulators for treating or preventing AD.

We thank NIH P01 AG10491 (S.G., M.E.E.), P50 AG05138 (Mary Sano; S.G., D.L.D, P.R.H.), and F31AG039890-01A1 (H.B.)

8 Mitochondrial Aging and Regeneration in Stem Cell Reprogramming

Andrew Browne, Robert Sebra, Gang Fang, Elodie Drapeau, Joe Friedman, Eric Schadt, Joseph Buxbaum, Anne Schaefer

Icahn School of Medicine at Mount Sinai

Induced pluripotent stem cells (iPSCs) offer tremendous therapeutic potential for a variety of reasons including their ability to be derived from widely available cells such as fibroblasts and their potential to be differentiated into any human cell type. Possible applications of iPSCs include cell replacement or gene therapy; however, there is a strong debate as to whether iPSCs may still harbor some age-related changes despite seeming very similar to embryonic stem cells (ESCs). While most current research has focused on changes to nuclear DNA during reprogramming, mitochondrial DNA (mtDNA) is a prime candidate carrier of age-related damage due to its elevated exposure to reactive oxygen species (ROS), which can cause mutations or chemical modifications to mtDNA over time that could persist after reprogramming. Through the use of third generation sequencing technologies, the DNA sequences and base modification profiles of mtDNA purified from fibroblasts and iPSCs of young and old patients, as well as ESCs, are being assessed to determine the effects of aging and reprogramming on mtDNA. If it is determined that mitochondria do undergo age-related changes that are reversed during reprogramming, the repair mechanism can then be identified and exploited, whereas evidence that such damage occurs and is not repaired could hold grave implications for the prospective therapeutic applications of iPSCs.

Research funded by the NIMH

9 Overexpression of protein regulator RGS-14 in visual area 2 rescues perirhinal lesion-induced impairments in recognition memory in monkeys.

Philip Browning[1], Paula Croxson[1], Zafar Khan[2], Mark Baxter[1]

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The protein regulator of G protein signaling-14 (RGS-14) is associated with synaptic plasticity in the rat and monkey brain. The overexpression of RGS-14 in visual area 2 (V2) massively increases the duration of object recognition memory in normal rats. In monkeys object recognition memory depends on information flow from V2 to the inferior temporal cortex. We hypothesized that overexpression of RGS-14 in V2 could rescue lesion-induced impairments in object recognition memory. We trained 2 monkeys on a difficult object recognition task, where they had to remember multiple lists of 20 objects each day, at delays up to 10 minutes. Perirhinal cortex lesions significantly impaired memory in both monkeys. Following a second surgery to inject lentivirus to overexpress RGS-14 in V2, both monkeys showed an improvement in recognition memory skewed towards trials in which the delay was long, suggesting a memory-specific improvement (and not just a general improvement in vision or attention). Although the apex of the pathway for object recognition is the perirhinal cortex, this study suggests that enhancement of activity in upstream areas may be a successful approach to the treatment of memory disorders. The use of this technology could be useful in boosting processing in multi-synaptic networks and thus improving compensatory mechanisms following brain damage. (MSSM)

10 Adolescent THC exposure alters dendritic branching of prefrontal cortex pyramidal neurons and impulsive choice

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Human studies have linked adolescent cannabis use with increased risk of developing schizoaffective disorders and addiction. Rodent models of adolescent cannabis exposure suggest these long-term alterations in adult behavior may be, at least in part, causative. The prefrontal cortex (PFC) is an intriguing locus for potential developmental insults as it continues developing throughout adolescence. We examined THC adolescent exposure in relation to PFC development and related behaviors. Male Long Evans rats were administered THC during adolescence and examined in relation to: 1) dendritic complexity of pyramidal neurons in the PFC, 2) gene expression in the PFC, and 3) behaviors related to decision-making mediated by the PFC. Analysis of reconstructed neurons demonstrated alterations in dendritic branching differentially at 24 hrs and 2 wks after the last injection suggesting THC exposure during adolescence may disrupt the normal developmental trajectory of the PFC. qPCR identified genes related to endocannabioid signaling, glutamate neurotransmission, neurite remodeling, and synaptic adhesion that were dysregulated between 24hrs and 2wks in THC-treated animals. In addition, THC-treated animals exhibited increased impulsive choice behavior while effort-based decision making was not affected. We suggest alterations in the PFC and related behaviors induced by adolescent THC exposure may mediate increased vulnerability to schizoaffective disorders and addiction.

Supported by NIH grant DA023214

11 Active Avoidance Learning is Associated with Activation of Caudate and Suppression of Amygdala Activity.

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Background: Active Avoidance (AA) is an instrumental form of fear learning where the learner identifies an action that enables avoidance of a threatening stimulus. AA has been used to model both anxiety disorders and addiction in animals. Studying the neural mechanisms of AA in humans may offer new insight into the neurobiology of such psychiatric illnesses.

Methods: Twenty-eight healthy participants (ages 19-54, 14 female) completed an AA task during fMRI. Subjects learned via trial-and-error to shuttle a marker from one side of a virtual game-board to the other in order to avoid aversive stimuli. Using whole-brain general linear modeling we identified brain regions that exhibited changes in activity during AA.

Results: AA training suppressed amygdala activity bilaterally but elevated caudate activity bilaterally. Conclusions: The striatum was active during AA. This finding is consistent with the role of striatum in other forms of instrumental learning. Subjects also displayed less amygdala activity during AA than while at rest, which is likely to reflect a reduction in central nucleus signaling. Inhibition of the central nucleus, which projects to brainstem and hypothalamic nuclei that trigger automatic fear responses, may permit expression of more flexible and goal-directed behavior. As aversive learning that elicits changes in neurocircuitry implicated in psychiatric illness, future studies of AA in clinical populations could enrich our understanding of psychopathology's biological substrates.

Support: T32MH096678-01

12 Comparison of the connections of laryngeal motor cortex in humans and monkeys using diffusion tractography

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The laryngeal motor cortex (LMC) is essential for the production of learned but not innate vocalizations. Therefore, LMC damage renders human patients unable to speak and sing, while having no apparent effects on monkey vocalizations. Using MRI diffusion tractography, we aimed to identify network differences between humans and non-human primates, which may provide evolutionary perspective on the unique human ability to control learned voice production.

We compared 5 macaque monkeys and 13 healthy controls. We chose bilateral LMC seed regions in the motor cortex, based on previous studies of syllable production (humans) and laryngeal muscle stimulation sites (monkeys). Probabilistic tractography maps were averaged to assess the percentage overlap between monkeys and humans, and thresholded ($p \leq 0.05$ corrected).

Overall, there was a large degree of similarity between the brain-wide connections of LMC in humans and macaque monkeys, but there were also differences between species. Monkeys had much greater connectivity with anterior cingulate regions, which are particularly important for the production of species-specific vocalizations. Humans had more specific connections with the posterior temporo-parietal, middle/posterior cingulate motor and cerebellar areas, supporting a more active sensorimotor integration with the motor pathways originating from the LMC. These differences in LMC structural connectivity may underlie the ability to learn and control voluntary voice production, such as speech and song, in humans.

Funding: Charles H. Revson Foundation (PC), R00DC009629, R01DC011805 (KS)

13 Histone arginine methylation in the nucleus accumbens in response to chronic cocaine and stress

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Histone methylation on Lys (K) residues has been linked to a number of neurological and psychiatric disorders, including drug addiction and depression. In particular, we have shown that drug- and stress-induced long-term changes in gene transcription and neuronal function involve reductions in global levels of dimethylation of Lys9 on histone H3 (H3K9me2) in nucleus accumbens (NAc), changes mediated by repression of the H3K9 methyltransferase G9a. 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), that asymmetrically or symmetrically dimethylate Arg.

First, we investigated the effects of a chronic cocaine regimen (20 mg/kg, i.p., daily for 7 days) on PRMT expression in the NAc of mice. Parallel studies are exploring PRMT regulation in stress models. These novel findings suggest that Arg methylation of core histone tails may play an important role in addiction- and stress-related changes in gene transcription in brain.

14 Convergent, but gender specific, gene-expression pathways underlying individual differences in response to trauma: regulation by glucocorticoid-receptor

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Identification of molecular pathways associated with individual differences in the behavioral response to trauma is essential for understanding PTSD neurobiology. The use of animal models is necessary given the methodological constraints in human studies.

We exposed rats to predator scent stress (PSS) and, a week after, measured anxiety and arousal. Rats responded heterogeneously to the stressor and with the use of cut-off behavioral criteria, we identified rats displaying a PTSD-like syndrome(~25%) and those completely recovered(~25%). In tissue obtained 24h later, using bead-microarrays, gene-expression was evaluated in blood and three brain areas (amygdala, hippocampus, frontal cortex).

A gene-expression overlap across tissue demonstrated the existence of convergent signaling pathways underlying individual differences in response to trauma. Furthermore, there were pathways shared by both genders (e.g.,oxidative-stress response in blood, mTOR and neurotrophin/TRK signaling in hippocampus). Among the differentially expressed genes in PTSD-like rats, those regulated by the glucocorticoid-receptor(GR) were over-represented (e.g.,FKBP5,NPY). In females, GR was significantly involved in all tissue, but in males only in blood. In accordance, in blood, an active inflammatory response was present in both genders, whereas, in the brain, altered norepinephrine-related signaling was present only in PTSD-like females. In a follow-up study, corticosterone administration, 1h after PSS, was able to prevent the occurrence of PTSD-like rats.

GR-regulated gene-expression underlies individual differences in response to trauma, yet with tissue-specific gender differences.

Funded by DoD(W81XWH-08-2-0021).

15 Differential Expression of the Lynx Family in Visual Cortex: Implications for Critical Period Plasticity

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The ability of the mammalian neocortex to adapt based on experience greatly declines after a developmental phase known as the critical period. Recent findings from our lab revealed that lynx1, a protein that binds and inhibits signaling through nicotinic acetylcholine receptors (nAChR), acts as a brake to limit ocular dominance plasticity following the critical period via increased expression. Lynx1 belongs to a larger lynx family of proteins with high sequence homology. Another member of the lynx family, lypd6, has also been shown to bind and modulate nAChRs. However, lypd6 binding potentiates calcium currents through nAChRs. We hypothesize that members of the lynx family may act in concert to regulate critical period plasticity through modulation of nAChRs. We utilize in situ hybridization to show that expression of lypd6 and close homologue, lypd6b, declines across development in visual cortex. Further, we show the differential cellular and laminar distribution of lynx1 and lypd6 in visual cortex, suggesting potentially unique functions and/or circuits. By using a combination of molecular and physiological techniques, we will attempt to elucidate the contribution of lynx family members to visual cortical plasticity and understand how nicotinic homeostasis is achieved.

Funded by NIDA T32 Training Grant: 5T32DA007135-29 (M.D.), MCHDI, Knights Templar Eye Foundation, Whitehall Foundation, March of Dimes

16 Functional connectivity between insula and amygdala predicts habituation to repeated negative images

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Behavioral habituation during repeated exposure to aversive stimuli is an adaptive process. However, the way in which changes in self-reported emotional experience are related to the neural mechanisms supporting habituation remains unclear. We aimed to probe these mechanisms by repeatedly presenting negative images to healthy adult participants and recording behavioral and neural responses using functional magnetic resonance imaging (fMRI). Results indicated significant habituation behaviorally as well as in amygdala, occipital cortex, and ventral prefrontal cortex (PFC) activity, whereas bilateral posterior insula, dorsolateral PFC, and precuneus showed sensitization. Posterior insula activation during image presentation predicted greater negative affect ratings for both novel and repeated negative images. Further, repeated negative image presentation was associated with increasing functional connectivity between posterior insula and amygdala, and this increasing connectivity predicted increasing behavioral habituation. These results indicate that habituation is subserved in part by insula-amygdala connectivity and involves a change in the activity of bottom-up affective networks.

Funding: NIH R01 MH077813 to HWK

17 Suprathreshold Galvanic Vestibular Stimulation as an analog of vestibular dysfunction

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In the past we have shown that exposure to increasing amplitudes of Galvanic vestibular stimulation (GVS) induces a corresponding increasing deficit in postural control, cognition and autonomic function. Previous studies have suggested that suprathreshold GVS induces a similar pattern of postural instability as the one observed on bilateral vestibular loss. The aim of the present study was to determine whether different current intensities would affect somatosensory, visual, and vestibular sensory system similarly to patient affected by vestibular deficits. We assessed postural control in unilateral (right and left) and bilateral vestibular loss patients, an aged matched healthy control group, and during pseudorandom binaural bipolar GVS in healthy subjects at one of three current amplitudes (1 mA, 3.5 mA, 5 mA). Balance was assessed with sensory organization test (SOT) that quantifies the effectiveness of vestibular, visual and somatosensory input to postural control. Results showed that GVS significantly affects vestibular control of posture compared to baseline at all current amplitudes, whereas somatosensory and visual performance was unaffected. Vestibular patients showed a significant decrease in vestibular and visual response compared to control. Suprathreshold GVS 5 mA showed a similar large effect size to unilateral and bilateral vestibular loss patients relative to their aged matched control.
NASA NCC 9-58 and NNX09AL14G

18 Sensorimotor adaptation to Galvanic Vestibular Stimulation: a longitudinal study.

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Our previous study showed that exposure to Galvanic Vestibular Stimulation (GVS) induces temporary postural deficits similar to the ones experienced by astronauts after microgravity exposure. Preliminary evidence suggests that repeated exposures to GVS might induce adaptation of sway response. We studied whether repeated exposure to pseudorandom GVS over a 3 month period facilitates the adaptation response. Twenty healthy subjects were randomly assigned into 2 groups: suprathreshold (5mA) GVS, and subthreshold (1mA). The test battery included: Romberg, sensory organization test (posturography), dynamic visual acuity, and torsional eye movement. Each test was performed with no GVS, and then with 10 min of GVS per session for 12 consecutive weeks. Sensorimotor adaptation was also measured during two follow up sessions at weeks 18 and 36. Results showed that subthreshold GVS did not affect vestibular scores. Suprathreshold GVS significantly decreased vestibular scores during the first few weeks, with postural performance returning to baseline around the 6th week of exposure. This improvement was maintained during the follow up sessions. Our results suggest that 60 min of subthreshold GVS are sufficient to elicit adaptation to the stimulus. No significant changes were shown in low-level vestibulo-ocular reflexes during torsional eye movement, or vestibulo-spinal reflexes during Romberg; confirming that adaptation only occurs at the level of the CNS. NASA NCC 9-58; NNX09AL14G

19 Cell Type-Specific Epigenetic Remodeling in Prefrontal Cortex during late prenatal and postnatal development across species.

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Little is known about cell-type specific or species-specific regulation of gene expression in pre-frontal cortex (PFC) development by epigenetic mechanisms due to the heterogeneity of neuronal and glial populations in the PFC region.

We recently discovered evidence of coordinated epigenetic regulation of histone 3 lysine 4 trimethylation (H3K4me3) landscapes at more than 1000 transcription start sites (TSS) and other regulatory DNA within the neuronal epigenome of the human PFC, with progressive changes (either up- or down-regulation) starting before birth and continuing deep into adolescence. From these findings, we hypothesize that cortical neurons undergo a preprogrammed remodeling of histone methylation landscapes around transcription start sites during the extended period of mammalian brain development. Future studies are aimed at further characterizing H3K4me3 profiles of macaque and mouse and identifying cis-regulatory features of TSS that are developmentally regulated in the human, macaque and mouse cortex through large-scale profiling of H3K4me3 binding sites. Of particular interest is TSS with conserved AP-1 early response motifs, and various multiple PAX and STAT transcription factor motifs.

Supported by the National Institutes of Health (PI: Schahram Akbarian)

20 PRC2 governs adult neuron specification and function

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The Polycomb Repressive Complex 2 (PRC2) plays a key role in controlling the expression of genes during early brain development. PRC2 function is executed by one of its catalytic methyltransferase components Ezh2 or Ezh1 that use histone H3K27 trimethyation to suppress the expression of neuronal and non-neuronal genes in a lineage-specific fashion. After completion of development, neurons continue to express Ezh1/2 and display high levels of H3K27 methylation at various gene loci. The preservation of PRC2 function in the adult brain suggests a possible role in maintenance of neuronal differentiated states. We hypothesize that in the adult brain, PRC2 switches its function from regulation of differentiation to regulation of neuronal specialization. In support of this model, we found that PRC2 deficiency in adult neurons abrogates the brain region-specific pattern of neuronal gene expression. These gene changes are associated with distinct behavioral defects and are accompanied by slow neurodegeneration. We propose that, similar to its role in early lineage differentiation, the PRC2 complex acts to preserve postnatal specialization of individual neurons and is essential for maintaining the neuron-specific patterns of gene expression required for highly specialized functions.

21 Genetic Background Modulation of the Phenotype in a Shank3 mouse model of autism

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Haploinsufficiency of SHANK3, caused by chromosomal abnormalities or mutations that disrupt one copy of the gene, leads to a neurodevelopmental syndrome called Phelan-McDermid Syndrome that can include absent or delayed speech, intellectual disability, neurological changes, and autism spectrum traits. The SHANK3 protein forms a key structural part of the post-synaptic density. Changes in synaptic plasticity and behavior due to a mutation at a single locus are quite frequently modulated by other loci, most dramatically when the entire genetic background is changed. In mice, each strain of laboratory mouse represents a distinct genetic background. We have assessed the effects of three genetic backgrounds - C57BL/6, 129SVE, and FVB - on the phenotype of Shank3- wild-type, heterozygous and null mice in sensory-motor, social, learning and memory behaviors and seizure susceptibility. We observed moderate strain differences in anxiety, social and fear conditioning tests. When such differences are identified, quantitative trait locus analysis is feasible, and can lead to identifying modifier loci that change the severity of the phenotype. and can become additional targets for drug development. Furthermore we have shown a strong reduction of seizure induced by pentylenetetrazol, a GABA antagonist, in heterozygous and null across the three strains of mice. Further characterization of the GABA neurotransmission in Shank3 mice could reveal disrupted pathways and provide interesting therapeutic targets in Shank3-haploinsufficiency syndromes.

Funding R01MH093725

22 Impairments of chromatin remodeling and synaptic plasticity in the striatum of human heroin abusers

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As heroin abuse continues to have detrimental impacts, underlying neurobiological disturbances that could better guide treatment interventions need further exploration. Abnormal gene transcription is evident in opiate users, but no information exists regarding related epigenetic mechanisms, key regulators of transcription, in human drug users. As such, we studied the human striatum to characterize epigenetic marks and genes related to synaptic plasticity, dysregulation of which is a core feature of addiction disorders.

We used a homogeneous postmortem collection of human heroin abusers to explore transcription of genes related to synaptic plasticity and glutamatergic neurotransmission in the striatum (microarray, Nanostring, qPCR), as well as to assess associated epigenetic mechanisms (Western blot, ChIP).

We observed marked perturbations of gene expression and epigenetic regulation. In the nucleus accumbens, we found heroin-related transcriptional changes of chromatin remodeling enzymes and of genes involved in synaptic plasticity and glutamatergic neurotransmission. In the dorsal striatum, NCOA1 acetyltransferase and global histone H3 acetylation significantly increased with years of heroin use, and showed negative correlations with heroin toxicology. In addition, the gene body of selected glutamatergic genes was significantly hyperacetylated.

Overall, the current data suggest that epigenetic perturbations, particularly the hyperacetylation of histone H3, and thus the resulting more open chromatin configuration, might be intimately involved in the regulation of heroin-induced striatal synaptic plasticity.

Supported by the NIH grant DA15446.

23 Modulation of Insula Activity During Emotion Regulation Using Real-Time fMRI

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Background: Real-time functional magnetic resonance imaging (rtfMRI) represents a recent methodological advance whereby feedback of the blood-oxygenation-level-dependent (BOLD) signal allows for high spatial-resolution on-line monitoring of brain activation by subjects. Although previous rtfMRI research indicates subjects can increase insula activity using feedback, down-regulation of insula activity may be a better therapeutic target given the role of the insula in processing negative emotional stimuli.

Methods: Subjects are trained to use cognitive strategies to reduce negative emotional response to disgust images. During scans, subjects try to reduce insula activation to disgust images ("REDUCE" trials) using real-time feedback of BOLD signal from this region. On "LOOK" trials, subjects view disgust or neutral images without trying to regulate brain response. After each trial, subjects rate how negative they feel.

Results: Four healthy subjects (of 21 planned), ages 18-50, were recruited. Subjects reported significantly less negative emotion during REDUCE trials than LOOK trials (2.23±0.65 vs. 2.72±0.97, $p=0.001$), as well as less negative emotion following neutral relative to negative images (1.23±0.51 vs. 2.48±0.86, $p<0.001$). Analysis of brain activity is pending further scans.

Conclusions: Healthy individuals presented with negative images are able to decrease their levels of negative emotion using cognitive strategies, and feedback provided via rtfMRI may be an effective means of enhancing this capacity.

Funding: Le Foundation (5/28/2012-5/27/2014)

24 Olfactory Conditioning in Social Decision Making

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Background: The fundamental attribution error (FAE) is a well-documented phenomenon in which people attribute behavior of others more heavily to dispositional attributes (personality) and under-weigh situational attributes (circumstances). This experiment examines the effects of olfactory conditioning with an unpleasant odor on the FAE and underlying neural circuitry using functional magnetic resonance imaging. We hypothesized that olfactory conditioning would make subjects more prone to the FAE, and this would be linked to decreased activation of the dorsolateral-prefrontal-cortex (DLPFC) and increased activation of subcortical structures.

Methods: Subjects are presented in the scanner with faces of two people, one of which is paired with an unpleasant odor during a conditioning task. In the subsequent FAE task, subjects are presented with behavioral and situational information about each person, and subsequently asked to rate (1-8) how morally appropriate the behavior is, whether it's caused by situation or disposition, and how much they like the person.

Results: Seven healthy subjects (of 20 planned) were recruited. Subjects rated people paired with odor as significantly less likeable ($p=0.002$) and their behavior as significantly more influenced by disposition than situation ($p=0.004$). We expect situational attributions will entail increased DLPFC activity; dispositional attributions will recruit subcortical areas.

Conclusions: Olfactory conditioning with unpleasant odors appears to increase FAE susceptibility in healthy individuals, which may be relevant to disorders of social decision making such as Borderline Personality Disorder.

Funding: Le Foundation

25 Effects of Phthalate Exposure on the Developing Rat Brain

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Phthalates are endocrine disrupting chemicals and components of many household items. Epidemiological studies demonstrate a correlation between in utero exposure to phthalates and impaired neurobehavior. To mechanistically explore the affects of phthalate exposure on neurodevelopment, we examined the brain transcriptome of offspring of rat dams adminstered 50mg/kg·day di-2-ethylhexyl phthalate or (DEHP) or corn oil control during pregnancy and lactation. Because phthalates differentially affect males and females, we stratified our analyses by sex. We found that a subset of sexually dimorphic genes was altered by phthalate treatment in males, indicating "feminization" of gene expression. Striking sex differences were observed, with DEHP exposed males but not females exhibiting upregulation of genes involved in immune response. There was no increase in IL-6 levels in the serum of the DEHP exposed animals, suggesting that systemic inflammation does not contribute to the observed changes in the brain. Treatment of cultured rat microglia with the active DEHP metabolite MEHP induced IL-6 gene expression. In contrast, no response was observed in cultured astrocytes or neurons. Taken together, our studies suggest a novel mechanism by which phthalates alter the development of the brain by the induction of microglial-dependent local inflammation in a sex-specific manner.

These studies are supported by a Pilot Project Grant to Sarah Evans from the Mount Sinai School of Medicine Children's Environmental Health Center.

26 Role for the Granin Protein VGF in Dense Core Secretory Vesicle Biogenesis and Hypertension

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Secretion of hormones, growth factors, and neurotransmitters from dense core secretory granules (DCGs) in neuronal and endocrine cells is a highly regulated process. DCG biogenesis involves the interaction of multiple resident proteins, including the granins chromogranin A (CgA) and chromogranin B (CgB), which physiologically regulate blood pressure. The granin family member VGF, a neuronal and endocrine secreted protein and neuropeptide precursor, is selectively expressed in neural and endocrine tissues, including adrenal medulla, and is processed into bioactive peptides and secreted via the regulated pathway. We therefore investigated whether VGF plays a role in DCG biogenesis. Expression of exogenous VGF in cells that lack a regulated secretory pathway resulted in the formation of DCG-like structures and depolarization-induced secretion. Germline VGF ablation led to decreased DCG size in noradrenergic adrenal chromaffin cells, increased adrenal norepinephrine and epinephrine content, decreased adrenal CgB content, increased plasma epinenephrine levels, and hypertension. Our studies establish a role for VGF in blood pressure regulation and in DCG biogenesis, the latter potentially impacting other endocrine and neuronal cells with regulated secretory pathways.

27 Brain tissue sodium concentration in multiple sclerosis

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Inflammation, demyelination and axonal degeneration occur within the white matter in the brain in Multiple Sclerosis (MS). While action potential propagation cannot be supported by demyelinated axons efficiently, the expression of Na channels along demyelinated axon regions can lead to restoration of the conduction even in the absence of remyelination. Unfortunately, sodium influx through persistently activated Na channels may lead to an accumulation of intra-axonal sodium, promote reversal of the sodium/calcium exchanger and may lead to a lethal overload in intra-axonal calcium. Therefore, sodium MRI may provide an indicator of cellular and metabolic integrity and ion homeostasis in patients with MS.

Previous Na-MRI studies in MS patients reported an increase (compared to healthy controls) of brain tissue sodium concentration which represents a weighted average of the extracellular and intracellular sodium content. In this study, we use single-quantum and triple-quantum filtered Na-MRI at 7T to quantify intracellular sodium concentration (ISC) and intracellular sodium volume fraction (ISVF) in 26 MS patients (16F; 44.81±12.5 yrs) and in 26 age and gender matched healthy controls (15F; 44.23±14.7yrs).

Our preliminary results show an increase in ISC and decrease in ISVF in MS patients compared to healthy controls. These results are in agreement with the hypothesis of accumulation of intracellular sodium and tissue damage in MS.

This study was supported in part by NIH Grant R01NS051623.

28 Long-term Cognitive Effects of Metabolic Syndrome

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Metabolic syndrome is an amalgamation of disorders including hypertension, obesity, and impaired glucose metabolism. In addition to this, metabolic syndrome has been associated with impaired cognitive function. It is believed that the cognitive effects caused by metabolic syndrome at an early age could remain even after the loss of metabolic syndrome's symptoms. Here we induced metabolic syndrome in mice at an early age using a high fat diet alongside Standardized Grape Polyphenol Preparation (SGP). SGP has been shown to prevent the accumulation of amyloid beta – a peptide which composes the plagues in Alzheimer's Disease – and improve cognitive function. After 16 weeks of treatment the mice were put back on a regular low fat diet and their cognitive function was tested. Those mice which had suffered from metabolic syndrome showed a significant decline in cognitive function compared to control, despite the loss of insulin resistance. In addition we also saw improvement in mice treated with grape seed extract, compared to control. We are currently conducting electrophysiology studies to further explain the results observed.

29 Homeostatic adaptations of VTA dopamine neurons underlie resilience to severe social stress

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The neurophysiological basis of resilience to stress-induced depression is poorly understood. Utilizing cell-type-specific electrophysiological and optogenetic approaches, we unexpectedly found that the resilience phenotype, which has a control-level firing activity of ventral tegmental area (VTA) dopamine neurons, showed dramatically increased hyperpolarization-activated cation channel-mediated current (Ih), an ionic mechanism underlying the hyperactivity of these neurons in susceptible phenotype, and observed that resilience also showed significantly increased potassium (K+) channel-mediated currents. We also revealed that further increase of dopamine neuron hyperactivity in the susceptible phenotype, by enhancing Ih or by optogenetic stimulation, induced a homeostatic increase of K+ currents and behaviorally converted the susceptible phenotype to resilient, a conceptually novel antidepressant effect. These results demonstrate that resilience is maintained by stabilizing the activity of VTA dopamine neurons through the homeostatic balance of dramatically increased Ih and actively counteracting K+ currents, and provide direct evidence that promoting resilience shows treatment efficacy.

Supported by R01MH092306, F32 MH096464 and J&J/IMHRO.

30 Cadherin 8 in the molecular control of prefrontal-striatal circuit development

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Autism spectrum disorders (ASDs) are characterized by impaired social interactions, communication deficits, and repetitive behaviors. These behavioral abnormalities have been associated, in part, with developmental defects in the prefrontal cortex (PFC) and PFC-striatal projections, and have been linked to synaptic dysfunction. Genetic deletions, copy number variants, and mutations of genes encoding cell adhesion molecules have been linked to ASDs. A recent study identified a rare familial microdelection of a single gene on chromosome 16q21, which encodes Cadherin 8 (Cdh8). Cdh8 is a synaptic adhesion molecule that plays an important role in laminar development and synaptic plasticity. We hypothesize that Cdh8 is essential for the development of PFC-striatal circuitry, and predict that disruption of Cdh8 leads to abnormal behaviors associated with ASDs. Preliminary data indicated that Cdh8 mRNA and protein are highly enriched in the PFC and striatum. Ultrastructural analysis revealed that Cdh8 concentrates at corticostriatal synapses. We will evaluate the impact of shRNA-mediated Cdh8 knockdown on mouse PFC-striatal connectivity using in utero electroporation. We will examine PFC-striatal axonal projections of transfected neurons and determine how Cdh8 knockdown affects synapse numbers and morphology of D1- and D2-receptor expressing subpopulations of striatal neurons. These studies will reveal how Cdh8 controls the molecular development and organization of PFC-striatal circuitry, and whether Cdh8-dependent deficits contribute to ASDs.

Funding: Simons Foundation

31 Small Molecules promoting Oligodendrocyte Lineage Progression

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Oligodendrocytes are the myelin-forming cells of the central nervous system and play an essential role in modulating neuronal function. Previous studies revealed histone deacetylation as critical in regulating oligodendrocyte progenitor differentiation. Histone acetylation is the result of the equilibrium between lysine acetyltransferases, which add acetyl groups and deacetylasesx that remove them. Therefore, small molecules inhibiting acetyltransferase activity might be beneficial in mimicking deacetylation. In this study, using a target structure-guided approach, we developed and tested three different small molecules called Olinone, CM417 and MS683. They represent selectively inhibitors of bromodomains, protein domains present in several transcriptional regulators and responsable for binding to acetylated lysine residues. We show that Olinone, MS683 and CM417, in a dose-dependent manner, favor the progression of progenitors towards a myelinating phenotype. Our study indicates that bromodomain inhibitors represent a promising venue to modulate myelin repair in demyelinating disorders.

Supported by Conduit Grant UL1RR029887

32 Cerebrospinal fluid from multiple sclerosis patients induces oxidative stress and mitochondrial dysfunction in unmyelinated neurons

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Axonal damage is critical for permanent disability in MS patients but current therapies have not proven to stop or prevent neurodegeneration of which pathogenesis is largely unknown. The evidence of extensive cortical lesions suggests that cerebrospinal fluid (CSF) might contribute to progression of disease. In order to assess whether components of the CSF can be toxic to neurons in MS we used a xenogenic system consisting on rat primary neuronal cultures incubated with CSF from MS patients or controls. A bioenergetic study of the cells showed an increased oxidative damage in cells treated with CSF of MS patients compared to controls, as well as an impairment on mitochondrial function and axonal beading. Furthermore, the effect on neuronal bioenergetic profile significantly correlated with levels of neurofilament light chain in the CSF samples. In summary, these data show that factors released in the CSF can promote MS progression by causing a direct damage to neurons. This study will help to elucidate new molecular targets for neuroprotection and to find surrogate markers for diagnosis and prognosis of MS patients.

Grant: NMSS (RG-4134-A9)

33 Nicotinamide Riboside attenuates BACE1 mediated Amyloidogenesis through PGC-1a mediated signaling pathway in Alzheimer' disease

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In this study we tested the hypothesis that Nicotinamide riboside (NR) treatment in an AD mouse model could attenuate Aβ toxicity through the activation of promotes peroxisome proliferator-activated receptor (PPAR)-γ co-activator 1 (PGC)-1α-mediated β-secretase (BACE1) degradation. we found 1) dietary treatment of Tg2576 mice with 250 mg/kg/day of NR for three months significantly attenuates cognitive deterioration in Tg2576 mice and coincides with an increase in the steady-state levels of NAD+ in the cerebral cortex; 2) Application of NR to hippocampal slices (10μM) for 4 hrs abolishes the deficits in LTP recorded in the CA1 region of Tg2576 mice. 3) NR treatment promotes PGC-1α expression in the brain coinciding with enhanced degradation of BACE1 and the reduction of Aβ production in Tg2576 mice. Further in vitro studies confirmed that BACE1 protein content is decreased by NR treatment in primary neuronal cultures derived from Tg2576 embryos, in which BACE1 degradation was prevented by PGC-1α-shRNA gene silencing; 4) Both NR treatment and PGC-1α overexpression enhance BACE1 ubiquitination and proteasomal degradation. Our studies suggest that dietary treatment with NR may benefit AD cognitive function and synaptic plasticity, in part by promoting PGC-1α-mediated BACE1 ubiquitination and degradation, thus preventing Aβ production in the brain.

34 The functional and neurobiological correlates of behavioral predictors of resiliency to social defeat

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Depression is a neuropsychological disorder that affects millions of people, however, two thirds of patients are resistant to classical anti-depressants. Other drug-resistant neuropsychological disorders, such as schizophrenia and Alzheimer's Disease, have recently found success via pre-symptomatic treatment. Although this method sounds promising, before pre-symptomatic treatment may be utilized,adequate predictive measures are necessary. Social defeat is a well-accepted animal model of depression. Using this model, previous research has demonstrated the involvement of the mPFC and hippocampus in resiliency to depression. With this in mind, we developed a non-invasive behavioral paradigm to quantify activity in these regions prior to defeat and correlate this activity to functional and neurobiological mechanisms. We found that good performance on a PFC-based task and poor performance on a hippocampus-based task predicted resiliency.To observe if the neurobiological correlate of this behavior, we analyzed cFos expression in various regions of the prefrontal cortex and found that while there was no significant difference between absolute numbers of puncta per region, there are some promising trends in relative activity which may become more pronounced as data continues to be analyzed. Taken together, these results demonstrate the promis of this method for predicting resiliency to social defeat.

35 Age, gender, and education are associated with cognitive performance in an Israeli elderly sample with type 2 diabetes

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Objectives: To evaluate the relationships of age, education, and gender with performance on neuropsychological tests in a cognitively intact, elderly Israeli sample with type 2 diabetes.

Methods: In cognitively intact Israelis, ages 65-84 (N=862), multiple regression assessed associations of performance on 17 neuropsychological tests, including the CERAD battery, with age, education, and gender.

Results: Higher education and younger age were consistently associated with better performance. Women outperformed men on all memory tasks; men outperformed women on two non-verbal measures.

Conclusions: In a cognitively intact, elderly Israeli sample with diabetes, better test performance is associated primarily with higher education, followed by younger age and gender differences. Although type 2 diabetes is associated with cognitive deficits, it recapitulates the patterns of relationships between cognitive performance and demographic characteristics seen in non-diabetic samples.

Grants awarded: NIA R01 AG034087 (Beeri), NIA P50 AG05138 (Sano), Helen Bader Foundation (Beeri), Irma T. Hirschl Scholar (Beeri), American Federation for Aging Research Young Investigator (Ravona-Springer), Alzheimer's Association NIRG-11-205083 (Ravona-Springer)

36 Medial prefrontal cortex inactivation impairs flexible shifting amongst behavioral strategies and associated hippocampal beta/gamma activity.

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The spatial milieu provides context for episodic memories. This allows environmental cues to evoke memories of prior experience that can be used to adaptively guide behavior. When many experiences can be drawn upon the brain must select the most relevant of these based on other factors such as motivation and/or current reward contingencies. Here we describe ongoing work examining how the medial prefrontal cortex (mPFC) works together with the hippocampus to select appropriate behaviors in a single environment. Animals performed a series of tasks that were identical with respect to sensory input and overt behavioral demands, but could be solved using either spatial navigation (hippocampal dependent) or cue-response (non-hippocampal dependent) strategies. Inactivation of the mPFC produced a marked behavioral inflexibility such that animals were impaired at shifting from one spatial strategy to another (e.g., from 'go east' to 'go west', referred to as spatial reversal learning). Delayed inactivation experiments revealed that the mPFC is not involved in reversal learning per se, but instead plays a role via processes that occur during learning of associations preceding reversals. Inactivation of the mPFC abolished gamma activity in the hippocampus during learning of initial associations, but beta and theta oscillations were unaffected. Inactivation during spatial reversals abolished beta activity but not theta. Current efforts utilizing optogenetics to refine our understanding of mPFC and hippocampal involvement in spatial reversal learning are also described.

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

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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. We have previously shown that HDAC1 is translocated from the nucleus to the axoplasm in MS. To further explore how nuclear export results in axonal damage, we used experimental autoimmune encephalomyelitis (EAE), a disease model of MS which displays and ascending paralysis and axonal damage. We found that pharmaceutical grade, blood-brain barrier permeable inhibitors (KPT compounds) of CRM1 are able to reverse clinical symptoms in EAE. KPT-treated EAE mice regained motor function and this correlated with both decreased inflammatory lesions in the spinal cord and fewer amyloid precursor protein deposits within damaged axons. The peripheral immune system was also modified in drug-treated mice, as indicated by a reduction in the number of CD8+ T cells. 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.

Grants support: NSRO1-69385 to PC; MSSC and FRSQ fellowships to JDH.

38 Using a dual luciferase assay to probe the mechanisms of hallucinogenic effects.

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Egr-1 is an immediate early gene induced in frontal cortex pyramidal neurons by hallucinogenic 5-HT2A receptor agonists. Non-hallucinogenic 5-HT2A agonists do not induce Egr-1, suggesting that activity at the Egr-1 promotor is a useful marker for studying the aspects of 5-HT2A signaling that are relevant to hallucinogenic activity. Preliminary experiments suggest that HEK-293 cells expressing 5-HT2A receptors can be used to study these pathways using Egr-1 promoter activity as a readout. A luciferase reporter under the Egr-1 promoter was co-expressed with 5-HT2A receptors in HEK-293 cells, and luciferase activity measured after the application of hallucinogenic and non-hallucinogenic 5-HT2A agonists. Additionally, dose-response curves were constructed for the hallucinogen DOI, with the 5-HT2A receptor was expressed alone or along with metabotropic glutamate receptor 3 (mGluR2). Paralleling published experiments in mice, Egr-1 promoter activity was increased in the DOI condition over the lisuride condition. Dose response curves showed that mGluR2 co-expression enhances the action of DOI. Further experiments will further investigate the predictive validity of this assay for studying the mechanisms of hallucinogen action at the cellular level.

Funding source: NIH R01 MH084894

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

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Shank3 is a scaffolding protein that forms a key structural part of the postsynaptic density of excitatory synapses, where it recruits glutamate receptors and binds cytoskeletal elements regulating glutamate signaling. Haploinsufficiency of SHANK3 causes a monogenic form of autism spectrum disorder (ASD). Recent studies from Shank3-deficient mouse models indicated that deficiency of the Shank3 proteins leads to synaptic dysfunction and behavioral deficits relevant to symptoms of ASD. To further analyze the effect of Shank3 deficiency we have developed a genetically modified rat model with a targeted disruption of Shank3. We are applying electrophysiological and biochemical analysis to study the changes in synaptic functioning and neuronal circuitries, and behavioral analysis to relate changes to higher order processes. Moreover, we are using genome-wide transcriptional analysis to reveal the perturbed pathways and networks associated with ASD. Our first results reveal that reduced levels of Shank3 lead to deficits in synaptic plasticity, and affects connectivity between ASD associated brain regions. By further characterizing this model we will be able to define molecular and cellular components that could be targeted for developing therapies for SHANK3-haploinsufficiencies and ASD.

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

40 Disturbances in the construction of prediction. Part II The Oscillon.

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The neuron model of brain function superseded the reticular or continuity model. The ascendancy of the neuron model, initiated by Schafer and Cajals, was crowned by Hodgkin and Huxley's defining the action potential and all-or-nothing transmission along the neuron. The here-to-there signal deeply embedded a concept of location in the understanding of brain function. Ramone advised against abandoning the reticular model and Brown autioned against a reductive direction in the teasing out of reflex arcs. Lesion studies also suggested there was more to brain function than location.

Reductive thinking has run the ship of neurobiological research onto mereological shoals. The mereological, or compositional, fallacy suggests that examining the details of function in components of a complex system will not reveal how the whole works. Llinas demonstrated a resonant oscillatory activity of neurons with gap junctions that allows escape from the mereological towards global function with reticular and continuity implications. In oscillatory signaling the sender of the message, the message, and the recipient are one--a complex system that sustains an illusion of direct contact with reality so that we move intelligently into our predictions. We are "the frail stuff that dreams are made ON." Dreams, consciousness, and predictions are not made OF anything. They are constructs made ON oscillating neurons or oscillons--global signaling. We do not think with our brains. We do not take our stomachs out to dinner. WE go out to dinner.

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Bidirectional regulation of the fosB gene using synthetic zinc-finger transcription factors for the study of addiction and depression.

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Both the expression level and chromatin state of the fosB gene is known to influence sensitivity to drug and stress exposure in rodents. Designer transcription factors, such as zinc finger (ZF) proteins and transcription activator-like (TAL) effectors, can be used to target enzymatic moieties to specific genomic loci. We have targeted the fosB gene promoter using a suite of zinc fingers and TAL effectors, which activate fosB gene expression in vivo. Further, by coupling chromatin-modifying enzymes to a specific DNA-binding protein, it is possible to regulate the chromatin state of a given gene via chemical modification of nearby histone proteins or the gene itself. Previous work has demonstrated repression of the fosB gene by the histone methyltransferase, G9a. To determine whether histone methylation of the fosB gene alone underlies the behavioral effects of blocking G9a activity in vivo, we have targeted the fosB gene using both ZF domains coupled to the G9a catalytic domain. We have found that the FosB-ZF-G9a fusion protein represses fosB expression in vivo and methylates histone H3 specifically at the fosB promoter, as well as modulates fosB-dependent behavioral phenotypes.

Sponsored by NIDA T32 5T32DA007135-29

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Regulation of the nuclear structure during oligodendrocyte differentiation

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Oligodendrocytes(OLGs) are the myelin forming cells of the central nervous system. The differentiation of OLGs from progenitor cells(OPCs) entails nuclear morphological changes that include:size reduction,decreased nuclear pores and extensive chromatin condensation.These changes are lineage specific and allow to distinguish OLG-nuclei from other cell types in the brain. We show that,as differentiation progresses,there are changes in the expression of nuclear envelope components,such as decreased levels of Emerin(Emd),Lamin b1(Lmnb1) and Lamin b receptor(Lbr), and increased levels of Sun1, Syne1 and Lamin A(Lmna). These molecules are known to modulate nuclear structure and therefore we hypothesized that they could functionally interact with the chromatin modifying enzymes to drive the nuclear changes that take place during differentiation. Our lab has previously reported the essential function of Hdac1/2 in developmental myelination,and now we report that these enzymes interact with Emd and that silencing Hdac1 or Hdac2 prevents the formation of heterochromatin and the reduction of the nuclear size. Likewise,down-regulation of Emd,Lbr,Lmna,Syne1 and Lmnb1 in vitro promotes abnormal nuclear shape and decreases heterochromatic markers(i.e H3K27me3),suggesting a role in OLG-nuclear reorganization. In vivo studies support these results,since OLG-nuclei in mice carrying mutations in the Lmna gene also show decreased levels of heterochromatin markers. These data suggest that changes in the nuclear structure during differentiation involve multiple protein complexes that mediate the formation of heterochromatin at nuclear periphery.

Founding:NS-RO142925-08,NS-RO142925-S1,F31 NS083344-01.

43 Elevated plasma MCP-1 concentration following traumatic brain injury as a potential "predisposition" factor associated with an increased risk for subsequent development of Alzheimer's disease.

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We explored the feasibility of identifying aberrantly regulated proteins from TBI cases that might provide insights on molecular mechanisms contributing to TBI complications. Using antibody arrays and ELISA assays, we found three protein species, including monocyte chemotactic protein-1 (MCP-1), that are differentially regulated in plasma of TBI compared to healthy control cases. We found significantly higher contents of MCP-1 in the plasma of TBI cases from two independent cohorts, a civilian and a veteran study cohort, which supports the identification of MCP-1 as a plasma TBI biomarker. Moreover, we found plasma MCP-1 contents are correlated with the severity of TBI and the index of compromised axonal fiber integrity in the frontal cortex. In parallel studies, we found elevated MCP-1 expression in post-mortem frontal cortex specimens from mild cognitive impairment (MCI) cases. Both TBI and MCI subjects are at elevated risk for AD dementia. Based on these findings and the role of MCP-1 in promoting inflammatory responses and myelin degradation, we propose that induction of MCP-1 following TBI might be a potential “predisposition” factor that imposes higher risk for AD or accelerated aging.

44 Genome-wide study of DNA methylation reveals epigenetic alterations in multiple sclerosis brains

Jimmy L Huynh, Paras Garg, Seungyeul Yoo, Michael J Donovan, Jun Zhu, Andrew J Sharp and Patrizia Casaccia

Epidemiological evidence suggests that environmental factors modulate the susceptibility to develop multiple sclerosis (MS), although the molecular mechanisms responsible for disease onset remain elusive. Recent studies indicate that environment-gene interactions may result in DNA methylation changes. We therefore used the Illumina HumanMethylation450 array to perform a genome-wide analysis of DNA methylation in normal-appearing white matter (NAWM) tissue from 28 MS brains and 19 non-neurological controls. Differences between these two groups were detected at hundreds of loci. These differences were subtle but consistent and reproducible. Hypomethylation was detected in genes involved in myelin antigen processing (e.g., CSTZ) and oligodendrocyte apoptosis (e.g., IRF8), while hypermethylation and corresponding decreased protein levels were observed for molecules involved in oligodendroglial survival response to stress (e.g., NDRG1). We suggest DNA methylation as an important molecular determinant that alters the molecular composition of NAWM in MS brains, rendering the tissue more prone to pathological processes.

45 Analysis of gene expression after chronic treatment with the class I and II HDAC inhibitor SAHA in mouse frontal cortex

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Histone deacetylases (HDACs) are epigenetic regulators that condense chromatin structure and repress gene transcription. Preclinical and clinical assays suggest that HDAC inhibitors, such as suberoylanilide hydroxamic acid (SAHA), could be promising therapies to improve memory function. In this study, we characterized the gene expression responses occurring in frontal cortex of mice after chronic administration of SAHA. Mice were injected chronically for 21 days, and sacrificed on day after the last injection. Patterns of gene expression were measured by microarray and quantitative real-time PCR (qPCR) assays. Animals that had received chronic SAHA treatment displayed dramatically increased gene expression in comparison to control animals. Further analysis of the transcriptome revealed that, in SAHA-treated mice, several of the differentially expressed genes were specifically associated with mechanisms that govern cellular assembly and/or synaptic plasticity. Among these, qPCR analysis showed that two genes, Gbf1 and Abhd16A, were increased and 7 genes, Copa, Itch, Eif5, Hp1bp3, Ssr3, Ube2g1, and Anapc1, were decreased in fontal cortex of mice chronically treated with SAHA, as compared to controls. These results suggest that HDACs may represent a novel target for drug development in the treatment of psychiatric disorders, with focus on cognition, memory and sensory motor gating.

46 Here's Looking at You: Using Eye Gaze to Examine Changes in Neural Activity Following Cognitive-Behavioral Social Skills Therapy for Children with Autism

Karim Ibrahim, Latha Soorya, Danielle Halpern, Sarah Soffes, Michelle Gorenstein, Alexander Kolevzon, Joseph Buxbaum, Ting Wang

Department of Psychiatry

This study investigates the neural effects of cognitive-behavioral (CBT) social skills treatment using a previously validated fMRI task examining sensitivity to eye gaze in emotional faces. We hypothesize that children with autism will show more normative activity in brain regions important for emotion processing (e.g., medial and ventrolateral prefrontal cortex) following CBT-based treatment.

Verbally fluent children with ASD (ages 8-11) were randomized to the CBT or child-directed play group. Both groups consisted of 12 weekly 90-minute sessions with a concurrent parent group. Behavioral assessments and event-related fMRI were conducted at baseline and after treatment. While undergoing fMRI, children viewed photographs of emotionally expressive faces depicting anger, fear, disgust or a neutral expression. Faces displayed either a direct or averted gaze looking to the observer's right or left.

Whole-brain and region-of-interest (ROI) analyses are being conducted to examine changes in neural activity following treatment within and between groups. ROIs include the ventrolateral prefrontal cortex and the superior temporal sulcus, among others. Predictors of treatment success using regression analyses will be examined. By exploring the relationship between changes in brain activity and social behaviors, we hope to develop hypotheses about the neural mechanisms underlying response to treatment.

This work was supported by the NIMH, Autism Speaks, and NARSAD.

47 Primary cilia assembly and signaling are required for normal development and repair of corneal tissue

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Damage and abnormal repair of the corneal layers due to trauma, diseases or aging can compromise corneal transparency and lead to blindness. We have recently shown that primary cilia are required for normal patterning of the corneal endothelium (CE) and re-assemble on corneal endothelial cells (CEC) involved in repair. We show that cilia assemble during development of the corneal epithelium and stroma but mostly disassemble in adults. We have detected ultrastructural differences of the primary cilia in the three corneal cell types that suggest distinct functions. Moreover, upon corneal epithelial injury we have observed a higher number of ciliated cells in newly migrated corneal epithelium on the injured area than we did in intact corneas. To determine the role of cilia during repair of different corneal tissues we have performed a mechanical injury of the corneal epithelium and endothelium in conditional IFT88 knockout mice. Upon injury and inactivation of IFT88 cilia failed to re-assemble in all corneal layers. CEC involved in repair failed to polarize and elongate toward the wound like they do in wild-type. In these mice healing of epithelial circular wound is also delayed compared to healing of wild-type epithelium. These results suggest that the presence of cilia is required for proper repair of corneal tissues and identify the cilium as a possible pharmacological target in corneal repair.

48 HIV-related cognitive impairment shows bi-directional association with dopamine receptor DRD1 and DRD2 polymorphisms in substance dependent populations

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It has been postulated that drugs of abuse act synergistically with HIV, leading to increased neurotoxicity and neurocognitive impairment. The CNS impacts of HIV and drug use converge on the mesocorticolimbic dopamine system, which contains two main receptor subtypes: dopamine receptor 1 and 2 (DRD1, DRD2). DRD1 and DRD2 have been linked to substance dependence; whether they predict HIV-associated neurocognitive disorder (HAND) is unclear. Using an advanced-stage HIV+ population, we observed that both DRD1 and DRD2 polymorphisms were associated with drug dependence ($P<0.05$) in Caucasian subjects, but not African-Americans. We examined the polymorphisms for associations with neuropsychological performance in several cognitive domains while controlling for drug dependency. In the Motor domain, we observed an association for a two DRD2 polymorphisms ($P<0.05$) in Caucasian subjects. The effects differed for substance dependence groups as the direction of the correlations with DRD2 were opposite to what was seen in subjects without these dependencies. In African-American subjects, associations were observed in nearly every domain and again, the direction of the correlation differed between substance dependence groups. We conclude that studies to examine genetic risk for HAND must carefully account for substance dependence patterns, as the neurobiological substrates of cognition in HIV populations may have variable relationships with the dopaminergic system.

49 Ultra-high field MRI visualization and characterization of Gray Matter lesions in post-mortem Multiple Sclerosis samples.

Jonkman, L. MSc., Fleysher, L. PhD., Geurts J. PhD, Inglese, M. PhD.

Multiple Sclerosis (MS) is a multifocal, inflammatory/demyelinating and neurodegenerative disease of the central nervous system (CNS) affecting an estimated 2.5 million individuals worldwide. MS is predominantly known for its White Matter (WM) damage. However, studies during the last decade have also confirmed widespread tissue damage in the Gray Matter (GM) which contributes to disease progression, physical disability and cognitive deficits. Nevertheless, GM lesions are often missed on conventional MRI scans due to its small size, scarcity of inflammation and partial volume effects from adjacent cerebrospinal fluid and WM. The introduction of high and ultra-high MRI scanners and specific MRI sequences have dramatically improved GM detection due to higher signal to noise ratio, spatial resolution and image contrast. This poster shows preliminary results of high field (7T) image sequences (T2-weighted and T2*-weighted) that can visualize and identify different types of GM lesions in post-mortem brain slices. We will show high quality images (image resolution 100µm x 100µm) identifying different cortical lesion types: leukocortical lesions, intracortical lesions and subpial lesions. A better visualization of these GM lesions could improve our understanding of GM pathology (by correlating these results with histopathology) and eventually the association between radiological involvement and clinical findings such as physical and cognitive deficits in MS patients. Eventually, these could lead to identification of effective MRI markers and new therapeutical targets.

50 Investigations into the role of midbrain dopamine neurons in mediating alcohol preference behaviors

Barbara Juarez, Allyson Friedman, Dipesh Chaudhury, Marshall Crumiller, Jessica Walsh, Stacy Ku, Ming-Hu Han

The progression of alcohol-use disorders involves a series of neuroadaptations in a number of circuits throughout the brain. The recruitment of the mesolimbic dopamine reward circuit is essential in mediating alcohol's action in the brain. Studies using inter-strain comparisons of mice displaying specific alcohol preference behaviors (low or high) have found physiological differences of dopamine neurons of the ventral tegmental area (VTA) between the two alcohol preference strains. However, because these studies compare mice from two genetically distinct populations, it is hard to truly correlate the neuroadaptations observed with alcohol preference behavior. In order to escape this confound, we have generated a 24-hour 2-bottle choice escalated alcohol drinking model that dissociates alcohol preference behavior within one inbred mouse strain, the C57s. The separation of low alcohol preferring mice and high alcohol preferring mice within one genetically inbred line allows us to make INTRASTRAIN comparisons of neuroadaptations that might underlie alcohol preference behaviors. Using anesthetized in vivo single-unit electrophysiology, we found that VTA dopamine neurons of low alcohol preferring mice have higher firing rates and higher bursting activity when compared to their high alcohol preferring littermates. Mimicking this increased activity in the VTA of high preference mice subsequently reduced alcohol preference behavior within 24 hours. Our preliminary results show that distinct neuroadaptations within the dopamine system might underlie specific alcohol preference behaviors.

T32MH087004

51 In vivo analyses of caspase-4 in inflammation and Alzheimer's disease

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Caspase-4 has been proposed to be a primate-specific member of the inflammatory caspases. We have previously found that caspase-4 mRNA is significantly upregulated in the brain of Alzheimer disease (AD) subjects. However, due to the absence of the gene in the mouse genome, physiological function of caspase-4 has remained unknown.

The role for caspase-4 in AD was investigated by crossing caspase-4 mice, which express human caspase-4 with APPsw/PS1deltaE9 mice. Caspase-4 expression was upregulated in male APPsw/PS1deltaE9/CASP4 mice and this upregulation was specific in brain regions relevant to AD. When spatial learning ability was tested by Barnes maze, all mice showed normal acquisition at 7 and 13 month. However, male APPsw/PS1deltaE9/CASP4 mice showed significant impairment upon reversal of target compared to control mice at both age. Quantitative pathological analysis indicated an effect of Caspase-4 on microglia regulation. Electrophysiological analysis in the hippocampal slices showed a decrease in synaptic plasticity measured by long-term potentiation in CASP4 mice at 14 month-old but not in 4 week-old mice in comparison to the wild-type mice.

We thank Mount Sinai Alzheimer Disease Research Center (Dr. S Gandy, Dr. P Hof, and Dr. M Sano, PI; Drs. O Gunal and JD Buxbaum, PL U01 P50 AG005138-28) for supporting this study.

52 Behavioral deficits in Alzheimer's mice reversed by Group II mGluR inhibitor with pro-neurogenic, Abeta-reducing and anxiolytic properties

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One hallmark of Alzheimer's disease (AD) is accumulation of neurotoxic amyloid beta (Abeta) oligomers in the brain. Activation of Group II metabotropic glutamate receptors (Gp II mGluR: mGlu2, mGlu3) triggers production and release of Abeta peptides from isolated synaptic terminals, which is selectively suppressed by antagonist pretreatment. We have assessed the therapeutic potential of chronic pharmacological inhibition of Gp II mGluR in APP (Alzheimer's amyloid precursor protein) mice. To achieve inhibition of Gp II mGluR in the brain, orally bioavailable prodrug BCI-838 was used to deliver its active metabolite BCI-632. Chronic (3-month) treatment with BCI-838 was associated with reduction in levels of brain Abeta monomers and oligomers, correction of transgene-related behavioral deficits, reduction in anxiety behavior, and stimulation of hippocampal neurogenesis. Group II mGluR inhibition may offer a unique package of relevant properties as an AD therapeutic by providing acute symptomatic benefit, attenuation of neuropathology, and stimulation of repair.

Funding: The American Health Assistance Foundation (S.H.K.), National Institutes of Health Grant AG10491, Cure Alzheimer's Fund, and VA MERIT Review Award I01BX000348 (S.G.), the James S McDonnell Foundation, Mather's Foundation, NIMH, Ellison Foundation, NINDS, NIMH, NIA and JPB Foundation (F.H.G.).

53 β-Hexosaminidase-targeted pharmacological chaperone therapy corrects behavioral phenotype in a mouse model of familial cerebral amyloid angiopathy

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β-Hexosaminidase catabolizes GM2 gangliosides and its deficiency causes lysosomal storage disorders. Deficiency in β-hexosaminidase activity also leads to accumulation of ganglioside-bound Aβ and APP derived C-terminal fragments in human and mouse brains (Keilani et al., JNeurosci 2012). GM2 and GM3 gangliosides are found in the cerebrovasculature and promote assembly of Dutch mutant Aβ peptides that cause familial cerebral amyloid angiopathy (CAA). Dutch APP transgenic mice accumulate Aβ oligomers in the cerebrovasculature and within neurons and develop cognitive behavior deficits. Hypothesis: Increasing β-hexosaminidase activity to reduce GM2 levels will reduce Aβ oligomerization and deposition in the cerebrovasculature and prevent behavioral changes in Dutch APP transgenic mice. Method: Male Dutch APP transgenic mice (age 3 months old) were orally gavaged with either vehicle or the β-hexosaminidase-targeted pharmacological chaperone AT3108 (3, 10, 30 and 100mg/kg) five days/week for 3 months. At 6 months, behavior was tested using the elevated plus maze (EPM) and the novel object recognition (NOR) test. Results: Treatment of Dutch APP transgenic mice with the β-hexosaminidase-targeted pharmacological chaperone AT3108 prevented onset of cognitive decline in the NOR test and reduced anxiety in the EPM. Conclusion: β-hexosaminidase-targeted pharmacological chaperones show promise in a mouse model of familial CAA and may be useful for management of the human CAAs.

Supported by the Alzheimer's Drug Discovery Foundation.

54 Effects of chronic and acute stimulant exposure on brain connectivity hubs

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Background: The spatial distribution and strength of 'hubs' that facilitate information processing are essential features of the brain's network topology, and are particularly susceptible to neuropsychiatric disease. Despite growing evidence that drug addiction alters functioning and connectivity of discrete brain regions, little is known about whether chronic drug use affects this network-level organization, or if it can be modified by therapeutic agents acting on dopamine. We used functional connectivity density (FCD) mapping to evaluate the effects of chronic and acute stimulant exposure on brain hubs, i.e., regions with high numbers of global (gFCD) and/or local (lFCD) connections.

Methods: 19 individuals with cocaine use disorders (CUD) and 15 healthy controls completed resting-state fMRI scans following oral methylphenidate (20 mg) or placebo in randomized order.

Results: CUD showed increased gFCD and lFCD in the ventromedial prefrontal cortex, posterior cingulate/precuneus, and putamen/amygdala. Across subjects, methylphenidate decreased gFCD in the SMA/postcentral gyrus and lFCD in bilateral putamen/thalamus.

Conclusions: Increased density of global and local connections to default mode network hubs in CUD suggests inefficient overrepresentation of resource-expensive network components, consistent with other psychopathologies such as schizophrenia. However, methylphenidate reduced the density of local connections to the putamen/thalamus, regions of core relevance to habits and addiction, suggesting that abnormalities in these hubs could be modified by treatment.

Funding: 1R01DA023579 (RZG); 1F32DA030017-01 (SJM)

55 Meta-signature analysis of post-mortem brain regions

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Network2Canvas (N2C) is a web application that provides an alternative way to view networks. N2C visualizes network nodes by placing them on a square toroidal grid. These nodes are then clustered together on the grid using simulated annealing to maximize local connections. The grid is interactive, implemented in HTML5 and the Java Script library D3. We applied N2C to create canvases for gene-gene functional association networks connecting terms from databases and datasets such as ENCODE, Gene Ontology, KEGG, the Epigenomics Roadmap, CCLE, and MGI-MP. N2C also has functions to perform enrichment analyses. Given lists of genes, N2C highlights enriched terms on the canvas as well as computes the degree of clustering for these enriched terms. We applied N2C to analyze gene expression signatures from various brain regions from normal tissue and in disease. Such visualization provides a global view of cellular regulation including histone modifications patterns, transcription factors activity, and important pathway meta-signatures.

Sources of funding: NIH grants R01GM098316-01A1, P50GM071558-05, R01DK088541-01A1, and U54HG006097-02S1

56 Identification of a novel parkinsonism-causing gene implicates dysfunctional synaptic endocytosis in disease development

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Early-onset parkinsonism (EOP) is characterized by tremor, hypokinesia, muscular rigidity, and postural instability. To elucidate the genetic causes underlying EOP in a consanguineous Iranian family, we performed homozygosity mapping and whole-exome sequencing. A homozygous point mutation in a gene coding for a polyphosphoinositide phosphatase, which is implicated in the regulation of endocytic traffic at synapses, was identified as disease-causing. This mutation resulted in a significant reduction in phosphatase activity in vitro and mice with a heterozygous knockout of the gene exhibited a decrease in dendritic arborization complexity of dopaminergic neurons in the substantia nigra pars reticulata. We concluded that this mutation causes EOP in humans due to phosphatase deficiencies and subsequent impairment of synaptic activities. Further investigations in the dysfunctional synaptic mechanisms associated with parkinsonism are required. Additionally our findings suggest phosphoinositide metabolism as a possible novel therapeutic target in Parkinson's disease.

Funding: Parkinson's Disease Foundation (Lucien Côté Early Investigator Award; CPR), NIH/NINDS (R01NS060809 and R01NS072359; ZY), and the Michael J. Fox Foundation (ZY).

57 The Plexin-B2 receptor drives the invasive migration of glioma cells

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Glioblastoma multiforme (GBM) is the most malignant adult brain tumor, with a median survival time of fifteen months. GBM is commonly treated with surgical resectioning, but due to their highly dispersive nature, malignant tissue is likely left behind, and recurrence is often imminent. The aggressive scattering of cancer cells suggests that cell motility programs may regulate tumor spreading. Likely candidates include the plexin receptors and their ligands, semaphorins, which compose the largest family of guidance cues and are crucial during nervous system development. We have previously identified the plexin family member, Plexin-B2, as a key mediator of neuronal precursor migration. Furthermore, in analyses of GBM samples taken from over 1000 patients, Plexin-B2 was consistently upregulated compared to normal tissue, and its expression levels directly associated with tumor malignancy, making it a possible target for effective cancer treatment. However, how Plexin-B2 functions in tumor cells remains unclear. Here, we used cell-based assays to identify signaling mechanisms involved in Plexin-B2-mediated glioma migration, as well as the effects of Plexin-B2 stimulation on cell morphology. To examine the role of Plexin-B2 in tumors in vivo, we created a glioma line expressing a stable Plexin-B2 knockdown and transplanted those cells into the brains of SCID mice to compare how tumor growth and migration differs in the absence of Plexin-B2 signaling.

58 Progranulin-induced Neuroprotection From Glutamate Toxicity is Mediated by TNFα Receptor 2

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Progranulin (PRGN) is a secreted growth factor and implicated in Frontotemporal Dementia (FTD). We have reported that PRGN has neurotrophic activities and promotes neuronal survival following glutamate-induced toxicity. Several receptors for PGRN have been reported, including TNFα Receptors 1 and 2 (TNFR1 and TNFR2, respectively).

Primary cortical neuronal cultures derived from wild-type (WT), TNFR1 -/-, and TNFR2 -/- mouse embryos were prepared. For survival experiments, neurons were pre-treated with 35nM of recombinant PRGN for 1 hour followed by 50mM of glutamate for 3 hours to induce neurotoxicity. For western blots, cells were treated with 15nM PRGN for 5, 10, 30 and 60 minutes.

We have shown that PRGN reduces cell death in WT and TNFR1 -/- neurons. In contrast, PGRN-treated and non-treated TNFR2 -/- neurons showed no statistically significant difference in cell death. We have previously shown that PRGN executes neuroprotective functions through the ERK pathway. PRGN-induced ERK phosphorylation was significantly increased in WT and TNFR1-/- neurons, but not in TNFR2 -/- neurons. The downstream target of pERK is c-Fos. We have observed an increase in c-Fos expression following PRGN treatment in WT and TNFR1 -/- neurons, but not in TNFR2 -/- neurons.

These findings show that TNFa Receptor 2 is the main receptor through which PRGN performs its neuroprotective function in primary cortical neurons in vitro.

59 Ketamine Safety for Treatment-Resistant Depression

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BACKGROUND: Ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant depression (TRD). Despite the promise of a novel treatment for refractory depression, the safety profile of ketamine in this population has not been fully described. Herein we report the largest study to date of the safety of ketamine in TRD.

METHODS: This analysis included 205 intravenous ketamine infusions (0.5 mg/kg) administered across 3 clinical trials in TRD (total N=97). The impact of ketamine on hemodynamic functioning, dissociative, psychomimetic and general adverse events (AEs) were measured following each infusion.

RESULTS: Of the 205 infusions, 4 infusions were discontinued due to AEs (1.95%). The total dropout rate was 3.1%. Ketamine increased mean systolic and diastolic blood pressure by 19.7±1.3 mmHg and 13.3±0.9 mmHg, respectively. Ketamine increased heart rate by 8.6±1.0 BPM. Ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms. In all cases, ketamine induced changes returned to baseline within 4 hours post-infusion.

CONCLUSION: In this large group of patients with TRD, ketamine was safe and well tolerated. Further research investigating the safety and efficacy of ketamine in severe and refractory depression is warranted.

RO1MH081870; K23MH094707; UL1TR000067

60 Novel Roles of PAD2 in Oligodendrocyte Development and Disease

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In the central nervous system (CNS), peptidyl arginine deiminase 2 (PAD2) 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 PAD2 and citrullinated myelin basic protein were detected in the brain of MS patients and correlated with increased protein antigenicity. However PAD2 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. In the present study, we show that PAD2 is expressed by oligodendrocytes and astrocytes, but not cortical neurons in primary CNS culture. More importantly, PAD2 is up-regulated at transcript and protein levels during oligodendrocyte differentiation both in vitro and in vivo, supporting its role in oligodendrocyte differentiation. Increased PAD2 levels were accompanied by increased histone H3 citrullination during 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 roles of PAD2 in oligodendrocyte differentiation and address the question of whether PAD2 can become a therapeutic target for myelin repair (funding: NS-R37-42925)

61 The role of VGF in hippocampal-dependent memory formation

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BDNF plays an essential role in regulating synaptic plasticity, neurogenesis, and neuroprotection. Lowered BDNF levels in the brain and peripheral circulation can be caused by reduced gene expression or aberrant protein sorting, which is known to predispose patients and animal models to mood disorders and memory impairment. Many previous studies that investigate mechanisms underlying memory and depression examine changes in BDNF expression, while regulated secretion of BDNF in this context is less understood. Expression of VGF (nonacronymic), a secreted neuropeptide precursor, is downstream of BDNF signaling. Our lab previously showed that VGF-derived C-terminal peptide enhances synaptic potentiation in hippocampal slices, which requires precursor BDNF processing and BDNF-TrkB signaling. VGF germline knockout mice exhibit impaired memory performance and a pro-depressive phenotype, similar to BDNF knockout mice. Here, we ask what is the functional role of VGF in adult hippocampus and if VGF regulates proBDNF release and/or processing. Our preliminary data showed that VGF expression was induced transiently after memory training. In addition, specific VGF deletion in adult hippocampus impaired contextual fear memory. At the molecular level, VGF and VGF-derived peptide enhanced BDNF downstream signaling pathway. Our results indicate functional interplay between BDNF and VGF in hippocampus-dependent memory formation.

Funding source: NIMH grant 5R01MH086499-02 to S.R.J.S.

62 NRBF2, a novel PI3K-III complex component, positively regulates autophagy and maintains neuronal homeostasis.

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Class III PI3K plays a central role in regulating autophagy. Via formation of different complex with regulating partners, PI3-III modulates different steps of autophagy. For example, Atg14L complex controls autophagsome formation, while UVRAG complex regulates autophagosome maturation. Our study identified a novel component of PI3K-III complex namely Nuclear receptor-binding factor 2 (NRBF2). Further study revealed that NRBF2 interacts with both Atg14L and UVRAG, positively regulate kinase activity of PI3K-III. Knocking out NRBF2 in cells and in mice resulted in reduced autophagic function. Specifically, NRBF2 modulate both initial step and maturation step of autophagy by engaging Atg14L complex and UVRAG complex, respectively. NRBF2 KO mice displayed abnormal p62 accumulation in the brain and liver, and developed motor function impairment. Collectively, our study showed that NRBF2 is an in vivo and in vitro positive regulator of autophagy, and plays an important role in maintaining the physiological function of central nervous system.

63 Fear learning decreases inhibition in the lateral amygdala through TrkB signaling

Elizabeth K. Lucas and Roger L. Clem

Fear learning is mediated by plasticity in the amygdala, and brain derived neurotrophic factor (BDNF) signaling through the tyrosine receptor kinase B (TrkB) contributes to the induction of this plasticity. During Pavlovian fear conditioning, information conveying the conditioned stimulus (CS) and unconditioned stimulus (US) converges in the lateral amygdala (LA). While much research has focused on CS-US pairing-induced plasticity in excitatory neurotransmission in the LA, the roles of inhibitory interneurons, which express high levels of TrkB, have remained enigmatic. We found significant decreases in the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in the LA 24 hours after CS-US pairing, a result attributable to decreased GABA release as miniature IPSC frequency was also attenuated in paired animals. Systemic administration of the small molecule TrkB antagonist ANA-12 four hours prior to fear conditioning abolished learning-induced diminution in sIPSC frequency, suggesting that decreased inhibition in paired animals may be mediated by BNDF signaling. However, in ANA-12 treated paired mice, sIPSC amplitude and area were enhanced, and the paired pulse ratio of evoked IPSCs was facilitated at 25 ms interstimulus interval. Additional experiments will be required to determine if the effects of ANA-12 on CS-US pairing are due to pre- or postsynaptic mechanisms. Future studies will investigate the contribution of individual interneuron populations, as well as TrkB signaling within these populations, on fear learning.

64 E2F1 modulates the expression of chromatin modifiers, which orchestrate OPC differentiation

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Differentiation of oligodendrocyte progenitor cells (OPCs) into mature oligodendrocytes requires a strict coordination between cell-cycle-exit and differentiation programs. These events are partly mediated by post-transcriptional modification of histones. Here we provide evidence that the E2F family of transcription factors orchestrate the expression of chromatin modifiers that regulate OPC differentiation. First we show that expression of the activating E2F1 decreases during oligodendrocyte differentiation and it is correlated with cell-cycle-exit, while the repressive E2F4 levels remain elevated. ChIP-seq experiments with E2F1 performed during early phase of OPC differentiation identified the expected targeted genes involved in cell-cycle-regulation (Cdc2a, Ccna2) and novel genes in the category of epigenomic modifiers (Uhrf1, H2a.z, Hmgb2). We validated these results by using ChiP-analysis in proliferating and differentiating OPCs. We identified binding of E2F1 and RNA polII to the Uhrf1 promoter in proliferating OPC and in turn, Uhrf1 occupancy on the late myelin gene Mog, associated with markers of repression. Upon differentiation, we detect a switch from activating E2F1 to repressive E2F4 and HDAC1 complexes binding to the Uhrf1 promoter, thereby resulting in down-regulation of Uhrf1 and induction of Mog expression. Our data suggest a model in which E2F1 and E2F4 far apart of the molecular switch regulating the transition from cell cycle to oligodendrocyte differentiation.

Sources of funding RO1-NS52738

65 Physiological function of autophagy protein Beclin1 in controlling neuronal membrane homeostasis and survival

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Beclin1 is an essential autophagy protein in the class III PI(3)kinase complex; its stimulation of the lipid kinase activity of Vps34, which initiates formation of double-membrane autophagosomes. To characterize Beclin1 function in the brain we made multiple Beclin1 transgenic mice including GFP-Beclin1 and conditional knock-outs in the cerebellum and hippocampus. Deletion of Beclin1 in PCs caused cell loss by 1M, far earlier than deletion of autophagy genes suggesting that Beclin1 is required for multiple pathways. Ultra-structural examination of knock-out brains revealed aberrant membranes, abnormal endosomes/lysosomes and mislocalized phospholipid. Characterization of these mouse models revealed a critical role for Beclin1 in the endocytic-lysosomal pathway.

Autophagy and its key regulator Beclin1 are required for proper neuronal function. Sustained basal autophagy is crucial for cytosolic protein turnover and maintenance of neuronal homeostasis and plasticity, whereas altered autophagy is observed in neurological disorders such as AD and PD. Autophagy degrades misfolded proteins and is a therapeutic target for neurodegenerative diseases. The molecular mechanism of autophagy and Beclin1 function in the CNS is not well understood.

Our study suggests a critical role of Beclin1 in controlling neuronal membrane trafficking. Beclin1 acts as a nexus point between autophagic, endosomal and lysosomal trafficking and degradation pathways all of which are critical for neuronal homeostasis.

NIH-5R01NS060123-04

66 The impact of adolescent THC on mesolimbic microRNA regulation

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There is continued debate regarding the long-term impact of adolescent cannabis use on future drug addiction vulnerability. Several studies support the so-called ‘gateway’ hypothesis, showing that early adolescent cannabis (or THC) exposure predicts future drug use. In order to model the neurobiology of this phenomenon, our lab has investigated the long-term impact of adolescent THC exposure and characterized dysregulation of genes into adulthood. Alongside epigenetic mechanisms, recent attention has been given to microRNAs (miRNAs), a class of small, non-coding RNAs that regulate gene expression post-transcriptionally. Here, we seek to determine the potential contribution of miRNAs to THC-mediated neuroadaptations. Focusing on the nucleus accumbens – a region involved in reward, motivation and goal-directed behavior – we evaluate the expression of several miRNAs in adult rats, and show that miR-212 is elevated after adolescent THC exposure. Concomitant decreases in known targets of this miRNA, namely the transcription factor Mecp2, were observed after adolescent THC. These findings imply that disruption of miR-212 after adolescent THC exposure impacts neuroplasticity and transcriptional regulation. We are currently conducting a multiplexed approach to study a broad array of miRNAs in association with adolescent THC exposure. After candidate miRNAs are identified using this approach, in silico analysis will identify protein-coding genes that likely interact with the differentially regulated miRNAs.

Funded by DA030359

67 Higher Order Chromatin in Schizophrenia

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Downregulation expression of GABA synthesis enzyme GAD1/GAD67 is considered one of the more frequently replicated alterations in the prefrontal cortex of schizophrenia patients. Recent studies using chromosome conformation capture (3C) at the GAD1 locus in mice show a highly significant interaction frequency between two histone 3 lysine 4 trimethylation (H3K4me3) sites, which typically mark transcription start sites (TSSs) and other types of regulatory and non-coding DNA. This finding opens up the intriguing possibility that higher order, three-dimensional chromatin structures are involved in the regulation of GABAergic gene expression and altered in psychiatric disease.

Likewise, we observed higher order chromatin structures in the major histocompatibility complex (MHC) region of chromosome 6 (chr6:27,000,000 – 34,000,000), including a chromosomal loop formation that involved rs13194053, a schizophrenia associated single nucleotide polymorphism (SNP). The MHC region of chr6 (chr6:27,000,000-34,000,000) contains a large number of schizophrenia associated SNPs, many of which are located in intergenic regions. A functional role for non-transcript H3K4me3 sites and intergenic SNPs associated with psychiatric disease would not be surprising given that many intergenic regions are thought to regulate, via chromosomal loopings, the expression of upstream and downstream genes. We are characterizing these SNPs and higher chromatin order using derivatives of 3C.

Supported by NIH R01 MH093332 (PI: Schahram Akbarian)

68 Gene × withdrawal reactivity to drug cues in addiction: Multimodal evidence

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Functional polymorphisms in the dopamine transporter gene (DAT1 or SLC6A3) modulate responsiveness to salient stimuli, such that carriers of one 9R allele of DAT1 (compared with homozygote carriers of the 10R allele) show heightened reactivity to drug-related reinforcement and withdrawal symptoms in addiction. Here for the first time we examined these factors in tandem, using multimodal neuroimaging and behavioral dependent variables in 73 cocaine-addicted individuals and 47 healthy controls. We hypothesized and found that cocaine-addicted carriers of a 9R-allele exhibited higher responses to drug cues – but only when they were in a state of acute cocaine withdrawal as indicated by positive cocaine urine screens (a state characterized by intense craving). Importantly, this responsiveness to drug cues was reliably preserved across imaging and behavioral probes: psychophysiological event-related potentials, self-report, simulated cocaine choice, and functional magnetic resonance imaging. Because drug cues contribute to relapse, our results identify the DAT1R 9R allele as a vulnerability allele for relapse under conditions of acute drug deprivation.

Funding: Supported by NIDA grants 1R01DA023579 (RZG), 1F32DA030017-01 (SJM), and 1F32DA033088 (MAP).

69 Creb-binding protein in dietary restriction and Huntington's disease

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Dietary restriction (DR) extends lifespan and protects against age-related maladies including neurodegenerative diseases. The transcriptional cofactor CREB-binding Protein (CBP) is required to elicit salubrious effects of DR in C. elegans. Here we show that CBP is induced in hypothalamic tissue after a 30% caloric intake reduction for 3 weeks in wild-type mice. As we observed in C. elegans, DR produced a gene expression profile indicating decreased glucose metabolism and increased ß-oxidation. Interestingly, CBP induction, or its homolog P300, was predictive of metabolic genes promoting this profile. Similar molecular responses were observed in liver tissue. Secondly, based on reports that DR delays onset of Huntington's disease (HD), as well as data showing that polyQ aggregates sequester CBP and inhibit its functions, we evaluated effects of DR in the YAC128 transgenic mouse model of HD. In these studies we monitored mice carrying a complete human form of the huntingtin protein, as well a the polyQ repeat, which were subjected to DR (food removed every other day) for 18 weeks. Our data shows that DR in HD mice significantly improves latency to fall and maximum acceleration in rotarod assays. Additionally, locomotor activity, baseline blood glucose, and body weight were corrected and a trend towards normal circadian rhythms was observed. Upon sacrifice, we corroborated that CBP was induced in the hypothalamus, and that neuroendrocrine gene markers corroborate previous observations in a 30% caloric reduction.

70 Charaterization of 5-HT2A-mGlu2 receptor heteromerization and its role in psychoactive-like behavioral effects.

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G protein-coupled receptors (GPCRs) are responsible for the majority of transmembrane signal transduction in cells. GPCRs have been considered to exist as monomers. Nevertheless, recent studies suggest that GPCRs also form complexes. Heteromers are of particular interest because they have been shown to exhibit specific pharmacological and signaling properties as compared to homomeric GPCRs.
Serotonin 5-HT2A and mGlu2 receptors have been involved in schizophrenia, as well as in the molecular mechanism of antipsychotic drugs. Previous findings demonstrate that the 5-HT2A receptor and the mGlu2 receptor form a heterocomplex through which serotonin and glutamate modulate the pattern of G protein coupling in brain frontal cortex. Here, we investigated the molecular mechanisms involved in intracellular trafficking and signaling of the 5-HT2A -mGlu2 complex, and its psychoactive-like behavioral function. We showed that 5-HT2A co-localizes with mGlu2 in the same intracellular membrane compartments. We demonstrated that any two out of three residues (A6774.40, A6814.44, A6854,48) located at the intracellular end of the transmembrane domain 4 are necessary for the mGlu2 to be assembled as a GPCR complex with the 5-HT2A receptor. Based on these structural findings, we demonstrated that heteromeric formation is necessary to induce the behavioral response to hallucinogenic drugs in mouse. These observations may help the development of more specific and effective therapeutic drugs.

71 Prenatal cannabis exposure leads to long-term disturbance of striatal chromatin modifying enzymes

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Marijuana is the most commonly abused illicit drug by pregnant women and is linked to deficits in cognition, attention and impulsivity in their offspring. The striatum is a key component of the neuronal circuitry associated with such behaviors. Our group previously showed that prenatal cannabis exposure disrupts transcriptional regulation of striatal neuropeptidergic genes through aberrant epigenetic chromatin modifications, consequently influencing behavior in adulthood. Regulation of chromatin gene accessibility is catalyzed by chromatin modifying enzymes (CMEs), which has been shown to influence addiction vulnerability. To investigate the effects of early developmental exposure of Δ9-tetrahydrocannabinol (THC) on chromatin regulation, pregnant female rats were treated with daily IV injections of either THC or vehicle from gestation day 5- postnatal day 2. The offspring were studied as adults to assess THC's long-term effects on CME in the dorsal striatum. A qPCR screen revealed reduced mRNA expression of Setdb1, a histone methyltransferase, in THC-exposed offspring. Setdb1 is a promising candidate for involvement in the long-term impact of prenatal cannabis given its role in both brain development and behavior. Reduced Setdb1 mRNA expression was also evident in the striatum of human fetuses exposed in utero to cannabis. Experiments are underway to determine the relationship of Setdb1 to the direct transcriptional regulation of genes known to be dysregulated by prenatal THC.

Funding: NIH DA023214, DA12030, F31-DA031559

72 Neural mechanisms associated with attention switching

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A key component of human cognition is the ability to switch between various states of attention. While neural mechanisms associated with internal focus have been examined, the mechanisms underlying switching attention to external cues remain unspecified. The current study sought to explore this process in healthy individuals. Fourteen healthy controls performed a novel switching task while brain activity was measured using functional magnetic resonance imaging. Subjects performed an internally focused (IF) imagination task or an externally focused (EF) visuospatial working memory task before switching to an EF target detection (TD) task. Subjects also completed the consideration of future consequences (CFC) questionnaire, which measures propensity for future thought. The IF task elicited greater activity in default mode network (DMN) than the EF task, including ventromedial prefrontal cortex and posterior cingulate cortex. When looking at correlations with CFC scores, greater activity in somatosensory cortex during the IF task and greater activity in the DMN during TD following the IF task were positively correlated with higher scores. This suggests that individual differences in personality traits are associated with differential neural response when engaging and disengaging from an internal state of attention. These findings have implications for obsessive-compulsive disorder and depression, which are characterized by excessive internal focus.

73 Minocycline for bipolar depression

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Background: Minocycline is an antibiotic with multiple mechanisms relevant to the pathophysiology of bipolar disorder: modulation of glutamate neurotransmission, anti-inflammatory, antioxidant and neuroprotective effects. We report the first study to test its efficacy in bipolar depresion.

Method: N=12 subjects with bipolar disorder type I (75% males, mean age 44.4 ± 3.2 years) experiencing acute depressive symptoms started an 8-week treatment with open minocycline added to their current mood stabilizing treatment. We administered depression severity scales every two weeks. We collected proton magnetic resonance spectroscopy (1H-MRS) before and after treatment (from two 2.0 x 3.0 x 3.0-cm3 voxels, centered on ACC and on the occipital cortex) to detect changes in glutamate-glutamine (Glx) levels during the 8-week treatment.

Results: Over 8 weeks, treatment with minocycline was associated with significant improvements in depression severity: 67% of subjects were treatment responders (≥ 50% reduction in MADRS severity score from baseline) and 45% achieved remission (defined as endpoint MADRS ≤ 10). Minocycline-treated subjects (N=7) had significant decreases in the combined glutamate-glutamine (Glx) levels (20.9% decrease, p=0.017) in the ACC from baseline to endpoint (week 8).

Conclusion: Minocycline may be an effective adjuvant treatment for bipolar depression. MRS results are consistent with the hypothesized role of minocycline in reducing excessive glutamate and glutamate-mediated excitotoxicity in brain areas involved in mood regulation.

74 The neural mechanisms of fear reversal without awareness

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Most fear modulation research has focused on the shift from fear to safety, emphasizing extinction training. The brain is adaptive however, and flexibly updates fear behavior in changing environments. This “fear reversal” has been tested by unexpectedly switching fear-conditioned stimulus with safety-predicting stimulus, showing predictable activation of the amygdala and striatum during fear transition as well as dissociative activation of the ventromedial prefrontal cortex (VMPFC) when distinguishing between previously fear conditioned stimuli and naïve stimuli. During awareness this modification is often slow, but research employing unconscious stimulus presentations has shown faster subcortical routes exist in fear conditioning. In a recent fear reversal study participants were conditioned outside of their awareness via continual flash suppression (CFS). CFS manipulates binocular rivalry by presenting a static low contrast image to one eye and suppressing it with a continuously moving, high contrast image presented to the opposite eye. Findings show that fear acquisition and reversal does occur outside of awareness but peaks much more quickly, suggesting a subcortical pathway for fear modulation also exists. Our present study attempts to recreate these results while utilizing fMRI in an attempt to trace this subcortical pathway. We hypothesize that unaware exposure to the fear reversal paradigm will display an increased activation of both the thalamus and amygdala, some small level of activation to VMPFC, and no significant activation to other cortical areas.

75 A novel isoform of THAP1 opens new insights into dystonia related genes

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Dystonia includes a group of movement disorders characterized by painful, involuntary muscle contractions. THAP1 (THanatos-associated-domain-containing Apoptosis-associated Protein 1) is a zinc-finger transcription factor with a predicted M_r of 25kDa that exerts pro-apoptotic function. Little is known about THAP1 expression in the nervous system. We sought to determine whether the tissue distribution of THAP1 yields clues to its function. We used shRNA to verify that a commercial polyclonal (ProteinTech) and a newly produced monoclonal antibody (NeuroMAB) recognize transfected THAP1. We then used plasmid and viral-mediated overexpression, SDS-PAGE, immunoprecipitation, oligonucleotide column chromatography, and mass-spectrometry to characterize THAP1. In peripheral tissues and cell lines, both antibodies recognize proteins at 30kDa, either a doublet (polyclonal) or the upper band of the doublet (NeuroMAB), which is increased by overexpression in all cells. Both antibodies also recognize a heterogeneously sized species at 50kDa, exclusively in primary neurons and neuronal tissue. The upper 30kDa and the 50kDa are enriched by oligonucleotide affinity chromatography. The upper 30kDa has a methylated glutamine in the nuclear localization signal. We are investigating whether the 50kDa represents a dimer required for DNA binding in neurons. This novel 50kDa THAP1 isoform may result from post-translational modifications with important functional implications in dystonia, and may explain how mutations in a diffusely expressed protein result in an exclusively neurologic disease.

Funded by NIH

76 Impairment in reward prediction is worse in less frequent chronic cocaine addicted individuals.

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Reward-prediction-error (RPE) reflects the difference between expected and experienced outcomes and is vital in reinforcement learning to guide future behavior; a process that may be impaired in addicted individuals. To test this hypothesis we studied the feedback negativity (FN), an event-related potential component that reflects neural processes underlying violation of expectation. We examined the effects on FN within individuals with cocaine use disorder (CUD), differentiated on recency of cocaine use; determined objectively by urine status for cocaine on study day. Subjects were 26 controls (HC), 30 CUD positive for cocaine (CUD+), and 23 CUD negative for cocaine on study day (CUD-). Following the gambling choice, where reward probability was indicated by a cue, participants made reward predictions on each trial of the gambling task. Results show an interaction between prediction and group [$F(2,76)=3.77, p=0.028$], such that the FN amplitude was larger for unpredicted outcomes compared to predicted outcomes in HC [$t(25)=2.62, p=0.015$] and CUD+ [$t(29)=2.46, p=0.020$], but not in CUD- ($p=0.279$). These results extend our previous reports of accentuated compromise in reward processing in CUD- to impairments in RPE; for the first time in human neuroimaging study of drug addiction. Abnormal computation of RPE specifically during withdrawal may result in difficulties in updating the value of alternative behavioral options and culminate in relapse to drug use.

Funding: 1F32DA033088-01

77 Exploring SETDB1/KMT1E Mediated Epigenetic Mechanism in Brain

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Epigenetic modifications such as DNA and histone methylation mediate selective gene expression in cell type specific manner. Alterations in these epigenetic modifications contribute to mood and psychosis spectrum disorders, including depression and schizophrenia. Mechanisms implementing these epigenetic modifications onto chromatin interface with genes and environment together establishing and shaping brain functions.

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

To better understand SETDB1 mediated epigenetic mechanism, here we purified SETDB1 complex from human cells and identified 112 distinct proteins including known SETDB1 associated cellular factors MCAF1, KAP1 and HP1. Brain specific Setdb1 conditional knock out mice was generated to study the role SETDB1 epigenetic repression machinery in brain functions.

ACKNOWLEDGEMENTS
We thank UMMS Proteomics and Mass Spectrometry Facility. This work is supported by NIMH grant RO1 MH 086509-01A1.

78 A Novel Mouse Model Of Alzheimer's Disease Reveals Changes To Dendritic Spine Morphology

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In the APPE693Q Dutch mutant (DU) mouse model, the level of endogenous high molecular weight soluble oligomeric amyloid beta (oAβ) correlates with diminished performance in the Morris water maze (MWM). These mice accumulate intracellular oAβ, with no visible plaques. Since these behavioural data provide important clues regarding the toxic species of Aβ, the objectives of the current project were to examine morphological changes to individual neurons and dendritic spines in 12 month-old DU mice and non-transgenic (WT) littermates. This will shed light on how different Aβ conformations can confer cognitive changes in AD. Neuronal morphology and dendritic changes were assessed by intracellular filling of pyramidal CA1 neurons with Lucifer Yellow followed by high resolution 3D reconstruction of cells using laser scanning confocal microscopy.

Our results reveal no significant differences in dendritic length and complexity in DU mice compared to WT. No differences in thin or stubby spine density were observed, however a significant decrease in apical mushroom spine density was found in DU mice compared to WT. This is the first study to demonstrate that oAβ impacts dendritic spines in a model of AD with no plaque pathology.

This study was funded by the Alzheimer's Association, the Alzheimer's Disease Research Center, and with contributions from The Friedman Brain Institute.

79 The Fundamental Attribution Error in Borderline Personality Disorder

Marianne Reddan, Tobias Brosch, Harold Koenigsberg, Daniela Schiller

When interpreting the behavior of others, people often ignore situational factors and generate dispositional (personality-based) explanations. This failure to integrate situational information into one's attributions is known as the Fundamental Attribution Error (FAE). We hypothesized that individuals with Borderline Personality Disorder (BPD), who often have volatile interpersonal relationships and express inappropriate anger, are especially prone to commit the FAE. In this study we tested this hypothesis and investigated the neural correlates of FAE. BPD and control subjects completed an FAE task during fMRI scanning. Each trial contained a unique scenario with one piece of behavioral information and one piece of situational information presented separately. Participants then judged whether dispositional or situational causes explained the behavior, and how much they liked the person described. Behavior. BPD patients made dispositional attributions when assessing negative behaviors, and situational attributions when assessing positive behaviors. Furthermore, regardless of the behavior's valence, BPDs "liked" characters less than controls. Neuroimaging. FAE committal in both cohorts was associated with reduced BOLD signal in dlPFC during the encoding of situational information, suggesting failure of a controlled correctional step subserving the integration of situational information into attributions. A stronger reduction in activation, however, was observed in BPDs relative to controls. BPDs exhibited hyperactivation of the amygdala in response to negative information, which may underlie their indiscriminate disliking of the characters. These results suggest BPD therapies targeting dlPFC activation may improve patient social interactions.

80 Balkanizing the Rodent Orbitofrontal Cortex? Preliminary Evidence from Spatial Reversals.

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Animals respond to changing contingencies to maximize reward. The orbitofrontal cortex (OFC) is implicated in many processes that require behavioral flexibility, particularly when established contingencies change. Anatomical, functional imaging, and lesion studies of primates suggest that the medial (mOFC) and lateral OFC (lOFC) mediate dissociable functions during reward and decision-making processes. However, most studies in rodents have focused on the lOFC. Using reversal learning tasks on a radial-maze, we have shown that lOFC lesions can either improve or impair adaptive responding depending on whether contingencies change rapidly or rarely, respectively. Errors made to previously non-rewarded arms (non-perseverative) accounted for performance differences. Here, we used identical tasks to evaluate the contribution of rodent mOFC to flexible spatial responding. Preliminary results suggest that rats with mOFC lesions were also impaired when contingencies changed rarely, but performed at normal levels when contingencies changed rapidly. Unlike rats with lOFC lesions, rats with mOFC lesions committed more errors to previously rewarded arms (perseverative). Together with findings from delay and probabilistic discounting tasks in rats, these results suggest mOFC may promote the exploration of novel options when contingencies change. Ongoing experiments using simultaneous dual-site recording and inactivation techniques will evaluate how OFC subregions coordinate with the hippocampus to integrate reward history with memory for events to serve goal-directed behavior; and achieve the enviable balance between exploration and exploitation.

81 Diagnosis-by-genotype deficit in amygdala habituation to negative emotional stimuli among BDNF 66Met carriers with borderline personality disorder

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Background: Borderline (BPD) patients have emotion-processing deficits and lack the normal habituation of amygdala activity to repeated emotional stimuli seen in healthy volunteers. We aimed to investigate the genetic underpinnings of this neural deficit, by testing the impact of brain derived neurotrophic factor (BDNF) genotypes on amygdala reactivity to repeated emotional pictures in BPD patients compared to healthy and psychiatric controls.

Methods:3 groups underwent event-related fMRI: BPD (n=19),schizotypal personality disorder (SPD, n=18),and healthy controls (n=20). Task:unpleasant, neutral, and pleasant pictures presented twice. Amygdala responses were examined with a mixed-model multivariate analysis of variance including BDNF rs6265 SNP genotype (ValVal vs Met-carriers).

Results: We found a Diagnostic group×Genotype×Picture type×Novel/Repeat Picture repetition×Time interaction (F[40,64]=1.68,p=0.031,Wilks) indicating that Met-carrying BPD patients (but not Met-carrying SPD or HCs) showed increased and prolonged amygdala reactivity during repeated unpleasant pictures, but not during the novel presentation.

Conclusion: This BPD-specific abnormality in habituation is consistent with their high sensitivity to emotional stimuli with unusually strong and long-lasting reactions.

FUNDING: Grant R01MH073911 (EAH);Merit Award,Department of Veterans Affairs (ASN,9001-03-0051), grant UL1RR029887, NIH, and MIRECC

82 Mouse "Models" of DYT6/THAP1 Dystonia

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Early onset torsion dystonia (EOTD) is characterized by abnormalities in the control of movement with involuntary muscle contractions. Mutations in three causative EOTD genes have been identified: DYT1 (TOR1A), DYT6 (THAP1) and GNAL (Gαolf) but the pathophysiology remains unknown. Dysfunction of the nigrostriatal dopamine (DA) system is frequently found in dystonia patients, and its role is supported by the identification of mutations in GNAL.

THAP1 encodes a zinc-finger transcription factor, but its neuronal downstream targets are unknown. We postulate that abnormalities of the DA system may represent a final common pathway in dystonia.
We created two THAP1 mouse models. The first model is a constitutive knockin and a conditional knockout, B6;129Thap1-C54YtmLoxPFrt. THAP1C54Y is a naturally occurring missense mutation which prevents DNA binding of THAP1 in vitro. The second is D9-Thap1-C54Y-T2A-EGFP. D9 directs transgene expression to striatal projection neurons and Purkinje cells.

Up to six month of age, B6;129F1Thap1-C54YtmLoxPFrt mice do not demonstrate a spontaneous movement disorder. Baseline locomotor behavior and performance on the pole test are normal. Locomotor response to intraperitoneal saline and cocaine is decreased, but response to CGS21680 (A2AR agonist) is normal. The D9-Thap1-C54Y-T2A-EGFP mice show GFP expression in the striatum and cerebellum and normal torsinA protein. Experiments are ongoing for further testing of DA system and analysis of the transcriptome in THAP1 mutant mice.

Source of funding: NIH, BSDPF

83 Sex-specific effects of early emotional abuse on affective processing in bipolar disorder

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Childhood trauma (CT) is associated with affective processing biases in different psychiatric disorders but its effect in bipolar disorder (BPD) is unclear. Sex is believed to modulate clinical course, severity of BPD and to have an influence on affective processing. This study investigates the effect of sex and CT on affective processing in BPD.

Childhood Trauma Questionnaire (CTQ) was used to assess CT in fifty-six BPD patients. Iowa Gambling Task (IGT) (emotional decision making) and Affective Go/No-go(AGNG) (inhibitory response to negative/positive/neutral conditions) were administered to measure affective processing. Analysis of Variance (ANOVA) was used to evaluate the effect of sex and CT on IGT; Repeated-Measures ANOVAs were used to compare groups on accuracy and bias measures across conditions on AGNG.

Sex x Emotional Abuse (EA) interactions emerged: in the context of abuse females showed a more conservative cognitive style by selecting fewer cards from the disadvantageous decks [$F(1,49)=14.218;p<.001$] and showing a learning process throughout the task [$F(1,49)= 4.385;p=.041$)]. For the AGNG, a sex x EA interaction was revealed in the negative response bias with abused females showing a higher score (mean=8.38,SD=6.39) than abused males (mean=0.69,SD=1.19)[$F(1,46)=6.348;p=.015$].

Emotional abuse differently affects males and females with BPD in affective processing tasks. Further investigations are needed to elucidate pathophysiological mechanisms underlying this interaction.

84 Molecular Mechanisms of Glucose-induced Flavor Preference in Mice and C. elegans

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Studies suggest that sugars, particularly glucose, have high post-ingestive, taste-independent metabolic rewards that drive intake and thus contribute to the obesity epidemic. Our goal was to develop a learning paradigm to probe molecular mechanisms underlying post-ingestive reward development. In our mouse model, we show that glucose-induced flavor preference occurs after a 30-minute training session during which fructose and glucose, each paired with a neutral flavor, are presented simultaneously. Using mice which lack sweet taste signaling, we demonstrate that post-ingestive glucose-induced flavor preference develops rapidly, is stable, and resists reversal. We furthermore show that preference development depends on K-ATP channel-dependent glucose sensing and leptin signaling. Similarly, glucose produces odor preference in C. elegans, which is enhanced by prior food withdrawal and by blocking glucose metabolism. Glucose-induced odor preference is mimicked by serotonin (released from NSM neurons) signaling through ser-4 receptors. Dopamine D1-like signaling produces, and the D2 agonist bromocriptine blocks, glucose-induced odor preference. Our observations confirm that learned glucose-induced flavor preference is independent of taste or calories. We speculate that during a critical period early in life, flavor preferences are acquired in part due to association with glucose signaling, after which they persist independent of glucose signaling.

Supported by: American Diabetes Association Clinical Scientist Predoctoral Training Award, Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellows

85 Role of Poly-ADP-Ribosylation in Addiction

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Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein, found abundantly in most cell types, that can bind to DNA, histones, and other proteins. PARP-1 is capable of NAD+-dependent synthesis of a polymer, called poly(ADP-ribose) or PAR, on target proteins. PARP-1 plays at least two important roles in regulation of transcription. First, PARP-1 modifies histones and creates an anionic PAR matrix that binds histones, thereby promoting the decondensation of higher-order chromatin structures. Second, PARP-1 acts as a component of enhancer/promoter regulatory complexes. Recent studies have shown that both of these activities are critical for gene regulation in vivo. We find that PARP-1 and PAR are required for the maladaptive learning associated with addiction. PARP-1 activity and global levels of PAR are increased in the nucleus accumbens (NAc), a key brain reward region, of mice treated chronically with cocaine. Blocking PARP-1 poly(ADP-ribos)ylation activity through intra-NAc infusion of the PARP-1 inhibitor Tiq-A results in a blockade of locomotor sensitization to cocaine. Overexpression of PARP-1 in the NAc using viral-mediated gene transfer resulted in amplified locomotor sensitization, augmented conditioned place preference (CPP) and increased self-administration of a low dose of cocaine. We also found that overexpression of PARG, which removes the PAR mark, decreases locomotor sensitization and the rewarding effects of cocaine in the CPP paradigm. PARP-1 ChIP –Seq studies have uncovered target genes implicated in mediating lasting responses to cocaine; studies are underway to elucidate the mechanism by which PARP-1 is recruited to these target genes to alter their expression after chronic cocaine exposure.

86 Effects of LRRK2 on dendrites and synapses

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Mutations in leucine-rich repeat kinase 2 (LRRK2) are linked to Parkinson's disease but the function of LRRK2 is not well understood. It has become widely accepted that LRRK2 levels or its kinase activity, which is increased by the most commonly observed mutation (G2019S), regulate neurite length. But it is not known this corresponds to altered growth or retraction, whether axons or dendrites are impacted differentially. We compared several developmental milestones in primary hippocampus neurons cultured from mice overexpressing a BAC transgene overexpressing mouse wildtype-LRRK2 (LRRK2-WTOE) or mutant LRRK2-G2019S (LRRK2-G2019SOE), knockout mice (KO) and non-transgenic mice (NT). After three weeks on laminin, there is a sustained, negative effect of LRRK2-G2019SOE on dendritic growth and arborization. Young KO neurons cultured on a slower growth substrate, poly-L-lysine, show significantly greater axonal and dendritic motility without significant changes in length. LRRK2 has mixed effects on synapse development. KO neurons formed more inhibitory appositions, while LRRK2-G2019SOE neurons formed significantly more excitatory appositions. Endocytosis of FM dye was equal between genotypes, but the rate of exocytosis was significantly greater in KO and LRRK2-WTOE neurons. This suggests that LRRK2 kinase activity might have a negative effect on presynaptic function but some other LRRK2 function could be having a positive effect at the same time that counteracts the kinase activity.

Supported by the Michael J Fox Foundation.

87 ngs.plot – an easy-to-use visualization tool for global enrichment of next-generation sequencing data

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Next generation sequencing (NGS) technology can generate hundreds of millions of short reads in one run. NGS is now widely used in ChIP-seq and RNA-seq researches to explore the regulatory and expression mechanisms, such as in genome-wide identification of transcription factor binding sites, histone modification sites, and transcript expression profiles. A biological conclusion is often illustrated as figures. However, it takes substantial hands-on time and bioinformatic skills to turn raw sequencing data into a figure that answers a hypothesis. Here we introduce ngs.plot, an easy-to-use visualization tool for biological hypotheses investigation based on global enrichment of NGS data. Our program encapsulates technical details in a few commands or GUI and helps a researcher directly test a hypothesis in two easy steps: 1. Identify a genomic region of interest; and 2. Visualize the enrichment of any NGS samples at that region. Now ngs.plot has also been integrated into an online bioinformatic analysis platform - Galaxy to facilitate the experimental biologists to use. ngs.plot is developed as an open source project and will be freely available at http://code.google.com/p/ngsplot/.

(This research is sponsored by the seed grant to Professor Li Shen.)

88 Profiling Histone 3 Lysine 4 Trimethylation (H3K4me3) in the Male and Female Mouse Brain

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Recent findings have demonstrated that sexual differentiation of the brain is associated with epigenetic differences in males and females. The current study was designed to identify candidate genes that undergo differential histone 3 lysine 4 trimethylation (H3K4Me3) in the BNST region of the brain. The BNST and surrounding areas were microdissected from adult mouse brains and ChIP-Seq was performed. Differences in peaks between the male and female samples were examined within an interval of 2000bp upstream and 200bp downstream of the transcription start site. Roughly 150 genes with differential H3K4 methylation in male and female mice were revealed. The appearance of Xist, an RNA gene that is responsible for the initiation and spread of X-inactivation, and X-inactivation escapees such as Kmd5c that are known to be differentially expressed in males and females, helps to validate the list of candidate genes that were identified using the unbiased bioinformatics approach. Intriguingly, most of the remaining genes identified by the current method have not been previously linked to sexual differentiation. The differentially methylated genes identified in the current experiment could have substantial implications for our understanding of sex differentiation.

Supported by NIMH MH068482 (NGF)

89 Extracellular Histones: a novel inhibitor of axonal regeneration in the CNS?

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Axons in the injured adult CNS do not regenerate, in part due to inhibition by myelin debris. Outside the CNS, released histones are detected in response to inflammation. In the CNS, up-regulation of a cytoplasmic isoform of histone H1 was reported in neurons and astrocytes in a mouse model of prion disease and in humans with Alzheimer's disease. Conditioned media from naïve astrocytic cultures revealed secretion of Histones. This suggests that histones are released extracellularly in the CNS. Here, we show that primary rat cortical neurons extended long neurites when grown on permissive substrates; however, when we simultaneously added exogenous histones to the co-cultures, we observe significantly shorter neurites (up to 70% shorter). Using microfluidic chambers, a technique which isolates the cell bodies from the neurites, we plated cortical neurons on PLL and after one week we observed long neurites growing across the micro-grooves of the chamber. In contrast, when histones were applied to either the cell bodies or neurite-containing part of the chambers, we observed that neurites were unable to grow a significant distance past the micro-grooves. Furthermore, exogenous application of histones to primary cortical neurons activates Rho GTPase. We determined that levels of extracellular histones are increased in vivo after spinal cord lesions suggesting that they may inhibit axonal regeneration in spinal cord injury as well.

90 ELK1 transcription factor linked to dysregulated striatal mu opioid receptor signaling network and OPRM1 polymorphism in human heroin abusers

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Abuse of heroin and opiates has grown to disturbing levels, but minimal information exists regarding mu opioid receptor (MOR)-related striatal signaling relevant to the human condition. The striatum is central to reward and neurobiological changes in this region are central to the pathophysiology of addiction disorders. We examined molecular mechanisms related to MOR in postmortem human brain specimens from European Caucasian heroin abusers and in an animal model of heroin self-administration. A characteristic feature of heroin abusers was decreased expression of MOR and extracellular regulated kinase (ERK) signaling networks, concomitant with dysregulation of the downstream transcription factor ELK1. ELK1 protein in heroin abusers associated with the polymorphism rs2075572 in OPRM1 and correlated with history of heroin use, an effect reproduced in an animal model that emphasizes a relationship between heroin exposure and ELK1 dysregulation. An unbiased microarray that revealed ~20% of downregulated genes in human heroin abusers are ELK1 target genes. Using chromatin immuneprecipitation, we confirmed decreased ELK1 promoter occupancy of the target gene Use1. These data highlight ELK1 as a potential key transcriptional regulatory factor in striatal disturbances associated with heroin abuse.

Funding:DA15446.

91 Role of chromatin remodelers in the mouse nucleus accumbens in models of depression and cocaine addiction

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Previous work has demonstrated that certain enzymes that "write" and "erase' modifications on histone tails play important roles in the pathophysiology of addiction and depression. However, little is known about role of ATP-dependent chromatin remodelers. These ATPase-containing remodelers form complexes with accessory subunits and work in concert with chromatin modifiers to alter nucleosome structure and dynamics. Here, we show that repeated cocaine administration or chronic social defeat stress highly regulates the expression levels of four families of chromatin remodelers, but in particular the ISWI family, in the nucleus accumbens (NAc). Furthermore, utilizing viral-mediated gene transfer, manipulation of these ISWI remodeling complexes in the NAc alter susceptibility to both the depressive-like phenotype and addictive properties of cocaine. The localization of these complexes will be identified using ChIP/ChIP-sequencing. In addition, the packing state of chromatin will be examined in the nucleus accumbens after cocaine or stress treatment to determine whether changes in nucleosome positioning are caused by altered expression of chromatin remodelers. Together, these data point to an exciting new direction in studying how gross changes in chromatin states can alter gene expression and play an important role in the pathophysiology of psychiatric disorders.

Supported by NIDA and NIMH

92 A map for social navigation in the human brain

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Every social encounter is an opportunity to become more or less intimate with others and to gain or lose power over them. Over time, we learn to position ourselves within a social structure by using others as reference points. How does the human brain encode these social coordinates?

We hypothesized that the neural mechanisms underlying navigation in physical space are also employed to navigate social space and that these neural correlates could be found in the entorhinal cortex or hippocampus areas of the brain.

To test this hypothesis, we devised a task built on the principles of role-playing games. During the task, participants interact with several characters while undergoing functional MRI. Each interaction is translated to numerical values representing power and intimacy. These social coordinates are then used to draw a vector between each of those characters and the participant's point of view. The angle and distance of the vector are employed as predictors for BOLD signal analysis.

Throughout the social game, we observed activation of brain areas typically associated with social processes. Remarkably, our vector model specifically correlated with activation of the entorhinal cortex, suggesting the brain might have a social grid, just like it has a spatial one, and that we can extract the neural correlates of social structure as a function of geometric representations.

93 Functional Connectivity changes in Parkinson's Disease: A graph theory analysis of resing-state fMRI data

R.Teodorescu, K.Simonyan, M.Petracca, C.Moisello, M.Brys, A.Di Rocco, M.F.Ghilardi, M.Inglese

Parkinson's Disease(PD) affects not only the motor functions, but also the cognitive and emotional functions. Based on that, we studied PD functional connectivity outside the motor areas. For that purpose we used resting-state(RS) fMRI data in PD patients compared to healthy age-matched controls(HC).

Sixteen PD patients (8M/8F;62.93±6.88yrs;UPDRS=18.12±8.89;HAMD=6.4±3.92) and sixteen HC(8M/8F; 62.81±7.07yrs) underwent RS-fMRI acquisition using standard protocol. The data was pre-processed with ANATICOR and the brain was segmented in 206 bilateral regions(ROIs) based on the Eikhoff-Zille cytoarchitectonic atlas. Connectivity matrices were constructed by using Pearson's correlation coefficients on the ROIs. Brain Connectivity Toolbox functions were used for computing the network metrics. The matrices were thresholded on a wide sparsity range($5\% \leq S \leq 95\%$).

We detected for both groups the small-world network properties. For sparsities between 10-75%, λ was significantly higher($p<0.01$) in PD than HC. Global-efficiency was found lower for PD than HC($p=0.04$). We detected statistically significant decreased local-efficiency and increased nodal betweenness centrality in PD than HC($p \leq 0.0002$) in thalamic motor and premotor areas; lower number of degree hubs in PD than HC; reduced correlation for PD than HC in motor, premotor and prefrontal areas($p<0.05$). The subnetworks in PD show a statistical significant disconnection as compared to HC. A moderate inverse correlation was found between HAMD and the connectivity in the frontal-superior gyrus($r=-0.56;p<0.05$).

Our conclusion is that PD alterations can be detected by using this approach in motor and non-motor areas.

94 Functional Connectivity Analysis in African-Americans with Multiple Sclerosis

R.Teodorescu PhD, D.Carpenter PhD, J.Howard MD, W.Zaaraoui PhD, JP.Ranjeva PhD, J.Herbert MD, M.Inglese MD, PhD

Multiple Sclerosis(MS) shows faster development on African-American(AAs) patients as compared to Caucasians(CAs). We compared the functional connectivity(FC) of AAs and CAs MS patients at rest with the healthy controls(CTRLs) using resting-state(rs) fMRI imaging.

For this study, fifteen AAs(mean age 33.4±8.16 yrs; median EDSS=1.5), fifteen CAs(mean age 34.3±7.18 yrs; median EDSS=2) and fourteen CTRLs(mean age 32.8±11.4 yrs) were enrolled. The study was IRB approved and all participants gave written consent. Rs-fMRI of 250 volume of EPI(TR/TE:3600/28ms; FOV 244mm2; matrix 122x122; 50 slices; resolution 2mm x 2mm x 2.5mm), dual-echo TSE and high-resolution 3D-T1-TFE were acquired on a 3T scanner. FSL's MELODIC toolbox was used to perform a concatenated group ICA. A Dual Regression function was applied on the Independent Component(IC) time course from each subject. Between group analysis was performed using FSL's randomise function.

Five components were selected: anterior and posterior part of the default mode network(DMN); primary visual network; sensory-motor network(SOM); fronto-parietal network(FP). Compared to CTRLs, AAs showed an increased co-activation of the right middle frontal gyrus within the FP network($p<0.01$ uncorr.) and of the left postcentral gyrus within the SOM network($p<0.05$ TFCE corrected). Compared to CTRLs, the CAs showed an increased co-activation of the precuneus within the SOM network($p<0.01$ uncorr.).

Functional abnormalities were detected on the AAs within the SOM network, as compared to CAs with a statistically significant increased co-activation on the left post-central gyrus.

95 Modeling Predisposition to Schizophrenia

Ngoc Tran[1,2], Ian Ladran[1,2] , **Aaron Topol[1]** , Jeffrey Silvas[3], Yongsung Kim[2], Anthony Simone[2], Hyung Joon Kim[1], Eva Xie[1], Mohammed Abdelrahim[1], Gang Fang[1], Bin Zhang[1], John Yates[3], Fred Gage[3], Kristen Brennand[1,2]

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Though the characteristic symptoms of schizophrenia (SZ) generally appear late in adolescence, it is now thought to be a neurodevelopmental condition. To test if the basic molecular mechanisms underlying this disease occur prior to neuronal maturation, we differentiated SZ-specific hiPSCs into forebrain neural progenitor cells (NPCs). Our unbiased genomic and proteomic analysis observed altered cellular adhesion and oxidative stress proteins in SZ hiPSC NPCs; consistent with this, we observed aberrant migration and increased oxidative stress in SZ hiPSC NPCs. A genome-wide analysis identified six miRNAs misregulated in SZ NPCs; we now report that rescuing decreased miRNA-9 levels in SZ hiPSC NPCs partially restores aberrant migration. To confirm these findings across a larger cohort of patients, we generated hiPSC NPCs from ten patients with childhood-onset SZ (COS). COS is a rare and particularly severe form of the disorder, with an onset of psychosis prior to age twelve. Our hypothesis is that neural cells derived from patients with COS will have accelerated and/or more severe cellular phenotypes relative to those we have already reported for adult-onset SZ.

Funding: Brain and Behavior Research Foundation

96 Quantitative characterization of von Economo neurons in the anterior cingulate cortex in autism

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Von Economo neurons (VENs) are large bipolar neurons selectively found in the anterior cingulate cortex (ACC) and frontoinsular cortex (FI) of large-brained mammals. This morphologically distinct neuron may be part of the neural circuitry involved in sociability and attention networks and has been implicated in several neuropsychiatric disorders. Exploring VENs in autism will allow us to understand further the social deficits of which these neurons may be the substrate. A previous neuropathologic study quantifying VENs in the FI revealed a significant increase in the ratio of VENs to pyramidal neurons in children with autism. An earlier study on the ACC in a broad age-range of patients with autism led to conflicting results; our study hopes to address this by focusing on children with autism.

Our analysis focuses on VEN and pyramidal neuron number, morphology, and volume. Postmortem brains of 9 children with autism and 9 age- and gender-matched controls will be assessed using stereologic techniques. We expect to find VENs to be selectively affected in the ACC in children with autism; in comparison, we do not expect to find changes in pyramidal neuron number and size.

Funding: Seaver Foundation, Autism Speaks

97 Targeting tau aggresomes using retinoid X receptor ligand IRX4204

Merina Varghese*, Jun Wang*,@, Hanna Reding*,@, Mario Feruzzi#, Kenjiro Ono$, Giulio Maria Pasinetti*,@

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Tauopathies are neurodegenerative disorders characterized by pathological aggregation of tau protein into paired helical filaments in the brain and include progressive supranuclear palsy, corticobasal neurodegeneration, frontotemporal dementia and Alzheimer disease. Drugs that interfere with oligomerization and/or aggregation of tau are being explored as possible treatments for tauopathies.

IRX4204 is a selective retinoid X receptor ligand developed for cancer therapy. Our recent studies indicate that IRX4204 may have significant impact in treating tauopathies. Cross-linking of unmodified protein assay revealed that IRX4204 effectively prevents assembly of tau peptides into oligomers. Circular dichroism and electron microscopy studies showed that IRX4204 destabilizes β-sheet structure of pre-formed tau fibrils and unravels paired helical filaments isolated from Alzheimer disease brain. In our cellular model of tau aggresome formation, IRX4204 reduces the content of the intracellular insoluble tau fraction, important in tau aggregation. One of the mechanisms of IRX4204 action could involve increased proteasomal activation. Considering the beneficial modulation of pathological tau at multiple levels, bioavailability in the brain and an established safety record, IRX4204 is an ideal candidate for treating tauopathies.

Further studies in our laboratory will identify the mechanisms through which IRX4204 reduces tau aggregation and/or clearance in vitro. We will also test pre-clinical efficacy of IRX4204 in an animal model of tauopathy.

98 Firing Pattern-Specific Regulation of BDNF in VTA-to-NAc Pathway Is Stress-Contextual Dependent

Jessica Walsh*, Allyson Friedman, Haosheng Sun, Stacy Ku, Deveroux Ferguson, Elizabeth Heller-Mesznik, Michelle Mazei-Robison, Dipesh Chaudhury, Barbara Juarez, Samuel Golden, Daniel Christoffel, Scott Russo, Eric Nestler and Ming-Hu Han

Icahn School of Medicine at Mount Sinai

The efficacy of novel depression treatment with deep brain stimulation implicates major depressive disorder (MDD) as a neural circuit disorder. Studies have implicated the mesolimbic dopamine (DA) system in the pathophysiology of depression, with DA neurons in the ventral tegmental area (VTA) projecting to the nucleus accumbens (NAc). High firing activity of VTA DA neurons has been correlated with increases in BDNF levels in the NAc and plays an important role in determining susceptibility versus resilience. However, we do not know what molecular effector underlies the optogenetically induced susceptibility phenotype that has been seen in the VTA-to-NAc pathway (Nature, 2013). Utilizing optogenetic and viral-mediated gene transfer approaches, we found that phasic but not tonic optoactivation of VTA-to-NAc projections increased BDNF in NAc, a phenomenon that was blocked by knocking down BDNF in the VTA-to-NAc projection. Furthermore, we found the optogenetically induced BDNF to be stress contextual dependent: phasic activation was not able to increase BDNF in stress-naïve mice, whereas corticotropin-releasing factor (CRF) infusions into the NAc of stress-naïve mice induced an upregulation of BDNF in NAc, suggesting that CRF is responsible for the increase in BDNF seen in the NAc. These findings demonstrate that phasic firing-induced regulation of BDNF in VTA-to-NAc projection is stress-contextual dependent.

NIMH F31MH095425

99 ProSAAS-Derived Peptides are Colocalized with Neuropeptide Y and Function as Neuropeptides in the Regulation of Food Intake

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ProSAAS is the precursor of a number of peptides that are proposed to function as neuropeptides. ProSAAS mRNA is highly expressed in the arcuate nucleus, we examined the cellular localization of several proSAAS-derived peptides in this region and found that they colocalized with NPY, but not αMSH. Intracerebroventricular injections of antibodies to two proSAAS-derived peptides (big LEN and PEN) significantly reduced food intake in fasted mice, while injections of antibodies to two other proSAAS-derived peptides (little LEN and little SAAS) did not. Whole-cell patch clamp recordings of parvocellular neurons in the hypothalamic paraventricular nucleus, a target of arcuate NPY projections, showed that big LEN produced a rapid and reversible inhibition of synaptic glutamate release that was spike independent and abolished by blocking postsynaptic G protein activity, suggesting the involvement of a postsynaptic G protein-coupled receptor and the release of a retrograde synaptic messenger. Taken together with previous studies, these findings support a role for proSAAS-derived peptides such as big LEN as neuropeptides regulating food intake. Further characterization of big LEN and PEN peptide/receptor systems is likely to provide insights into feeding and bodyweight regulation.

Funding provided by NIDA interdisciplinary training grant in drug abuse research DA007135-28

100 Cross-generational effects of adolescent THC exposure on gene expression and DNA methylation

Corey T. Watson, Henrietta Szutorisz, XiaoChuan Liu, Paras Garg, Yanhua Ren, Li Shen, Andrew J. Sharp and Yasmin L. Hurd

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

Drug exposure during critical periods of development is known to have lasting effects, increasing ones risk for developing mental health disorders. With respect to marijuana (Cannabis sativa), human and animal studies have shown that adolescent exposure to Δ9-tetrahydrocannabinol (THC), the main psychoactive component of marijuana, influences drug seeking behavior in adulthood, and is associated with specific changes in gene expression and epigenetic modifications. Expanding on this paradigm, we have developed a rat model to explore the effects of adolescent THC exposure on subsequent generations with respect to phenotype, gene expression, and epigenetic mechanisms. Our studies have shown that parental THC treatment causes a spectrum of behavioral alterations in F1 offspring, including abnormal response to reward. Using RNA-seq and enhanced reduced representation bisulfite sequencing (ERRBS), we are now interrogating whole-transcriptome and epigenome-wide datasets generated from the nucleus accumbens of 32 animals (16 with parental-THC exposure and 16 without) to characterize relevant systems-level changes in gene expression and DNA methylation. Being the largest study of its kind, these data will ultimately provide novel insight into potential drug-related cross-generational epigenetic effects, and serve as a useful resource for investigators to explore novel neurobiological systems underlying drug abuse vulnerability.

Our research is supported by NIH grant DA033660.

101 The association of duration of type 2 diabetes with cognitive performance is modulated by long-term glycemic control

R. West [1], Ravona-Springer [2], Schmeidler [1], Leroith [1], Koifman [2], Price [2], Hoffman [2], Silverman [1,3], Heymann [4], Schnaider Beeri [1,2]

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It is not clear why duration of type 2 diabetes (T2D) is associated with increased cognitive compromise. Hemoglobin A1c (HbA1c) has also been associated with dementia and contributes to T2D complications. We examined whether the association of duration of T2D with cognitive functioning is modulated by HbA1C. 897 non-demented T2D elderly were assessed with a neuropsychological battery. Partial correlations examined the modulating effect of HbA1c on the relationship of duration of T2D with five cognitive measures, controlling for sociodemographic and cardiovascular factors.

An interaction variable of duration of T2D with HbA1c was associated with executive functioning (p=.009), semantic categorization (p=.028), attention (p=.015), and overall cognition (p=.009)—the associations of duration of T2D with cognition increased with increasing HbA1c levels. The interaction variable was not associated with memory (r=-.001).

Duration of T2D was associated with cognition in high HbA1c levels, suggesting that individuals with T2D may limit their risk of cognitive decline by maintaining long-term good glycemic control.

Supported by NIA grants R01 AG034087 to Beeri and P50 AG05138 to Sano, Helen Bader Foundation and Irma T. Hirschl Scholar award to Beeri, the AFAR Young Investigator award, and the Alzheimer's Association grant NIRG-11-205083 to Ravona-Springer.

102 Genetic deletion of Smad1 is protective following transient ischemic stroke

Jamie K. Wong, Lei Chen, Hongyan Zou

The bone morphogenetic protein (BMP) signaling pathway has previously been established to promote astrogliogenesis, at the expense of oligogliogenesis and neurogenesis (Gross et al., 1996). However, it is unknown whether Smad1, a transcription factor downstream of BMPs, mediates this lineage commitment bias toward astrocytes. Here, we investigated whether conditional knockout (cKO) of Smad1 driven by a nestin-Cre mediated recombination, affects cell fate determination in vivo, and whether these changes alter the pathophysiological response to a transient ischemic stroke. We found that Smad1 cKO mice exhibited a greater number of glial fibrillary acidic protein (GFAP)+ astrocytes than wild-type littermates, in an age-dependent manner. Surprisingly, at 1 week following a 1 hour middle cerebral artery occlusion (MCAO), reactive gliosis was attenuated in Smad1 cKO mice, as indicated by reduced immunoreactivity for markers of reactive astrocytes: GFAP, nestin and vimentin. S100+ astrocytes and Iba1+ microglia were also less abundant on the ipsilateral hemisphere. In contrast, greater immunoreactivity for GFAP and Iba1 was observed on the contralateral cortex of Smad1 cKO mice. Fewer activated caspase 3-positive cells were present in Smad1 cKO mice, indicating that Smad1 deletion may protect against apoptotic cell death following ischemic stroke. Together, these data suggest that genetic deletion of Smad1 may confer protection against transient ischemia, resulting in less reactive gliosis, inflammation, and cell death.

This work was supported by The American Heart Association and Whitehall Foundation.

103 Dynamic Regulation of 3-dimensional Chromosomal Architectures at the NMDA receptor GRIN2B gene locus in Prefrontal Cortex

Rahul Bharadwaj, Cyril J. Peter, Catheryne Whittle, Winfried Krueger, Theodore Rasmussen, Alexey Kozlenkov, Stella Dracheva, Carol Tamminga, Subroto Ghose, **Yan Jiang**, Schahram Akbarian

Higher order chromatin, including loop formations involving active promoters and distal non-coding DNA elements, is highly regulated in a tissue specific manner. Therefore, it will be important to map 3-dimensional genome architectures in human brain collected to identify regulatory DNA elements for neuronal and glial gene expression. Here we employ chromosome conformation capture (3C) assays in prefrontal cortex of controls and subjects with schizophrenia, encompassing 700 kilobases on chromosome 12p31.1 harboring GRIN2B/NR2B, encoding a NMDA receptor subunit broadly implicated in psychiatric disease. We identify multiple interactions of the proximal GRIN2B promoter with non-coding DNA spaced up to 470 kb apart, including tissue-specific chromosomal loopings that were reproducible in neuronal cultures differentiated from induced pluripotent and embryonic stem cells. Using an inducible expression system, we uncover putative enhancer elements competing for access to the GRIN2B promoter to facilitate gene expression, a process that is counterbalanced by repressive higher order chromatin regulated by histone H3K9 methyltransferase KMT1E/SETDB1 and heterochromatin-associated protein HP-1. Our findings suggest that physical interactions of non-contiguous DNA elements remain tractable in postmortem tissue, and exploration of 3-dimensional genome architectures is likely to provide novel insights into the neurobiology of major psychiatric disease.

Supported by National Institutes of Mental Health, Silvio O. Conte Center P50 MH096890(Dr. Nestler) and R01MH086509(Dr. Akbarian).

104 The Functional Role of Projection-Specific Noradrenergic Neurons in the Locus Coeruleus in Chronic Social Defeat Stress

Hongxing Zhang, Dipesh Chaudhury, Allyson Friedman, Jessica Walsh, Barbara Juarez, Stacy Ku, Junli Cao and Ming-Hu Han

Understanding the neural circuit mechanisms of resilience may provide therapeutic targets for the treatment of stress-induced major depression, however, these mechanisms remain incompletely understood. Locus coeruleus (LC) in the brainstem and its projecting areas such as ventral tegmental area (VTA) and medial prefrontal cortex (mPFC), have been implicated in depression. Here, in a chronic social defeat mouse model of depression, we injected retrograde lumaflours into the VTA and mPFC to investigate the firing activity of projection-specific noradrenergic neurons from the LC. Our electrophysiological recordings showed that LC-to-mPFC- and LC-to-VTA neurons fired significantly higher in the resilient, but not susceptible mice, as compared to control. In the on-going studies, the firing changes of these projection-specific LC neurons will be mimicked by use of optogenetic approaches to elucidate the functional role of these LC projections in behavioral susceptibility and resilience. We will inject retrograde Cre virus into the mPFC or VTA to infect LC-to-mPFC or LC-to-VTA neurons, followed by injection of Cre-inducible channelrhodopsin-2 (ChR2) or halorhodopsin (NpHR) into the LC, to test whether optogenetic activation of these projection-specific LC neurons promotes susceptibility or resilience. These studies will provide highly novel information about resilience neural circuit in the brain and potential circuit targets for depression treatment via the promotion of the naturally occurring resilience mechanism.

Supported by NNSF and NIMH

105 CX3CR1 deficiency delayed acute skeletal muscle injury repair by impairing macrophage functions

Wanming Zhao, Haiyan Lu, Xingyu Wang and Lan Zhou

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CX3C chemokine receptor 1 (CX3CR1) is also known as the fractalkine receptor or G-protein coupled receptor 13 (GPR13). In central nervous system, CX3CR1 has been demonstrated to play a developmental role in the migration and activation of microglia and a regulatory role in the pathogenesis of neurodegenerative diseases, including Alzheimer disease. But the role of CX3CR1 in the acute skeletal muscle injury repair is unknown. Here, we present our study showing that CX3CR1 was mainly expressed by the majority of intramuscular infiltrating monocytes/macrophages (MOs/MPs) in acutely injured muscles. CX3CR1 deficiency, although did not impair MO/MP recruitment to injured muscles, significantly reduced intramuscular macrophage phagocytic function and production of muscle trophic growth factor, insulin-like growth factor-1 (IGF-1). As a result, skeletal muscle regeneration in response to acute injury is delayed. We conclude that CX3CR1 is essential to acute skeletal muscle injury repair by rendering infiltrating macrophages appropriate phagocytotic and pro-regenerative functions.

This study is supported by U.S. National Institutes of Health grant R01 AR059702 (L.Z.).

106 Depression-associated GATA1 transcription factor in Alzheimer's disease synaptic function

Wei Zhao, Jun Wang, Giulio Pasinetti

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Background: Recent evidence suggests decreased expression of synaptic-related genes and loss of synapses in Major depressive disorder (MDD), and the decreased expression of synaptic-related genes is accompanied by an increased expression of GATA1 transcriptional factor (Kang et al., 2012). Depression has been linked to cognitive impairment, including Alzheimer disease (AD), but the exact nature of the relationship is poorly understood. In this study, we explored the association of GATA1 expression and AD neuropathology. We also examined the effect of GATA1 on the expression of genes related to synaptic function in neuronal cells.

Methods: Frontal cortex region (BM9) of post mortem brain samples from 24 subjects with or without history of life time depression were analyzed by qPCR for GATA1 and synaptic gene expression levels. Synaptic gene expression was also assessed in neuronal cells overexpressing GATA1.

Results: We found elevated GATA1 and decreased synapsin 1 expression in the BM9 region from subjects with history of life time depression. Interestingly, GATA1 expression level was positively correlated with the amyloid plaque count and neurofibrillary tangle (NFT). Overexpression of GATA1 in neuronal cells led to an altered expression of genes related to pre-synaptic function.

Conclusions: Our study for the first time suggests that the depression-associated transcription factor GATA1 expression may influence synaptic plasticity and eventually cognitive function in AD brain through mechanisms involving AD-type neuropathology.

2013 UPCOMING EVENTS

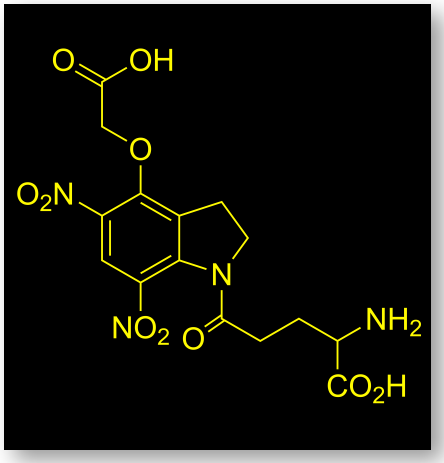

photo by Dr. Ellis-Davies

May

MSSM Commencement
May 10, 2013

September

MSSM 4th Annual Postdoc Day
Sept. 27, 2013

2013 Convocation
Sept. 30, 2013

November

Society for Neuroscience
Nov 9th-13th, 2013 San Diego, CA.

August

MD/PhD Retreat
August 9th-11th, 2013
(Hamilton Park, NJ)

Grad School Classes Begin
August 19, 2013

December

Grad School Winter Party
Dec. 17, 2013

Graduate Program information

The neuroscience curriculum has not undergone any major changes since last year's Retreat, but our Core 4 course taught in the Fall has undergone some minor tweaking to better integrate content from its two component advanced courses, Topics in Clinical Neuroscience, co-directed by Jenny Zou and James Murrough, which is team-taught by a diverse set of clinical research faculty and physicians, and Molecular Pathogenesis of Neurological and Psychiatric Disorders, directed by Patrizia Casaccia. With the recent opening of the Hess Center and relocation of a number of Neuroscience labs, an effort will be made to teach the Core Neuroscience courses at both Hess and IMI. The preliminary plan is to teach Core 1, Molecular and Cellular Neurobiology in IMI in the Fall of 2013, and Core 2 Systems Neuroscience and Core 3 Neural Basis of Behavioral Plasticity in Hess in the Winter/Spring of 2014. Seminars and journal club will also alternate locations in an easy to remember format—stay tuned for more information.

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 are again pleased to report on the many successful fellowship applications that our current graduate students and postdoctoral fellows garnered during this past year. Keep up the great work! It is a significant and prestigious achievement, particularly in this competitive funding climate, and is a great help to your advisor. 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), while the other supports graduate students (currently 2, increasing to 4 slots in 2014) and postdoctoral fellows (2 slots) carrying out mental health research. The former T32 will be renewed this May, so we ask that former and current trainees and training faculty please submit trainee information, biosketches, etc., when requested and in a timely manner, as we assemble this training grant proposal (for the 'good of the many' as Mr. Spock would say). In tough financial times, we really need to maintain and hopefully expand NIH T32 support. Lastly, we had an exceptional (and large!) group of students matriculate into the program in 2012, and look forward to welcoming a terrific pool of new graduate students matriculating this fall. The talent, diversity, and breadth of our students continues to rise every year.

George Huntley and Stephen Salton

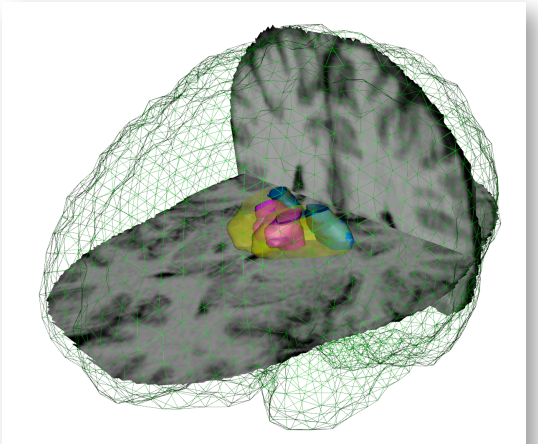

photo by Hazlett Lab