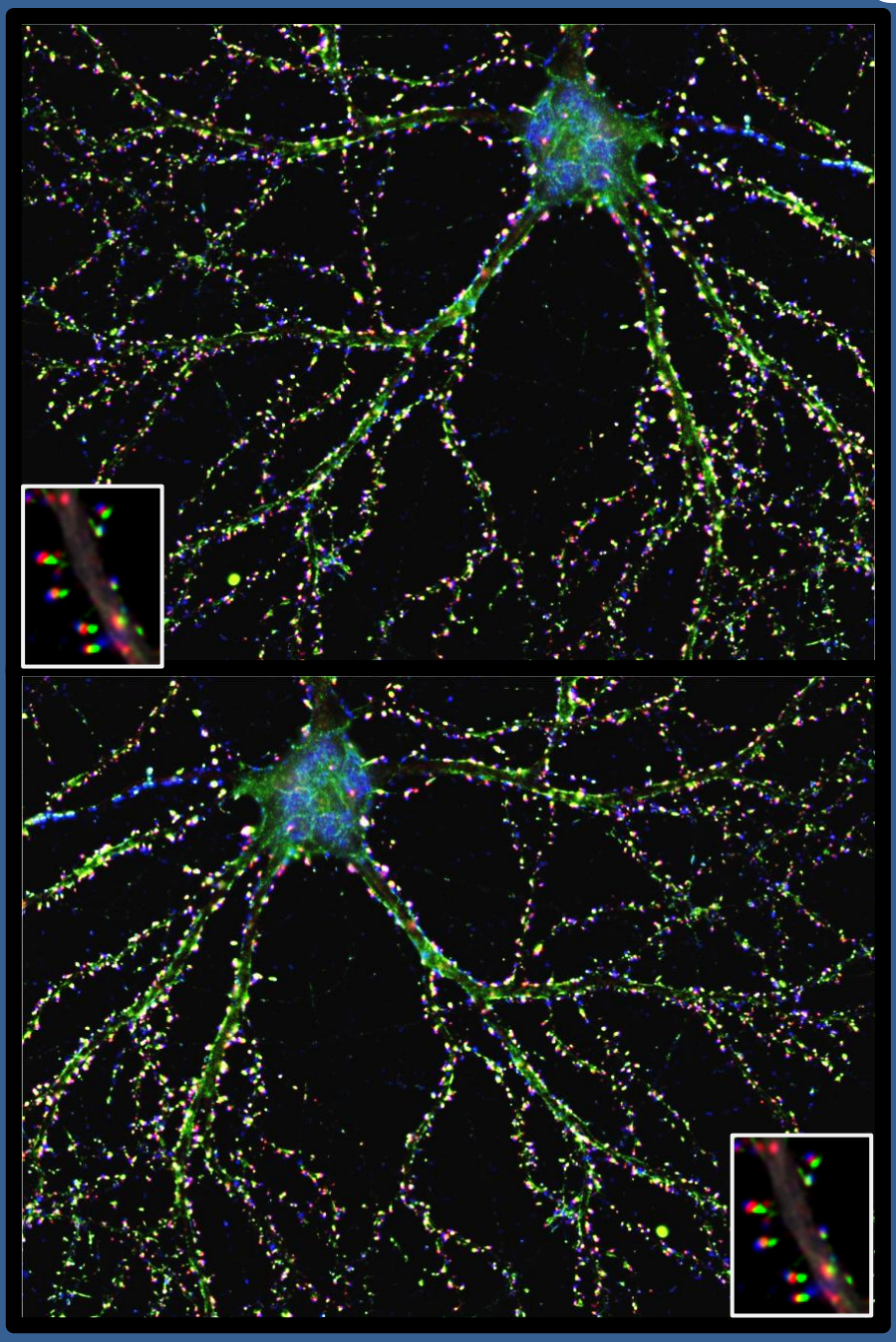
Chicago Chapter of the Society for Neuroscience 2014 Scientific Meeting

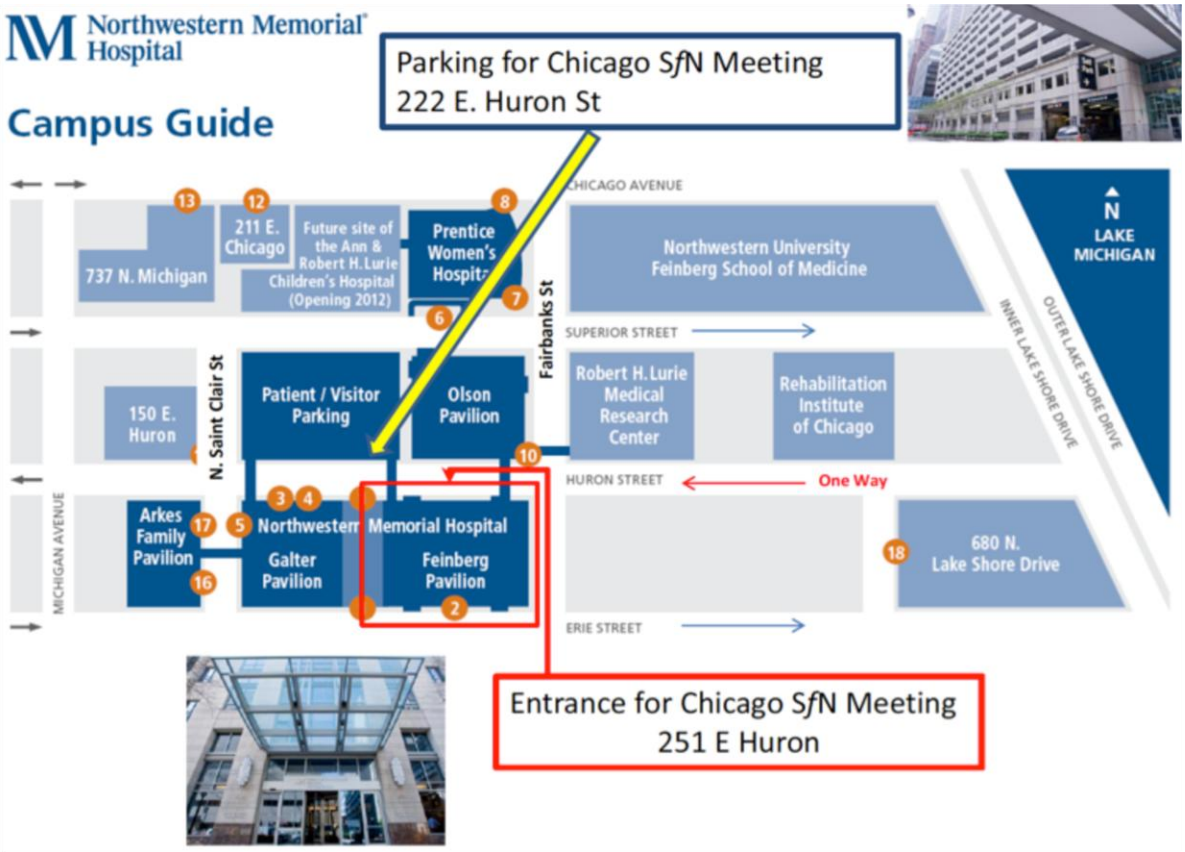


Friday, April 4, 2014

Northwestern Memorial Hospital

Map of Northwestern University downtown campus
Feinberg Pavilion, 3rd Floor Conference Center, 251 E. Huron St., Chicago, IL 60611

Meeting site for Chicago Chapter of S*f*N



Atrium, 3rd floor

- **Take the escalators or elevators to Conference Center on 3rd Floor.**
- **Please visit the corporate exhibitor tables in the Atrium on the 3rd floor.**
- **Posters should be removed by 4:00 PM.**
- **Vote for next year's Chicago Chapter S*f*N Officers and Councilors.**
- **Leave your completed ballot at the Registration Desk.**
- **Please give us your opinion by answering our survey; you will be included in a drawing for a $25 gift card. Your input is critical to making a better meeting next year.**

Parking

- **When exiting Northwestern Hospital's parking garage, please show your validated parking voucher for a parking discount (up to 7 hours $11 and 8 hours or more $24).**

Cover picture: The Figure on the cover illustrates some of the work from Dr. Mary Jo LaDu's lab (UIC), who is a CSFN councilor. The figure is a photomontage of immunofluorescence images of a mouse hippocampal pyramidal neuron from a day-21 neuron-glia co-culture showing synapse on spines; PSD95, a postsynaptic protein, is immunostained in red; synaptophysin, presynaptic protein, in blue and debrin, dendritic spine marker, in green. Adapted from the work published in "Nwabuisi-Heath E., *J Neurosci Methods*, 2012"

The Northwestern University Interdepartmental Neuroscience (NUIN) PhD program is a proud sponsor of the Chicago Society for Neuroscience.

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INDEX

Schedule of Events

7:30-10:00 AM	**Registration/Continental Breakfast**	**3rd floor**
8:00-8:45 AM	**Mentoring Panel** (with Keynote Speaker and Presidential Symposium Speakers) Chaired by Drs. Herrold and Norstrom	***Room B, C* ,D**
	Poster and Vendor Display set up	***Atrium, 3rd floor***
9:00-4:00 PM	**Poster Viewing and Vendor Display** All posters must be down by 4:00 PM at the latest	***Atrium, 3rd floor***
9:00-11:00 AM	**Presidential Symposium** ***"Molecular & Therapeutic Advances in Neurodegenerative Diseases"*** Chaired by Dr. DebBurman	***Room A***
11:00-12:00 PM	**Keynote Speaker** **Susan Lindquist, Ph.D.** Whitehead Institute/M.I.T. ***"From yeast cells to patient neurons: a powerful discovery platform for Parkinson's & Alzheimer's Disease"***	***Room A***
	Lunch Break	
12:00-2:00 PM	Poster Competitions Viewing/Judging	***Atrium, 3rd floor***
12:15-1:15 PM	Dr. Lindquist and Grad. Student Symposium participants lunch	***Room E***
12:30-1:30 PM	**Themed Lunch Tables: *"Diversity in Careers*"**	***Atrium, 3rd floor***
12:00-4:00 PM	**Chicago Public Schools Teachers Workshop**	**Room B, C, D & others**
	Plenary Afternoon Symposium	
2:00- 3:30 PM	***"Hot Topics in Neuroscience: Neuronal Circuits"*** Chaired by Dr. Pak	***Room A***
	Coffee Break	
3:30- 4:00 PM	Poster Viewing Remove poster at 4:00 PM	***Atrium, 3rd floor***
	Graduate Student Symposium	***Room A***
4:10- 5:45 PM	Selected Graduate Student Talks Chaired by Drs. Sodhi and DebBurman	
6:00-7:00 PM	**Reception and Business Meeting** Announcement of awards, recognition and election results immediately followed by Social Meeting	***Atrium, Room A***

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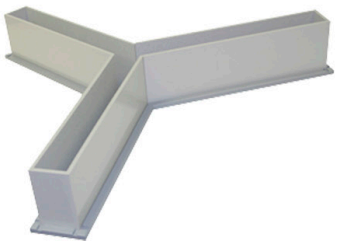

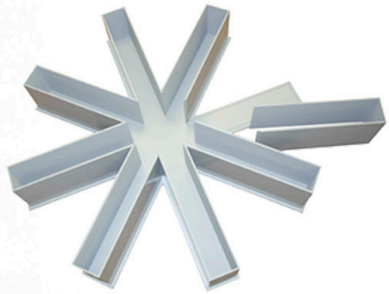

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Program

Presidential Symposium (Presented by Stoelting, Co.) *Room A*

9:00-9:15 Welcoming remarks by Dr. Shubhik DebBurman

"Molecular & Therapeutic Advances in Neurodegenerative Diseases"
Chaired by Dr. Shubhik DebBurman

9:15-9:45 **From Charcot to Lou Gehrig: Mechanisms and Therapy in ALS and Beyond**
PSA Don W. Cleveland, Ph.D.
Professor of Medicine, Neurosciences, and Cellular and Molecular Medicine University of California, San Diego

9:45-10:15 **Developmental Critical Periods and Alzheimer's Disease-**
PSB **Can Knowledge of One Help Cure the Other?**
Carla J. Shatz, Ph.D.
Professor of Biology and Neurobiology, Director of BIO-X, Stanford University

10:15-10:45 **SCA1-Linking Cellular Pathways to Therapeutic Interventions**
PSC Harry T. Orr, Ph.D.
Professor of Laboratory Medicine and Pathology, Director of Translational Neuroscience University of Minnesota

Keynote Speaker *Room A*

11:00-12:00 **"From Yeast Cells to Patient Neurons: a Powerful Discovery for Parkinson's and Alzheimer's Disease"**

Susan Lindquist, Ph.D.

Whitehead Institute for Biomedical Research / M.I.T. and H.H.M.I.

Dr. Susan Lindquist is a Member and former Director (2001-2004) of Whitehead Institute, a Professor of Biology at MIT, and a Howard Hughes Medical Institute investigator. Previously she was the Albert D. Lasker Professor of Medical Sciences from 1999-2001, and a Professor in the Department of Molecular Biology, University of Chicago, since 1978. She received a PhD in Biology from Harvard University in 1976, and was elected to the American Academy of Arts and Sciences in 1997, the National Academy of Sciences in 1997 and the Institute of Medicine in 2006.

Whitehead Member Susan Lindquist is a pioneer in the study of protein folding. She has shown that changes in protein folding can have profound and unexpected influences in fields as wide-ranging as human disease, evolution and nanotechnology.

Lunch Break

12:00-2:00 **Poster Viewing and Competitions** ***Atrium, 3rd floor***

12:00-1:30 Authors in **Post-doctoral Fellow Poster Competition** present.
Post-doctoral Fellow Poster Competition chaired by **Pascale Lacor, Ph.D., Northwestern University and Joel Voss, Ph.D., Northwestern University**

12:00-1:30 Authors in **Graduate Student Poster Competition** present.
Graduate Poster Competition chaired by **Hongkyun Kim, Ph.D., Rosalind Franklin University and Michelle Hastings Ph.D**., **Rosalind Franklin University**

12:00-1:30 Authors in **Undergraduate Student Poster Competition** present.
Undergraduate Poster Competition chaired by **Irina Calin-Jageman, Ph.D., Dominican University and Naomi Wentworth, Ph.D., Lake Forest College**

The Undergraduate Poster Competition is sponsored, in part, by Lake Forest College.

For poster titles and abstracts, go to pages 23 and 35, respectively.

Themed Lunch Tables ***Atrium, 3rd floor***

12:30-1:30 PM ***"Diversity in Careers"***

Know more about your professional options

Table 1 ***Teaching***
Robert Calin-Jageman, Ph.D.
Associate Professor, Psychology Department, Neuroscience Program Director, Dominican University

Table 2 ***Corporate***
Sonia Bhangoo, Ph.D.
Medical Writer II, Baxter Healthcare Corporation
Min Zhang, Ph.D.
Senior Research Scientist, AbbVie Inc.

Table 3 ***Government and Non-profit***
Heather Snyder, Ph.D.
Director, Medical & Scientific Relations, Alzheimer's Association
Mark M Rasenick, Ph.D.
Distinguished Professor, Department of Physiology & Biophysics and Psychiatry, University of Illinois at Chicago

Table 4 ***Administration and Law***
Michael T Kennedy, Ph.D.
Research Assistant Professor, Center for Genetic Medicine, Northwestern
Rekha Hanu, Ph.D.
Counsel-Intellectual Property, Akorn Pharmaceuticals

Chicago Public Schools Teachers Workshop

12:00-1:30 **Lunch-&-Learn Seminar with Dr. Lise Eliot** ***Room B,C,D***
"***Pink Brain, Blue Brain? Breaking Down Gender Divisions in the Classroom"***
Associate Professor of Neuroscience, Rosalind Franklin University

1:30-4:30 **Brain pedagogy activities** ***Other locations***

Co-sponsored by NU Graduate Student Association

Plenary Afternoon Symposium **(For abstracts, see page 16)** ***Room A***

"Hot Topics in Neuroscience: Neuronal Circuits"
Organized by Graduate Students: Leah Mayo, University of Chicago, Stephanie Tedford, Rush University, Yathindar Rao, Loyola University Chicago

2:00-2:05 **Introduction**
Yathindar Rao, Ph.D. candidate, Loyola University Chicago

2:10-2:30 **Targeting Neurocognition in the Treatment of Gambling Disorder**
PAS1 Jon Grant, M.D.
Department of Psychiatry and Behavioral Neuroscience, University of Chicago

2:30-2:50 **Emergent Properties of Neural Circuits: Observation and Analysis of**
PAS2 **Functional Networks in Sensory Neocortex**
Jason MacLean, Ph.D.
Department of Neurobiology, University of Chicago

2:50-3:10 **Long non-coding RNA control of seizure susceptibility**
PAS3 Jhumku Kohtz, Ph.D.
Department of Developmental Biology, Lurie Children's Research Center, Feinberg School of Medicine, Northwestern University

3:10-3:30 **Developing a Quantitative Model of the Mind and its Implications for**
PAS4 **Neuroscience**
Hans Breiter, M.D.
Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University

Sponsored by The Neuroscience Institute, Loyola University Chicago

Coffee Break — *Atrium, 3rd floor*

3:30-4:00 Visit the Posters and Exhibitors

Graduate Student Symposium **(For abstracts, see page 17)** — *Room A*

Chaired by Monsheel Sodhi, Ph.D., University of Illinois, Chicago
and Shubhik DebBurman Ph.D., Lake Forest College

4:10-4:15 **Brief Welcome and Introductory Comments by Dr. Monsheel Sodhi**
Depts. of Pharmacy Practice and Psychiatry, Center for Pharmaceutical Biotechnology, University of Illinois at Chicago

4:15-4:30 **BMP SIGNALING REGULATES THE TEMPO OF ADULT HIPPOCAMPAL PROGENITOR MATURATION**

GS1 **Allison Bond**
Interdepartmental Neuroscience Program (NUIN), Northwestern University
Advisor – Dr. Jack Kessler

4:30-4:45 **PHARMACOLOGICAL ACTIVATION OF THE MEDIAL VENTRAL PALLIDUM ELICITS INCREASED HYPOTHALAMIC FOS EXPRESSION AND ALTERS MACRONUTRIENT SELECTION IN RATS**

GS2 **Ignacio Rivero-Covelo**
Neuroscience Program, University of Illinois at Chicago
Advisor – Dr. R. David Wirtshafter

4:45-5:00 **NEURONAL REPRESENTATIONS OF NOVEL AND FAMILIAR VISUAL STIMULI IN MACAQUE INFERIOR TEMPORAL, PERIRHINAL AND PREFRONTAL CORTICES**

GS3 **Jillian L. McKee**
Committee on Computational Neuroscience, University of Chicago
A*dvisor – Dr. David J. Freedman*

5:00-5:15 **ONGOING TRANSLATION: DYSREGULATED PROTEIN SYNTHESIS MAINTAINS SYNAPTIC ADAPTATIONS DURING WITHDRAWAL FROM COCAINE SELF-ADMINISTRATION**

GS4 **Andrew Scheyer**
Dept. of Neuroscience, Rosalind Franklin University
Advisors – Drs. Marina E. Wolf and Kuei Y. Tseng

5:15-5:30 **THE ALTERNATIVE SPLICING OF ESTROGEN RECEPTOR B INCREASES FOLLOWING LOSS OF CIRCULATING 17B-ESTRADIOL IN AGED FEMALE RATS**

GS5 **Cody Shults**
Integrative Cell Biology Graduate Program, Dept. of Cell and Molecular Physiology, Loyola Stritch School of Medicine
Advisor – Dr. Toni R. Pak

5:30-5:45 **COCAINE ENHANCES PATHOPHYSIOLOGY INDUCED BY HIV-1 PROTEINS IN THE MEDIAL PREFRONTAL CORTEX**

GS6 **Wesley Wayman**
Dept. of Pharmacology, Rush University Medical Center
Advisors – Drs. T. Celeste Napier and Xiu-Ti Hu

The Graduate Student Symposium is sponsored in part by the Neuroscience Institute at Loyola University and the NUIN Program at Northwestern University

Featuring last year's winner of the Graduate Student Symposium
Ms. Yiyue Zhang and her Graduate Program

Yiyue (Cynthia) Zhang won the Graduate Student Symposium Open Competition at the 2013 annual meeting of the Chicago Chapter of the Society for Neuroscience. At the time of the award, Cynthia was a Ph.D. candidate in the Pharmacology Program at the Chicago Medical School in collaboration with the Department of Pharmaceutical Sciences in the College of Pharmacy. Under the supervision of Dr. Gloria Meredith, and in collaboration with Dr. Kathy Steece-Collier at Michigan State University, Cynthia investigated the structural plasticity of the excitatory innervation of the dorsal striatum in an animal model of levodopa-induced dyskinesia. Early on in this project, Cynthia took the lead in developing the EM protocol to carry out detailed stereological measurements of synapses in this rat model. She investigated synaptic changes in the corticostriatal and thalamostriatal inputs to the medium spiny neurons (MSNs). Her work provided compelling evidence that a rewiring of the dorsal striatum accompanies the dyskinesias. She found an increase in corticostriatal but not thalamostriatal contacts onto MSNs and discovered that there was an aberrant increase in mushroom spines that receive multiple excitatory inputs. These changes were directly linked to dyskinetic behaviors, since they were not found in any of the control groups, including the levodopa-treated group of parkinsonian rats that did not develop dyskinesias. Such circuit changes could impair the ability of striatal neurons to gate cortically driven signals and contribute to the development and persistence of dyskinesias.

Cynthia Zhang received her Ph.D. in August 2013 and has recently joined Dr. Mohamed Farah's lab in the Department of Neurology at the Johns Hopkins University as a postdoctoral fellow. In that lab, her studies focus on degeneration and regeneration in motor neuron disease models. At Rosalind Franklin University of Medicine and Sciences, the Interdisciplinary Graduate Program in Biomedical Sciences offers research training in neuroscience, pharmacology, pharmaceutical sciences, structural biology, synthetic and medicinal chemistry, physiology, cancer and viruses. Here, graduate students are able to fully develop in their chosen research field for a successful career in the biomedical sciences, as exemplified by Dr. Zhang's success.

6:00-7:00 **Reception and Business Meeting** ***Atrium, Room A***

Wine and Cheese Social ("EtOH Receptor Binding Study")

Election Results

Recognition of Councilors

Recognition of Chicago area students and student organizations for excellence in neuroscience education and outreach

2014 Chicago Brain Bee winners
2013 *Nu Rho Psi* National Chapter of the Year (Lake Forest College)
2013 S*f*N Next Generation Award (Northwestern University)

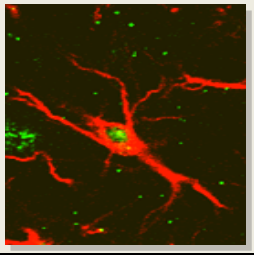
Announcement of prize winners

Undergraduate Student Poster Competition
Presented by Dr. Irina Calin-Jageman, Dominican University
and Dr. Naomi Wentworth, Lake Forest College

Graduate Student Poster Competition
Presented by Drs. Hongkyun Kim and Michelle Hastings,
Rosalind Franklin University

Post-doctoral Fellow Poster Competition
Presented by Drs. Pascale Lacor and Joel Voss,
Northwestern University

Graduate Student Symposium
Presented by Dr. Monsheel Sodhi, University of Illinois,
and Dr. Shubhik DebBurman, Lake Forest College



Loyola University Chicago
Neuroscience Research Institute
& Graduate Program

AREAS OF RESEARCH

Neurodegenerative Diseases and Neurotoxicity

Neuroendocrinology and the Autonomic Nervous System

Cellular Electrophysiology

Neurochemistry and Neuropharmacology

Neuroimmunology

CNS/PNS Injury and Repair

Neuroplasticity and Development

Brain and Behavior

Neural Control of Hemorrhagic Shock

Myelination and Demyelinating Disease

Neural Consequences of Binge and Chronic Alcohol Abuse

Loyola's Neuroscience Graduate Program provides a **rich, stimulating, and supportive research atmosphere** that enables students to appreciate the whole spectrum of neuroscience research, from the molecular to the behavioral.

Neuroscience Graduate Program Director:
Evan B. Stubbs, Jr. PhD
Evan.stuibbs@va.gov
http://www.stritch.luc.edu/neuroscience/

Neuroscience Research Institute Director
Wendy Kartje, MD, PhD
Wkartje@lumc.edu
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- Ion channel regulation
- Neuroendocrine control of behavior
- Functional interactions of plasma membrane with cytoskeletal elements

If you would like more information, please feel free to contact the department by calling the number listed above.

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ABSTRACTS

KEYNOTE SPEAKER

FROM YEAST CELLS TO PATIENT NEURONS: A POWERFUL DISCOVERY PLATFORM FOR PARKINSON'S AND ALZHEIMER'S DISEASE

S. Lindquist
Whitehead Institute for Biomedical Research and HHMI, Department of Biology, MIT, Cambridge, MA

Many neurodegenerative diseases result from basic problems in protein folding and homeostasis. These disorders appear to have little in common besides their devastating effects on patients and their families. However, they share the occurrence of complexes of misfolded, aggregated proteins in affected neurons. In Parkinson's disease (PD) the protein is alpha-synuclein (α-syn) and in Alzheimer's disease (AD) Aβ and tau are involved. Exploiting the highly conserved nature of eukaryotic cell biology and protein homeostasis mechanisms, we have developed yeast models for the pathologies caused by these proteins. Yeast cells offer unmatched opportunities for systematic, high throughput combinatorial analyses of causative factors and the discovery of pathology modifiers. Remarkably, each of the models exhibits cellular toxicity by a different mechanism and each yields a discovery platform directly relevant to human disease. Yeast cells overexpressing human α-syn or Aβ allow genetic and chemical screens, which would only be possible in yeast at such high throughput. Our α-syn screens yielded genes and compounds that rescued dopaminergic neurons in nematode, fruit fly and rat primary midbrain cultures as well as cortical human neurons differentiated from the iPS cells of patients with PD. Our Aβ screens revealed genes and compounds that specifically rescue neurons from Aβ, and other AD risk factors. Combining these discovery platforms with state-of-the art chemical genetics allowed the identification of compounds with high therapeutic potential as well as insight into their mechanisms of action.

PRESIDENTIAL SYMPOSIUM

MOLECULAR & THERAPEUTIC ADVANCES IN NEURODEGENERATIVE DISEASES

PSA

FROM CHARCOT TO LOU GEHRIG: MECHANISMS AND THERAPY IN ALS AND BEYOND

D. W. Cleveland
Ludwig Institute for Cancer Research and Dept. of Cellular and Molecular Medicine, Univ. of California at San Diego, La Jolla, CA

The genes whose mutation is now known to cause Amyotrophic Lateral Sclerosis (ALS) and/or frontal temporal dementia (FTD) are widely expressed, including SOD1, TDP-43, FUS/TLS and C9orf72. Mutation in SOD1 causes ALS through an acquired, non-cell autonomous toxicity unrelated to dismutase activity. Slowed disease progression has been achieved by a clinically feasible infusion of DNA antisense oligonucleotides (ASOs) that direct catalytic destruction of SOD1 mRNA widely within the non-human primate nervous system or by reducing mutant SOD1 expression within motor neurons and glia with a single peripheral administration of a replication defective viral delivery vector (AAV9) encoding an shRNA to target SOD1 mRNA destruction. These approaches are widely applicable for silencing causative genes in multiple neurodegenerative diseases beyond ALS, with clinical trials with the corresponding antisense oligonucleotides ongoing or planned in spinal muscular atrophy (the childhood motor neuron disease), myotonic dystrophy, and Huntington's disease. Identification of genes, whose mutation is causative of Amyotrophic Lateral Sclerosis (ALS) and frontal temporal degeneration (FTD) has revealed an unexpected convergence in disease mechanisms that includes errors in RNA binding proteins and RNA metabolism. Two of these genes encode widely expressed RNA binding proteins, TDP-43 and FUS/TLS. These two proteins have been demonstrated to act in mechanistically divergent roles in RNA pre-maturation, but their functions intersect in 45 RNAs that require the action of either TDP-43 or FUS/TLS, including the RNAs with the longest introns and which encode proteins related to synaptic function. Analysis of transgenic mice has demonstrated that age-dependent, mutant TDP-43- or FUS/TLS-dependent degeneration of lower motor neurons occurs with both loss of function and gain of toxicity, without loss of either protein from the corresponding nuclei or accumulation of aggregates. The most frequent genetic cause of ALS and FTD was identified in September of 2011 to be hexanucleotide expansion in a non-coding region of a previously unknown gene named C9*rf72.* Sense and antisense strand repeat-containing RNAs have been found to accumulate in distinct nuclear RNA foci, the hallmark feature of repeat expansion RNA-mediated toxicity. Antisense oligonucleotides (ASOs) have been developed that selectively target sense strand repeat-containing RNAs and reduce sense-oriented foci without affecting overall C9orf72

expression. Importantly, reducing *C9orf72* expression does not cause behavioral or pathological changes in mice, and induces only few genome-wide mRNA alterations. These findings establish ASO-mediated degradation of repeat-containing RNAs as an attractive therapeutic approach, with a clinical trial planned for 2015, less than four years after the founding discovery of the causative hexanucleotide expansion.

PSB
DEVELOPMENTAL CRITICAL PERIODS AND ALZHEIMER'S DISEASE- CAN KNOWLEDGE OF ONE HELP CURE THE OTHER?
C. J. Shatz
Bio-X, Stanford University, Stanford CA
Connections in adult brain are highly precise, but they do not start out that way. Precision emerges during development as synaptic connections remodel in a process requiring neural activity (action potentials and synaptic transmission). Activity also regulates neuronal gene expression. In an unbiased screen, Major Histocompatibility Class I (MHCI) genes were unexpectedly discovered to be regulated by activity and visual experience, expressed in neurons, and located at synapses (Corriveau *et al*., 1998). To assess requirements for MHCI in CNS, mutant mice lacking stable surface expression of all MHCI, or of specific MHCI genes Kb and Db, were studied. Synapse pruning in developing visual system fails, and ocular dominance (OD) plasticity in visual cortex is greater than in WT (Huh et al, 2000; Datwani et al, 2009). In a search for receptors that could interact with neuronal MHCI, PirB, an innate immune receptor, was found expressed in neurons throughout mouse CNS. In mutant mice lacking PirB, OD plasticity is enhanced (Syken *et al*., 2006), LTP and LTD are altered, and spine density on L5 Pyramidal neurons is increased. Thus, PirB, like MHCI, appears to act to “brake” synaptic plasticity. The commonality of phenotypes present in these mutant mice suggests a model (Shatz, 2009) in which PirB may bind and transduce signals from MHCI ligands in neurons. Together, results imply that these molecules, thought previously to function only in immunity, may also act at neuronal synapses to limit how much- or how quickly- synapse strength changes in response to new experience. They may also be crucial for controlling circuit excitability and stability in developing as well as adult brain. Changes in their function could contribute to developmental disorders such as Schizophrenia, and even to the synapse loss in Alzheimer’s Disease (Kim *et al.*, 2013).

PSC
SCA1-LINKING CELLULAR PATHWAYS TO THERAPEUTIC INTERVENTIONS
Harry T. Orr
Institute for Translational Neuroscience, University of Minnesota, Minneapolis, MN
Neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and the polyglutamine (polyQ) diseases share a common pathogenic mechanism: the abnormal accumulation of disease-causing proteins that is typically due to either the mutant protein's resistance to normal degradation or overexpression of the wild-type protein. Spinocerebellar ataxia type 1 (SCA1) is one of nine fatal inherited neurodegenerative diseases caused by expansion of an inframe CAG trinucleotide repeat. Each repeat tract encodes a stretch of glutamine residues in the affected protein; in SCA1 the protein is Ataxin-1 (ATXN1). SCA1 symptoms include loss of motor coordination and balance, slurred speech, swallowing difficulty, spasticity, and some cognitive impairment. A characteristic feature of SCA1 pathology is atrophy and eventual loss of Purkinje cells from the cerebellar cortex. Animal models of SCA1 show that neurodegeneration correlates with the level of mutant ATXN1. Decreasing the accumulation of mutant ATXN1 results in an age-dependent reversal of disease phenotypes. A multi-prong strategy is underway to identify and harness cellular pathways that promote the clearance of ATXN1 in affected areas of the CNS. One that is particularly exciting centers on the finding that phosphorylation at Ser776 is crucial to ATXN1 toxicity. This post-translational modification regulates the rate at which ATXN1 is cleared as well as its interaction with cellular proteins both of which have a seminal role in disease severity. Two kinases have been identified that phosphorylate S776 of ATXN1, Pka and Msk, for which small molecule inhibitors are being developed. Another approach under investigation is the use of adeno-associated viral (AAV) delivery of a microRNA (miRNA) targeting *ataxin-1* to SCA1 transgenic mouse cerebellum that improves motor phenotypes, transcriptional changes, and neuropathology. The results provide several therapeutic entry points for SCA1 and provide proof-of-principle for attacking this neurodegenerative disease as well as the other intractable neurodegenerative diseases.

PLENARY AFTERNOON SYMPOSIUM

HOT TOPICS IN NEUROSCIENCE: NEURONAL CIRCUITS

PAS1
TARGETING NEUROCOGNITION IN THE TREATMENT OF GAMBLING DISORDER
J. Grant
Department of Psychiatry and Behavioral Neuroscience, University of Chicago
There is an ongoing search in psychiatry for models of the neurobiological circuitry implicated in problematic behaviors. Greater understanding of such circuitry is likely to have ramifications for novel treatments. Cognitive markers are ideally situated as ‘objective markers’ on the pathway between genetic-environmental diatheses, brain function, and top-level overt behavior. This talk will address how cognition

may be a useful treatment target for gambling disorder as well as a range of other problematic behaviors.

PAS2
EMERGENT PROPERTIES OF NEURAL CIRCUITS: OBSERVTION AND ANALYSIS OF FUNCTIONAL NETWORKS IN SENSORY NEOCORTEX
J. MacLean
Department of Neurobiology, University of Chicago
Information in the brain is represented and processed by populations of interconnected neurons. However, we lack a clear understanding of the structure and organization of circuit wiring diagrams, particularly as we consider the mesoscale which spans multiple columns and layers. It is possible to use the correlational structure of spiking activity between neurons to generate functional wiring diagrams. We will discuss whether functional circuit architecture generalizes across the neocortex, testing the existence of a functional analogue to the neocortical microcircuit hypothesis, which has been proposed to govern underlying synaptic organization in the neocortex. We analyzed spontaneous circuit activations in primary auditory, somatosensory, and visual areas to generate functional graphs, where neurons were represented as nodes, and time lagged correlations between neurons were directed edges. Edge weights reflected the reliability of the lagged correlation, synonymous to the strength of the functional connection between two neurons. Label-independent features identified by investigating functional circuit topologies under a graph invariant framework suggest that functionally distinct areas of the neocortex carry features of a generalized functional cortical microcircuit.

PSA3
LONG NON-CODING RNA CONTROL OF SEIZURE SUSCEPTIBILITY
J. D. Kohtz
Developmental Biology, Lurie Children's Research Center Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago
In the past decade, long non-coding RNAs (lncRNAs) have emerged as a novel class of regulatory molecules with diverse functions. During this time, we have been investigating neuronal functions of *Evf2*, the first member of the lncRNA subclass of ultraconserved lncRNAs (Feng et al 2006). Previous work showed that *Evf2* is a transcriptional repressor in GABAergic interneuron precursors in the embryonic mouse brain (Bond et al. 2009, Berghoff et al. 2013). In adult mice lacking *Evf2*, we reported reduced synaptic inhibition in CA1 pyramidal neurons. Here, we show the results of a battery of behavioral tests performed on *Evf2* mutant mice. Tests of motor control, learning and memory, anxiety, anhedonia, and social interaction do not reveal significant differences between *Evf2* mutants and wildtype littermates. In the forced swim test (an acute stress test indicating behavioral despair), *Evf2* mutants have a beneficial response, exhibiting reduced immobility times. While reduced synaptic inhibition in the hippocampus predict spontaneous seizures, and abnormal EEG patterns, these are not observed in Evf2 mutants. However, when treated with threshold concentrations of the GABA inhibitor, pentylenetetrazol (PTZ), *Evf2* mutant mice exhibit increased seizure susceptibility, as indicated by EEG profiles and reduced latency times. These data suggest that the *Evf2* lncRNA controls circuitry in the adult brain, altering behavioral response to chemical- and stress-inducing agents.

PAS4
DEVELOPING A QUANTITATIVE MODEL OF THE MIND AND ITS IMPLICATIONS FOR NEUROSCIENCE
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GRADUATE STUDENT SYMPOSIUM

GS1
BMP SIGNALING REGULATES THE TEMPO OF ADULT HIPPOCAMPAL PROGENITOR MATURATION
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The adult brain continues to generate new neurons from neural stem cells in the subgranular zone (SGZ) of the hippocampus. The new neurons are thought to mediate adaptive functional changes in response to environmental stimuli. For example, exercise, environmental enrichment, and learning all stimulate hippocampal neurogenesis and enhance cognition. However, behavioral enhancement can occur in a time frame far shorter than the time required for proliferating stem cells to generate new neurons, suggesting that neuron generation occurs at a faster rate after environmental stimulation. The bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β superfamily of signaling ligands, and BMP signaling levels have been shown mediate environment-induced changes in neurogenesis. Here we investigated whether BMP signaling modulates hippocampal neural progenitor cell (NPC) maturation. We find that BMP signaling regulates the tempo of NPC maturation by directing their transition between states of quiescence and activation at multiple stages along the lineage. Virally mediated overexpression of BMP4 causes NPC cell cycle exit and slows the normal maturation of NPCs, resulting in a long-term reduction in neurogenesis. Conversely, overexpression of the BMP inhibitor noggin promotes NPC cell cycle entry and accelerates NPC maturation. Similarly, BMP

receptor type 2 (BMPRII) ablation in Ascl1$^+$ intermediate NPCs accelerates their maturation into neurons. Thus inhibition of BMP signaling is a mechanism for rapidly expanding the pool of new neurons in the adult hippocampus by tipping the balance between quiescence/activation of NPCs and accelerating the rate at which they mature into neurons.

This study was funded by the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS), NIH through Grant Number TL1R000108, as well as NIH NS 20013 and NS 20778.

GS2

PHARMACOLOGICAL ACTIVATION OF THE MEDIAL VENTRAL PALLIDUM ELICITS INCREASED HYPOTHALAMIC FOS EXPRESSION AND ALTERS MACRONUTRIENT SELECTION IN RATS

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Dramatic increases in the intakes of solid and liquid diets can be produced by activating the medial ventral pallidum (VPm) using injections of the $GABA_A$ antagonist bicuculline. The VPm projects to the lateral hypothalamus (LH), a structure that has been linked to the regulation of food intake and other homeostatic behaviors. It is likely then that the LH is part of the output circuit of VPm induced feeding. Here we studied the pattern of Fos expression, a marker of neural excitation, in the LH and after pharmacological activation of the VPm. In this work we injected N-Methyl-D-aspartic acid (NMDA) unilaterally in the VPm. Additionally, we injected NMDA unilaterally in the VPm to measure the effects that VPm activation with this amino acid has in food intake. Our results show that NMDA injections in the VPm significantly increased food intake in ad lib fed rats, indicating that feeding elicited by activation of the VPm can be induced through glutamatergic pathways. Furthermore, we measured the effect that unilateral injections of NMDA in the VPm had in the LH at AP -1.6, -2.6, and -3.6. Overall, this manipulation increased Fos expression in the perifornical LH by 40% compared with the vehicle injected side. Our results suggests the existence of a functional excitatory connection between the VPm and the LH. It is then possible for the VPm to influence the activity of a hypothalamic structure independently of the homeostatic signals. Different hypothalamic manipulations are known to alter macronutrient preference in rats. Given the implication of hypothalamic regions in VPm induced feeding, we explored the role that pharmacological activation of the VPm have in macronutrient selection. We show bicuculline injected into the medial ventral pallidum selectively increases fat intake compared to protein and carbohydrates. We also compared macronutrient intake after bicuculline injection under various feeding conditions including after feeding deprived and re-fed conditions. Our results show that the effects of blocking GABAergic neurotransmission in the medial ventral pallidum on macronutrient selection are significantly different from normal feeding to re-feeding conditions. These results suggest that GABAergic neurotransmission in the medial ventral pallidum might play a role in the regulation of fat intake specifically.

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GS3

NEURONAL REPRESENTATIONS OF NOVEL AND FAMILIAR VISUAL STIMULI IN MACAQUE INFERIOR TEMPORAL, PERIRHINAL AND PREFRONTAL CORTICES

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Previous studies have shown that the activity of neurons in prefrontal (PFC), perirhinal (PrC) and inferior temporal (ITC) cortices can differentiate between novel and familiar stimuli. However, the development of these neuronal familiarity effects, the relationship between the three areas and the link to behavior is not well understood. We compared neuronal activity among populations of ITC, PrC, and PFC neurons during performance of a novel vs. familiar categorization task. Subjects were familiarized with a group of images and then trained to distinguish them from novel stimuli by performing a delayed match-to-category (DMC) task, with novel and familiar images as categories. In the DMC task, a sample stimulus was followed by a memory delay and then a test stimulus. If the test stimulus belonged to the same category as the sample, the monkey was required to release a lever. This task design allowed us to compare the behavioral report of the monkey (novel or familiar) with the neural encoding of the stimuli. The monkeys were able to perform with greater than 90% accuracy and could also incorporate images familiarized with a different task. We recorded from 221 ITC, 210 PrC and 440 PFC neurons in two monkeys during DMC task performance. Using a linear discriminant analysis (LDA) based classifier, we were able to decode both category and stimulus identity from pseudo-populations of neurons. By training and testing the classifier on different sets of novel and familiar images, we were able to directly assess the strength of novel/familiar selectivity independent of any feature encoding. This revealed strong category and feature encoding in ITC and PrC, while PFC neurons showed stronger novel/familiar selectivity and weaker feature encoding. During the test period of the task, when subjects are comparing sample and test stimuli and deciding if they belong to same or different categories, we could decode the category of the test stimulus in all 3 areas, but with lower accuracy in PFC. When decoding the category of the sample stimulus and whether it was a match or nonmatch trial, neurons in PFC outperformed those in ITC and PrC in both

cases.Together, our results suggest that ITC, PrC, and PFC activity reflects the novelty or familiarity of stimuli, and that the three areas play distinct roles in solving a novelty vs. familiarity categorization task. Temporal cortex is involved in both visual feature representation and categorization, while frontal cortex encodes abstract category information, maintains this information into the test period to facilitate decision making, and encodes information pertaining to the behavioral output of the task (match vs. non-match). Supported by: NIH/NEI R01EY019041; NSF CAREER Award, NSERC PGSD

GS4

ONGOING TRANSLATION: DYSREGULATED PROTEIN SYNTHESIS MAINTAINS SYNAPTIC ADAPTATIONS DURING WITHDRAWAL FROM COCAINE SELF-ADMINISTRATION

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Prolonged withdrawal from extended-access cocaine self-administration is associated with a progressive intensification ("incubation") of cue-induced cocaine craving that is associated with profound adaptations in medium spiny neurons (MSN) of the nucleus accumbens (NAc). These adaptations include the accumulation of high-conductance, Ca^{2+}-permeable AMPA receptors (CP-AMPAR) and a switch in group I metabotropic glutamate receptor (mGluR) plasticity from primarily mGluR5-mediated transient synaptic depression to mGluR1-mediated long-term depression (LTD). To determine the role of protein synthesis in maintaining these adaptations, we conducted whole-cell patch-clamp recordings in NAc MSN in the presence of the protein translation inhibitors anisomycin, cycloheximide or rapamycin. All recordings were conducted in slices prepared from rats that underwent >45 days of withdrawal from extended-access cocaine self-administration or saline self-administration (controls). At this withdrawal time, the cocaine-exposed group exhibits markedly elevated cocaine craving compared to rats tested immediately after discontinuing cocaine self-administration. To assess the contribution of CP-AMPARs to NAc synaptic transmission, we measured the rectification index and sensitivity to the CP-AMPAR antagonist naspm. Both measures were elevated in slices from cocaine animals recorded under control conditions (aCSF), indicating a significant CP-AMPAR contribution (as expected from our prior studies), whereas incubation of slices with anisomycin or cycloheximide reduced these measures to levels observed in saline control rats. Similarly, protein synthesis inhibition restored mGluR5 function in cocaine-treated rats while abolishing mGluR1-LTD, resulting in a state functionally similar to that of saline controls. Together, our data indicate a critical role for protein synthesis-dependent mechanisms in sustaining the abnormally elevated CP-AMPAR transmission and altered mGluR plasticity found at NAc glutamatergic synapses. As these adaptations are directly linked to persistent enhancement of cocaine craving and resulting vulnerability to relapse, our findings suggest that aberrant regulation of protein translation may be an important contributor to addiction and perhaps a target for pharmacological intervention.

GS5

THE ALTERNATIVE SPLICING OF ESTROGEN RECEPTOR B INCREASES FOLLOWING LOSS OF CIRCULATING 17B-ESTRADIOL IN AGED FEMALE RATS

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Recent observations in the aging brain of both healthy and neurodegenerative individuals revealed global increases in alternative splicing (AS). Increases in AS has been observed in many cases of Alzheimer's and Parkinson's disease, where proteins linked to these diseases increase in their number of alternatively spliced variants. To further compound the effects of aging is the loss of estrogen associated with menopause in females. The loss of the major circulating estrogen, 17β-estradiol (E2), contributes to the loss of cognitive function and memory impairment observed in postmenopausal women. The nuclear steroid receptors through which E2 mediates its actions, ERα and ERβ, are both subject to AS. Recent studies have shown that the dominant negative ERα delta7 splice variant, which alters ERα signaling, increases in the aged female brain of both healthy and neurodegenerative patients. Other studies have linked increased expression of the dominant negative ERβ2 splice variant, which has decreased affinity to ligand, to decreased hippocampal neurogenesis and anxiety-like behaviors in female rats. Several ERβ splice variants have been described in the adult brain of both humans and rats; each variant structure altering the function of the receptor and/or its affinity for ligand. However, it is unknown how E2 deprivation effects the expressional profile of these splice variants. We hypothesized that E2 deprivation would increase ERβ splice variant expression in the aged female rat hypothalamus. In our model of surgically-induced menopause through ovariectomy (OVX), animals were ovariectomized to remove endogenous production of E2 and are then deprived of E2 for increasing amounts of time from 1 to 12 weeks. After varying deprivation periods (1, 4, 8, and 12 wks), animals were treated with either vehicle or 2.5ug/kg E2 for 3 consecutive days, and then sacrificed 1 day after the last treatment for tissue collection and data analysis. The results of these deprivation studies have shown that wild-type ERβ1 and ERβ splice variant increases with longer periods of E2 deprivation, up to 12 weeks post-OVX in the hypothalamus of aged female rats. Treatment with E2 resulted in attenuation in

some of the observed increases in splice variant expression, including ERβ1 expression. Interestingly, treatment with camptothecin, a topoisomerase inhibitor, results in an increase in ERβ splice variant expression in hypothalamic-derived GT1-7 cells. These data suggest that loss of circulating E2 may contribute to the AS of ERβ, which may be due to changes in E2 signaling pathways and splicing kinetics associated with regulating its normal expressional profile in the brain. Supported by: NIA RO1AG033605 (TRP)

GS6

COCAINE ENHANCES PATHOPHYSIOLOGY INDUCED BY HIV-1 PROTEINS IN THE MEDIAL PREFRONTAL CORTEX

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Despite combined antiretroviral therapy (cART), ~50% of HIV^+ patients in the USA are diagnosed with HIV-associated neurocognitive disorders (a.k.a., neuroAIDS). cART drugs do not readily cross the blood-brain barrier, so the brain can serve as a reservoir for infected cells that maintain HIV replication and secretion of toxic HIV-1 proteins. We documented that the cytotoxic HIV-1 protein, Tat, elicits gliosis, and revealed that expression of the pore-forming protein of voltage-gated L-type Ca^{2+} channels is enhanced in the medial prefrontal cortex (mPFC) of adult male rats. Protracted withdrawal from repeated exposure to cocaine (COC) also upregulates cortical L-channels and enhances excitability of pyramidal neurons in the mPFC. Because excessive Ca^{2+} influx can be toxic to neurons, we hypothesized that Tat-induced pathophysiology would be enhanced in the mPFC of cocaine-seeking rats. We utilized COC self-administration (COC-SA) followed by a protracted withdrawal to evaluate drug-seeking behavior in adult male rats. The readout for drug-seeking was the number of lever presses the rats made in the absence of the COC reinforcer upon re-exposure to the COC-paired cues (termed cue reactivity, CR). Saline-yoked rats were used as controls and only COC-exposed rats exhibited CR. One day after CR, the rats were killed and cortical slices were prepared for whole-cell patch-clamp recordings of mPFC pyramidal neurons. We determined that cocaine withdrawal was associated with depolarization of the resting membrane potential (RMP) and excessive firing evoked by depolarizing currents, as compared to saline-yoked controls. Bath-applied Tat facilitated RMP depolarization and neuronal firing in all neurons tested, but the magnitude of these effects was greater in the neurons recorded from cocaine withdrawn rats than in saline-yoked controls. The degree of COC-seeking was inversely related to spike amplitude during perfusion with low Tat concentrations (i.e., 2.5nM). These studies indicate that COC/Tat-mediated dysregulation of mPFC pyramidal neurons may contribute to the mechanisms underlying the co-morbidity of cocaine addiction and neuroAIDS. This work was supported by USPHSGs F31DA033206, R21DA033882, P30AI082151 and Daniel F & Ada L Rice Fdn.


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POSTER ABSTRACT TITLES

THEME A. COGNITION AND BEHAVIOR

A1 UG
A HIGH-IMPACT FORM OF LONG-TERM HABITUATION IN APLYSIA CALIFORNICA: BEHAVIORAL CHARACTERIZATION
G. Holmes[1], A. Cyriac[1], J. Lass[1], I. E. Calin-Jageman[1], R. J. Calin-Jageman[1]
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A2
EFFECTS OF THE NICOTINIC ALPHA-7 AGONIST ABT-107 ON REVERSAL LEARNING IN A RAT TOUCHSCREEN VISUAL DISCRIMINATION TASK
Z. Ding, J. Brown, L. E. Rueter, E. G. Mohler
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A3
VENTROMEDIAL PREFRONTAL CORTEX LESIONS REDUCE RADICALISM OF POLITICAL BELIEFS
I. Cristofori[1,2], V. Viola[3,4], A. Chau[1], W. Zhong[1,2], F. Krueger[5], G. Zamboni[6,7], J. Grafman[1,2]
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A4 PD
USING EYE-MOVEMENT TRACKING TO INVESTIGATE MECHANISMS OF WORD-OBJECT ASSOCIATIONS IN PRIMARY PROGRESSIVE APHASIA
M. Seckin[1], J. L. Voss[2], M-M. Mesulam[1], S. Weintraub[1], E. J. Rogalski[1],R. S. Hurley[1]
[1]Cognitive Neurology and Alzheimer's Disease Center, [2]Department of Medical Social Sciences Feinberg School of Medicine of Northwestern University, Chicago, IL

A5 PD
THE IMPACT OF RNA EDITING IN MAJOR DEPRESSION AND SUICIDE
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A6
DECISION-MAKING UNDER UNCERTAINTY IN PARKINSON'S DISEASE
I. Vilares[1], K. Kording[1,2,3]
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A7 G
CONNECTIVITY BETWEEN MEDIAL PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS IS NECESSARY FOR RESTRAINT OF IMPULSIVE REWARD-DIRECT BEHAVIOR
K. F. Manson, J. D. Roitman
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A8 G
NMDAR PHOSPHORYLATION MUTANT *GRIN2ADELTAPKC* MICE SHOW ANXIOLYTIC BEHAVIOR
D. Balu[1], J. R. Larson[2], J. V. Schmidt[1], J. P. Leonard[1]
[1]Department of Biological Sciences, University of Illinois at Chicago, Chicago, IL; [2]Department of Psychiatry, College of Medicine, University of Illinois at Chicago, Chicago, IL

A9 G
THE EFFECTS OF DOPAMINE AGONISTS PRAMIPEXOLE AND ROPINIROLE ON MOTIVATED MOTOR FUNCTION AND MOTOR DEFICITS ASSOCIATED WITH PARKINSON'S DISEASE
S. E. Tedford[1,3], A. L. Persons[1,3], T. C. Napier[1,2,3]
Depts. of Pharmacology[1] and Psychiatry,[2] and the Center for Compulsive Behavior and Addiction,[3] Rush University Medical Center, Chicago, IL

A10
PRECLINICAL CHARACTERIZATION OF A SELECTIVE α7 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST ABT-126: A NOVEL THERAPEUTIC AGENT FOR THE TREATMENT OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE AND SCHIZOPHRENIA
K.L. Kohlhaas, M. Gopalakrishnan, R.S. Bitner, D.J. Anderson, K. U. Drescher, J. H. Grønlien, M. Hu, J. Li, S. Markosyan, K. C. Marsh, E. G. Mohler, A. L. Nikkel, R. J. Radek, H. M. Robb, L. Rueter, M.R. Schrimpf, J. Waring, C-H. Lee
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A11
AEROBIC EXERCISE IS THE CRITICAL VARIABLE IN A COMPLEX ENVIRONMENT THAT ACCELERATES THE EXTINCTION OF COCAINE CONDITIONED PLACE PREFERENCE
A. M. Kobeissi, M. L. Mustroph, C. N. Kilby, H. Pinardo, J. R. Merritt, J. S. Rhodes
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A12 UG
ALZHEIMER'S MODEL: MEMORY AND LEARNING IN SCOPOLAMINE-INDUCED RATS WITH ORAL ADMINISTRATION OF TURMERIC & BACOPA MONNIERI MIXTURE
B. Leslie
Department of Neuroscience and Biology, Knox College, Galesburg, IL

A13 UG
WHAT MAKES A GOOD LEARNER? NEURAL EVIDENCE FOR VARIATOPM IN ENCODING STRATEGIES
B. Wells, W. J. Beischel, N. Mandel, I. Rymut, K. Patel, R. G. Morrison
Department of Psychology and Cognitive Affective Neuroscience Lab, Loyola University Chicago, Chicago, IL

A14 UG
THE SIGMA-1 RECEPTOR: A UNIQUE TARGET FOR TREATMENT OF BEHAVIORAL CHANGES DURING METHAMPHETAMINE ADDICTION AND WITHDRAWAL
T. O'Neal[1], E. Penick[2], J. Kirkley[3], H. Hoffmann[4]
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A15 UG
PALLIAL VOLUME AND SOCIAL GROUP SIZE IN THREE CORVID SPECIES
A. Kraemer[1], K. Gould[2], J. Templeton[1]
[1]Deparment of Neuroscience, Knox College, Galesburg, IL; [2]Department of Psychology, Luther College, Decorah, IA

A16 UG
ROLE OF VENTRAL TEGMENTAL AREA AND ROSTROMEDIAL TEGMENTAL NUCLEUS MUSCARINIC CHOLINERGIC RECEPTORS IN OPIATE-INDUCED LOCOMOTION
E. S. Dhillon[1, 2], N. Sharma[1], S. Steidl[1]
[1] Department of Psychology, Loyola University Chicago; [2] Department of Biology, Loyola University Chicago, Chicago, IL

THEME B. DEVELOPMENT

B1
OPTIMIS: A HIGH SPEED SPECTRALLY RESOLVED FLOURESCENCE MICRSOCOPE UTILIZING LINE SCAN EXCITATION
M. R. Stoneman[1], G. Biener[2], V. Raicu[2,3]
[1]Aurora Spectral Technologies, Shorewood, WI; [2]Department of Physics and [3]Department of Biological Sciences, University of Wisconsin-Milwaukee, Milwaukee, WI

B2
CHARACTERIZATION OF TRANSCRIPTION FACTORS EXPRESSED DURING CHICKEN RETINAL DEVELOPMENT
A. Blunier, D. Lawlor, J. Eisenberg, S. Georgi
Department of Biology, Augustana College, Rock Island, IL

B3 G
APOPTOSIS IN ADULT RAT DORSAL ROOT GANGLIA FOLLOWING PERIPHERAL NERVE CRUSH LESION
A. Zurney[1], M. Banks[1], K. Kristjansdottir[1], M. Fornaro[2]
[1]Department of Biomedical Sciences, Midwestern University, Downers Grove, IL; [2]Department of Anatomy, Midwestern University, Downers Grove, IL

B4 G
NEURONAL PROLIFERATION IN THE DORSAL ROOT GANGLIA FOLLOWING A PERIPHERAL NERVE CRUSH LESION
M. Banks[1], A. Zurney[1], K. Kristjansdottir[1], M. Fornaro[2]
[1]Department of Biomedical Sciences, Midwestern University; [2]Department of Anatomy, Midwestern University, Downers Grove, IL

B5 G
SCHWANN CELLS DEFICIENT IN MICRORNAS ARREST AT THE PROMYELINATING STAGE DURING DEVELOPMENT
H-P. Lin, R. Awatramani
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B6 G
ZINC-FINGER PROTEIN INSM1 REGULATES NEUROGENESIS IN SPIRAL AND VESTIBULAR GANGLIA AND IS EXPRESSED IN NASCENT OUTER HAIR CELLS
S. M. Lorenzen, A. Duggan, A. Osipovich, M. A. Magnuson, J. García-Añoveros
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B7 G
COMPARISON OF BRAIN DEVELOPMENT IN SOW-REARED AND ARTIFICIALLY-REARED PIGLETS
R. M. Jacob [1, 2], A. T. Mudd [2, 3], M. S. Conrad [2, 3], C. S. Lai [4], R. N. Dilger [1, 2, 3]
[1]Division of Nutritional Sciences, [2]Department of Animal Sciences, [3]Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL; [4]Abbott Nutrition, Abbott Labs, Columbus, OH

B8 UG
ROLE OF miR138 IN SCHWANN CELL PROLIFERATION
I. Oksuz[1], H. Lin[1], R. Awatramani[1]
[1]Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL

B9 G
LOCAL PREFRONTAL SHRNA KNOCKDOWN OF PARVALBUMIN EXPRESSION IS SUFFICIENT TO REPRODUCE THE DEFICITS IN PREFRONTAL CORTICAL INHIBITION ELICITED BY EARLY ADOLESCENT TREATMENT WITH MK-801
D. R. Thomases, E. Flores-Barrera, D. K. Cass, A. Caballero, K. Y. Tseng

Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, The Chicago Medical School, North Chicago, IL

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 UG
EVIDENCE FOR THE ROLE OF ENDOCYTOSIS IN PARKINSON'S DISEASE: INSIGHTS FROM A BUDDING YEAST MODEL
M. Tembo, M. Senagolage, J. Perez, A. Ayala, S. DebBurman
Neuroscience Program, Lake Forest College, Lake Forest, IL

C2 UG
TWO STORIES ABOUT PARKINSON'S DISEASE PROTEIN, α-SYNUCLEIN: TRUNCATIONS AND AMINO ACID DETERMINANTS
K. Campbell, M. Munoz, S. Chiren, C. Alvarado, J. James, A. Roman
Department of Biology, Lake Forest College, Lake Forest, IL

C3 UG
CREATION OF A-SYNUCLEIN SPLICE VARIANTS TO UNDERSTAND PARKINSON'S DISEASE
S. Bello Rojas, K. Hamid, N. Kukulka, S. DebBurman
Neuroscience Program, Lake Forest College, Lake Forest, IL

C4
MONITORING PD-RELEVANT PHENOTYPES IN IPSC-DERIVED NEURAL STEM CELLS FROM A SPECTRUM OF PARKINSON'S DISEASE PATIENTS FOR DRUG SCREENING AND FOR UNDERSTANDING THE BIOLOGY OF PD
B. J. Hammer[1], S. B. Hermanson[1], C. S. Lebakken[1], M. S. Piekarczyk[1], L. J. Reichling[1], T. Sampsell-Barron[1], D. V. Thompson[1], B. Schüle[2], J. W. Langston[2], K. Bi[1], D. R. Piper[1], K. W. Vogel[1]
[1]Thermo Fisher, Life Sciences Solutions, Cell Biology, Madison, WI; [2]The Parkinson's Institute, Basic Research Department, Sunnyvale, CA

C5
RNA EDITING LEVELS OF 5-HT2C AND GLUA2 ARE INCREASED IN SUICIDES WITH MAJOR DEPRESSION
M. Sodhi[1,2], T. M. Hyde[3], S. Green[4], J. E. Kleinman[3]
[1]Dept. Pharmacy Practice and Center for Pharmaceutical Biotechnology, College of Pharmacy, UIC, Chicago IL; [2]Dept. Psychiatry, College of Medicine, UIC, Chicago, IL; [3]Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, MD; [4]Department of Biological Sciences, University of Illinois at Chicago, Chicago IL

C6
THE INFLUENCE OF SECRETASE-DEPENDENT APP-CTF ACCUMULATION ON AXODENDRITIC DEVELOPMENT AND ASSOCIATED SIGNALING
C. Deyts, S. Herrera, S. Das, M. Clutter, G. Thinakaran, A, T. Parent
Department of Neurobiology, University of Chicago, Chicago, IL

C7
PALMITOYLATION OF SUPEROXIDE DISMUTASE 1 (SOD1) IS INCREASED FOR FAMILIAL ALS-LINKED SOD1 MUTANTS
S. E Antinone[1], G. D Ghadge[2], T. T Lam[3], L. Wang[2], R. P Roos[2], W. N. Green[1]
[1]Department of Neurobiology, University of Chicago, Chicago, IL; [2]Department of Neurology, University of Chicago, Chicago, IL; [3]W.M. Keck Biotechnology Resource Laboratory, Yale University, New Haven, CT

C8 PD
THE HISTONE DEACETYLASE HDAC3 IS ESSENTIAL FOR PURKINJE CELL FUNCTION, POTENTIALLY COMPLICATING THE USE OF HDAC INHIBITORS IN SCA1
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C9 PD
LOSS OF THE PARKINSONS'S DISEASE-ASSOCIATED PROTEIN DJ-1 (PARK7) RESULTS IN PATHOGENIC PHENOTYPES IN HUMAN MIDBRAIN DOPAMINERGIC NEURONS
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C10 PD
CHARACTERIZATION OF INNATE AND ADAPTIVE IMMUNE RESPONSES IN THE HSOD1^{G93A}-MCP1-CCR2 TRIPLE TRANSGENIC ALS MOUSE
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C11 PD
REORGANIZATION OF NUCLEUS ACCUMBENS PROPERTIES IN TRANSITION TO CHRONIC PAIN IN RAT
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C12 PD
EARLY DEFICITS IN SYNAPTIC, CELLULAR, AND NETWORK-LEVEL HIPPOCAMPAL CA1 FUNCTION IN PRESYMPTOMATIC ALZHEIMER'S MICE
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C13 PD
PROGRESSIVE DEGENERATION OF THE RETINAL AND SUPERIOR COLLICULUS NEURONS IN MICE WITH SUSTAINED OCULAR HYPERTENSION
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C14 PD
CDC42 AND RALA GTPASES FACILITATE TNF-A MEDIATED RELEASE OF MCP-1 FROM PERIPHERAL NERVE MICROVASCULAR ENDOTHELIAL CELLS
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C15
INCREASED MTDNA MUTATIONS WITH AGING PROMOTES AMYLOID ACCUMULATION AND BRAIN ATROPHY IN THE APP/LD TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE
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C16
ENVIRONMENTAL ENRICHMENT ENHANCES AKT/GSK3B, NEUROTROPHIN-3 AND CREB SIGNALING PATHWAYS IN WILD-TYPE MICE, BUT NOT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE
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C17
REDUCED LEVELS OF PRESENILIN-1 IN NEURAL PROGENITOR CELLS IN THE ADULT HIPPOCAMPUS INDUCES LEARNING AND MEMORY DEFICITS
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C18 G
CAV1.3 CHANNEL INHIBITORS FOR NEUROPROTECTION IN PARKINSON'S DISEASE
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C19 G
DIRECT CONVERSION OF ADULT SPINAL CORD-DERIVED OLIGODENDROCYTE PROGENITOR CELLS TO A NEURONAL FATE
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C20
DECREASED VIRAL VECTOR TRANSDUCIBILITY IN THE AGED RAT MIDBRAIN
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C21 G
ATTENUATION OF ALPHA-SYNUCLEIN INDUCED NEUROINFLAMMATION AND MICROGLIOSIS VIA RHO-KINASE INHIBITION: A POSSIBLE MECHANISM BEHIND FASUDIL-MEDIATED NEUROPROTECTION
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C22
ROLE OF trkB SIGNALING IN NEUROPROTECTIVE AND BEHAVIORAL EFFECTS OF LONG-TERM, HIGH-FREQUENCY SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION
D. L. Fischer[1,2], N. K. Polinski[1], C. J. Kemp[1], A. Cole-Strauss[1], J. W. Lipton[1], K. Steece-Collier[1], K. L. Paumier[1], T. J. Collier[1], C. E. Sortwell[1].
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C23 G
FLAVONOIDS AS POTENTIAL THERAPEUTICS FOR NEUROINFLAMMATION IN ALZHEIMER'S DISEASE
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C24 G
CAMKII A MECHANISM FOR PAIN IN MULTIPLE SCLEROSIS
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C25 G
THE GLO1/METHYLGLYOXAL PATHWAY AS A THERAPEUTIC TARGET FOR THE TREATMENT OF ANXIETY AND DEPRESSION
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C26 G
S-PALMITOYLATION MEDIATES DENDRITIC SPINE LOCALIZATION OF THE ALZHEIMER'S DISEASE BETA-SECRETASE, BACE1
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C27 G
SEX DIFFERENCES IN AGED RATS ON SENSORIMOTOR TASKS AND POST-STROKE RECOVERY
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C28 G
BEHAVIORAL RESPONSES TO ETHANOL ARE REGULATED BY THE LIM ONLY PROTEIN LMO3
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C29
LONGITUDINAL NEUROANATOMIC AND COGNITIVE TRAJECTORIES IN SCHIZOPHRENIA
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C30
AN ANTISENSE OLIGONUCLEOTIDE THAT TARGETS SPLICING TO TREAT USHER SYNDROME IN MICE
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C31 UG
TRANSPLANTED NEUROSPHERES DERIVED FROM GENETICALLY MODIFIED ADULT BONE MARROW MESENCHYMAL CELLS FOLLOWING CONTROLLED CORTICAL IMPACT (CCI): EFFECTS ON INJURY SIZE AND TRANSPLANT SURVIVAL
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C32 UG
A ROLE OF OVEREXPRESSED ALPHA-SYNUCLIEN IN ORGANIZATION OF THE PRESYNAPTIC AXONAL TERMINALS IN *C. elegans*
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C33 UG
SPECIFIC TRANSDUCTION OF CORTICOSPINAL MOTOR NEURONS BY AAV2 AFTER DIRECT INJECTION INTO THE MOTOR CORTEX
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C34 UG
RXR AGONISTS EFFECTS ON SOLUBLE LEVELS OF Aβ42 AND OLIGOMERIC Aβ DIFFERENTIALLY REGULATED BY HUMAN APOE GENOTYPES
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C35 G
NIEMANN-PICK DIESEASE TYPE C2 PROTEIN (NPC2; HE1) IS A CSF BIOMARKER OF MACROAUTOPHAGY
A. Mudd, R. Snyder, E. Eberle, W. Jesen, R. Martone
Covance Biomarker Center of Excellence

THEME D. HISTORY AND TEACHING OF NEUROSCIENCE

D1
CONCUSSION EDUCATION AS AN UNDERGRADUATE STUDENT ORGANIZATION AT DEPAUL UNIVERSITY
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D2 UG
EFFECTIVENESS OF THE "SLICE CONCUSSION EDUCATION PROGRAM" FOR CHICAGO YOUTH
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THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1
SEX-SPECIFIC EFFECTS OF REPEATED RESTRAINT STRESS ON NEURONAL ACTIVITY IN FEMALE AND MALE BASOLATERAL AMYGDALA
S. R. Blume, J. A. Rosenkranz
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E2
17B-ESTRADIOL REGULATES THE BIOSYNTHESIS OF MATURE MICRORNA AT MULTIPLE LEVELS IN THE AGED FEMALE RAT HYPOTHALAMUS
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E3 G
FUNCTIONAL IMPLICATIONS OF ESTROGEN RECEPTOR β POSTTRANSLATIONAL MODIFICATIONS IN NEURONS
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THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG
STRESS, SEX, AND BRAIN: FUNCTIONAL NEUROANATOMY OF KCa CHANNELS IN THE BASOLATERAL AMYGDALA
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F2
MODULATION OF $CA_V2.1$ CHANNELS BY CHOLESTEROL LEVELS
C. Weissmann, B. B. Ackerman, F. J. Urbano, O. D. Uchitel
IFIBYNE-CONICET, Insitute of Physiology, Molecular Biology and Neuroscience

F3
MODULATION OF NEURONAL VOLTAGE-GATED CALCIUM CHANNELS BY KELCH-LIKE-1 PROTEIN
P. P. Perissinotti[1], E. E. Ethington[1], J. Kalil[1], L. Cribbs[2], Y. He[3], J. Martin[1,4], M. D. Koob[3], E. S. Piedras-Rentería[1,4]
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F4
LONG-TERM POTENTIATION OF EXTERNAL GLOBUS PALLIDUS-SUBTHALAMIC NUCLEUS SYNAPSES FOLLOWING ACTIVATION OF MOTOR CORTICAL INPUTS
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F5 PD
REGULATION OF SYNAPSE STRUCTURE BY AN AUTISM-ASSOCIATED CADHERIN
K. R. Smith[1], K. A. Jones[1], K. Kopeikina[1], A. C. Burette[3], B. A. Copits[2], G. T. Swanson[2], R. J. Weinberg[3], P. Penzes[1]
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F6 G
NEURAL STEM CELL AND MICROGLIAL RESPONSES AFTER TRAUMATIC BRAIN INJURY AND REPEATED BINGE ALCOHOL
S.T. Ton, I. C. Vaagenes, S.-Y. Tsai, V. A. Husak, T.E. O'Brien, E. Alexander, D. Nockels, G. L. Kartje
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F7 G
CHARACTERIZING SOMATOSTATIN+ INTERNEURONS OF THE STRIATUM AND THEIR INHIBITORY INPUTS ONTO STRIATAL PROJECTION NEURONS
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F8 G
THE INTEGRATED STRESS RESPONSE IN PERINATAL WHITE MATTER INJURY: TARGETING AN ENDOGENOUS STRESS RESPONSE TO PROTECT AGAINST NEONATAL BRAIN INJURY
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F9
α-SYNUCLEIN EXPRESSION DEFINES INTRINSIC MOSSY FIBERS OF UNIPOLAR BRUSH CELLS
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F10 UG
HCO_3^--DEPENDENT, K^+-INDUCED INCREASE IN PROTON FLUX AT THE ENDFOOT OF ISOLATED MULLER CELLS OF THE TIGER SALAMANDER
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F11
CHARACTERIZATION AND FUNCTIONAL APPLICATIONS OF HUMAN IPS CELL-DERIVED MIDBRAIN DOPAMINERGIC NEURONS
C. Cliff, L. Chase, C. McMahon, J. Ma, N. Meyer, J. Grinager, C. Chavez, S. DeLaura, V. Ott, W. B. Wang, B. Swanson
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THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1 PD
AIMING FOR THE LESION: EXPLORING NEW DRUGS AND TRACERS SPECIFIC FOR DEMYELINATED AXONS
P. Brugarolas[1], J. E. Shanchez-Rodriguez[2], J. J. Lacroix[2], F. Bezanilla[2], B. Popko[1]
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G2 PD
A RAPID METHOD FOR EVALUATING RISK/REWARD DECISION-MAKING IN THE RAT USING INTRACRANIAL SELF-STIMULATION
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G3 UG
A COMPARISON OF HIPPOCAMPAL SUBFIELD MEASURE METHODS ABILITY TO DIAGNOSE EMCI PATIENTS
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G4 UG
AUTOMATED SEGMENTATION OF MOUSE MAGNETIC RESONANCE IMAGES INTO 568 REGIONS OF INTEREST
A. Walters[1], M. P. Schroeder[2], D. Procissi[3], K. Blizinsky[4,5,6], L. Wang[4,6]
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G5 UG
FOURIER TRANSFORM SPECTROSCOPIC INFRARED IMAGING FOR LABEL-FREE CELL-TYPE IDENTIFICATION IN NEURAL TISSUE
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G6 UG
THE RAT P3 ERP IN BEHAVIORAL CHAINS AS A FUNCTION OF CUE DURATION AND CUE SEPARATION.
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G7 UG
DIFFERENTIAL ABERRANT GENE EXPRESSION IN HETEROTOPIC:ORTHOTOPIC GLIOBLASTOMA MULTIFORME XENOGRAFTS AND CELL LINES USING A FOCUSED MICROARRAY APPROACH
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THEME H. SENSORY AND MOTOR SYSTEMS

H1
FUNCTIONAL COOPERATIVITY BETWEEN CANONICAL AND NON-CANONICAL SIGNALING PATHWAYS IN TGF-B2 MEDIATED ET-1 EXPRESSION
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H2 PD
EFFICIENT CODING OF VISUAL MOTION SIGNALS IN THE SMOOTH PURSUIT SYSTEM
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H3 PD
CORTICAL CATEGORIZATION AND CONTEXT OF SPEECH SOUND PRODUCTION
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H4 PD
INVESTIGATION OF THE TIMING AND EXTENT OF SENSORY NERVOUS SYSTEM DEGENERATION IN ALS
B. Genç[1], A. K. B. Lagrimas[1], R. Hess[2], M. V. Yasvoina[1], M. W. Tu[1], D. M. Menichella[3], R. J. Miller[3], P. H. Özdinler[1,4,5]
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H5 PD
DIFFERENT ROLES OF AXON GUIDANCE CUES AND PATTERNED SPONTANEOUS ACTIVITY IN ESTABLISHING RECEPTIVE FIELDS IN THE MOUSE SUPERIOR COLLICULUS
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H6
A NON-CANONICAL PATHWAY FROM COCHLEA TO BRAIN DETECTS TISSUE-DAMAGING NOISE AND MEDIATES AUDITORY NOCICEPTION
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H7 G
NEURAL SYNCHRONY IS IMPORTANT FOR LANGUAGE LEARNING: LINKS BETWEEN BEAT ENTRAINMENT AND NEURAL CONSISTENCY FOR SPEECH ENCODING IN PRESCHOOLERS
K. W. Carr[1,2], A. Tierney[1,2], T. White-Schwoch[1,2], N. Kraus[1-4]
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H8 G
MOLECULAR GENETICS OF PAIN IN SICKLE CELL DISEASE: ROLE OF THE MONOAMINE SYSTEM
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H9 G
KAINATE RECEPTOR COMPOSITION IN SENSORY NEURONS
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H10 UG
TWO ODOR RECEPTORS CONTRIBUTE COMPLEX AND DISTINCT SIGNALS THAT UNDERLIE ODOR CODING IN *DROSOPHILA* LARVAE
J. Grewal, C. Nguyen, C. Ebo, N. Fledderman, K. Kir, L. Milla, C. Lawdensky, S. A. Kreher
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H11 UG
MAPPING A HEDONIC HOTSPOT IN INSULAR CORTEX
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UG Undergraduate Student Competition
G Graduate Student Competition
PD Posdoctoral Student Competition

POSTER ABSTRACTS

THEME A. COGNITION AND BEHAVIOR

A1 UG
A HIGH-IMPACT FORM OF LONG-TERM HABITUATION IN APLYSIA CALIFORNICA: BEHAVIORAL CHARACTERIZATION

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Habituation is the simplest form of learning, but we know little about the transcriptional mechanisms that encode long-term habituation memory. A key obstacle is that habituation is relatively stimulus specific and is thus encoded in small sets of neurons, providing poor signal/noise ratios for transcriptional analysis. To overcome this obstacle, we have developed a high-impact protocol for producing long-term habituation of the siphon-withdrawal reflex (SWR) of *Aplysia californica*. Specifically, we constructed a computer-controlled brushing apparatus to apply low-intensity tactile stimulation over the entire dorsal surface of *Aplysia* at regular intervals. We found that 3 days of training (10 rounds of stimulation/day; each round 15 min at a 10 min ISI followed by a 15 min rest period) produces habituation with several characteristics which are favorable for mechanistic investigation. First, habituation is widespread, with SWR durations reduced whether the reflex is evoked by tactile stimulation to the head or the siphon. Second, habituation is high-impact, with 3-days of training producing decreases in SWR durations that are large (d = 3.5 – 6.4) and long-lasting (> 2 days). Third, long-term habituation is sensitive to the pattern of training, occurring only when brushing sessions are spaced out over 3 days rather than massed into a single session. At the transcriptional level, this habituation training produces regulation that is distinctive from long-term sensitization and which may involve a de-coupling of activity-dependent transcription. This work establishes a promising approach for determining how long-term habituation is transcriptionally encoded. This work was supported by NIH grant 1R15MH090998-01 to RCJ and ICJ.

A2
EFFECTS OF THE NICOTINIC ALPHA-7 AGONIST ABT-107 ON REVERSAL LEARNING IN A RAT TOUCHSCREEN VISUAL DISCRIMINATION TASK

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Patients with schizophrenia and neurodegenerative diseases demonstrate deficits in executive functioning such as cognitive flexibility. Since impairments in executive function are correlated with deficits in daily functioning, there is utility in finding novel medications that can enhance cognitive flexibility. Visual discrimination (VD) and reversal learning touch screen-based tasks have recently been developed for rodents (Bussey et al., 2011), but the effects of cognition enhancing drugs on touchscreen reversal learning have not been explored. This study investigated the effects of the alpha-7 nAChR agonist ABT-107 on the performance of rats in a touchscreen VD reversal learning task. Male Lister-Hooded rats were trained to discriminate two visual stimuli using food rewards. Once the task had been acquired, the stimulus-rewarded contingencies were reversed (first reversal). The rats were trained until they were stably performing the new VD at over 80% accuracy, and then the contingencies were reversed again back to the original acquisition criteria (second reversal). All rats received vehicle injections for 2-4 days before the first reversal. Rats were treated with ABT-107 beginning 2 days before the first reversal and were maintained on drugs throughout testing. Each rat received a training session (60 trials or 45 min) five days a week. Test compound or saline was administered 30 min before each training session. Rats receiving ABT-107 showed significantly higher accuracy on days 7-9, fewer omissions on days 5-9, more bias (responding to one side) on days 7-9, and faster correct and incorrect response latencies on Days 6-11 compared to vehicle rats during first reversal. Similarly during the second reversal, rats receiving ABT-107 showed significantly higher accuracy on days 9-12 and less side bias on days 10-11, but no difference in omissions and latencies when compared to vehicle rats.

The results showed rats receiving ABT-107 demonstrated higher accuracy, faster response latencies, and adopted an alternate strategy more quickly compared to vehicle rats in touch screen VD reversal learning. These data suggest that an alpha-7 nAChR agonist may provide therapeutic benefit for deficits in cognitive flexibility and executive function associated with schizophrenia and some neurodegenerative disorders. This study was sponsored by AbbVie, Inc. AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the abstract. All authors are currently employed by AbbVie and may own AbbVie stock. This poster was originally presented in November 2014 at the Society for Neuroscience meeting in San Diego.This study was sponsored by AbbVie, Inc. All authors are employees of AbbVie and may own stock.

A3

VENTROMEDIAL PREFRONTAL CORTEX LESIONS REDUCE RADICALISM OF POLITICAL BELIEFS

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Given its general importance in valuation, we decided to examine whether lesions to the vmPFC also modulated judgments of political opinions. Penetrating traumatic brain injury patients (pTBI; N=102) and healthy controls (HC; N=31) were tested with the Political Judgment Task that required them to rate their agreement with 75 statements expressing political opinions related to welfare, economy, political involvement, civil rights, and war & security. Each statement was also rated on three dimensions: radicalism, individualism, and conservatism. Voxel-based lesion-symptom mapping (VLSM) analysis showed that lower scores for the radicalism dimension (i.e., statements were rated as *less* radical than norms) were associated with lesions in the left and right superior, middle, and inferior orbitofrontal cortex (q(FDR)=0.01, corrected for multiple comparisons). After dividing the pTBI into three groups according to lesion location (i.e., vmPFC, dorsolateral prefrontal cortex (dlPFC) and parietal cortex), we found that the vmPFC, but not the dlPFC, group had lowered radicalism scores compared to parietal and HC groups (post-hoc comparison, p<0.01). These findings highlight the crucial role of the vmPFC for appropriately valuing political opinions and could help explain certain inappropriate social behaviors observed in patients who have lesions to the vmPFC.

A4 PD

USING EYE-MOVEMENT TRACKING TO INVESTIGATE MECHANISMS OF WORD-OBJECT ASSOCIATIONS IN PRIMARY PROGRESSIVE APHASIA

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The objective of this study is to demonstrate that eye-movement tracking provide a sensitive measurement for different levels of word-object linkage deficits during object naming. An inability to name objects, known as anomia, is one of the most common symptoms in Primary Progressive Aphasia (PPA). We developed a new method based on eye movements to investigate mechanisms of object naming and anomia. An eye tracker was used to measure viewing behavior during a word-picture matching paradigm. Participants (1 PPA and 4 controls) saw a single word cue followed by an array of 8 equidistantly displayed objects, and were asked to touch the corresponding object. Afterwards, participants were asked to name aloud each previously seen object.When the PPA patient demonstrated correct pointing to and naming of the target object (33.3% of trials), reaction times (RTs) and patterns of viewing behavior were similar to controls. When the patient pointed to the object but failed to name it (29.16% of trials), RTs were slower, and the patient viewed the target less (and distractors more) than for correct pointing and naming responses. Finally, when the patient could neither point to nor name the target object (37.5% of trials), RTs were even slower, and viewing was randomly distributed across objects with no preference for the target. Anomia was associated with significant difficulty in searching for visual objects, even on trials where the patient eventually pointed to the correct object, a situation often referred to as a "one-way" or retrieval based naming deficit. This eye-tracking paradigm offers a new approach for probing the mechanisms of object-word linkage impairments in anomic PPA patients. This work was supported by: NIH/NIA P30 AG13854, NIH/NINDS R01 NS075075 and NIH/NIDCD R01 DC008552.

A5 PD

THE IMPACT OF RNA EDITING IN MAJOR DEPRESSION AND SUICIDE

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Major depressive disorder (MDD) is a common debilitating and life-threatening disorder, affecting up to 20% of the population worldwide. Currently the molecular mechanism that underlies MDD is unknown, hindering the development of effective antidepressant therapies. Accumulating data indicate that RNA editing, a process that creates sequence changes in specific RNAs with profound physiological consequences, is increased in mood disorders. However, whether altered RNA editing is causally related to MDD is unclear. Multiple studies in humans and animals show that early life stress can cause MDD. Therefore, we investigated RNA editing in a mouse model of depression created by prenatal stress (PRS). Our preliminary analyses revealed increased RNA editing of GluA2 mRNA in the prefrontal cortex of PRS mice (ANOVA $F=5.90$, $df=1,8$, $p=0.045$) This is consistent with our observed increases in editing of both GluA2 and 5-HT2C mRNAs in postmortem brains of MDD subjects who committed suicide (MDD-suicide). To determine whether a generalized or specific alteration in RNA editing may underlie depressed behavior in PRS mice, the expression of RNA editing enzymes (ADAR1, 2 and 3) is also being analyzed. In parallel, a high-throughput screening assay has been developed and employed to identify inhibitors of ADAR activity for further investigation of the effects of RNA editing on depressive behavior in PRS mice. Identifying molecules that are altered in PRS mice may reveal molecular pathways that underlie depressive behavior, and also potential biomarkers and therapeutic targets for MDD and suicide. The authors thank the UICentre for funding this project.

A6

DECISION-MAKING UNDER UNCERTAINTY IN PARKINSON'S DISEASE

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Dopamine and putamen activity are crucial for decision-making under uncertainty. However, their specific role is still a subject of intense debate. To test potential roles, we had Parkinson's disease (PD) patients do a visual decision making task in which both prior and current sensory uncertainty (likelihood) were varied and where behavior is often predicted by Bayesian statistics. We found that many aspects of uncertainty processing were conserved in PD: both groups could learn prior distributions and utilize priors and current sensory information. However, in the PD group, in particular when off drugs, subjects showed a much weaker sensitivity to differences in likelihood uncertainty. Our results suggest that dopamine and putamen activity, which are affected by PD, have a crucial role in the processing of current sensory uncertainty. This work was supported by a PhD grant from Fundacao para a Ciencia e Tecnologia SFRH/BD/33272/2007, and by National Institutes of Health grants 2P01NS044393, 1R01NS063399 and 1R01NS074044.

A7 G

CONNECTIVITY BETWEEN MEDIAL PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS IS NECESSARY FOR RESTRAINT OF IMPULSIVE REWARD-DIRECT BEHAVIOR

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For an individual to survive, it is sometimes important to forgo immediate rewards in favor of choices that will better serve them (and others) in the long run. However, environmental stimuli that are associated with rewards often prompt approach and consummatory actions that are hard to override. Many studies have illuminated the neurological substrates responsible for the drive to approach rewarding stimuli. More specifically, activation of the medial prefrontal cortex (mPFC) has been implicated in the control of reward/value-based choices and extensive studies have shown that impulsive actions result when PFC does not function normally. In addition, mPFC projects to the nucleus accumbens (NAc), which projects to other basal ganglia structures well situated to integrate information about environmental cues and rewards to influence motor behaviors. However, it is less clear how these substrates are involved when an organism retrains their approach actions in the face of rewarding stimuli; that is, restrain their behavioral impulsivity. We tested whether the projection from mPFC to NAc is necessary for successful behavioral inhibition in an Impulsivity task. We used a novel variation of Go/No Go task to dissociate behavioral control from reward prediction that allowed us to draw conclusions about neural activity associated with the former. In the task, both correct Go trials and correct No Go trials were rewarded, allowing us to isolate neural influence associated with approach behavior without the influence of reward prediction error signals. We then pharmacologically inactivated neurons in two different conditions: bilateral inactivation of mPFC (i.e on both sides of the brain) and a combined inactivation of unilateral mPFC (one side) and contralateral NAc (opposite side). This second condition is a disconnection study, as it disrupts the connection between mPFC and NAc on both sides of the brain, but leaves half of each structure intact. We then characterized behavior in the Go/No Go task. We found that both inactivation of mPFC and disconnection between mPFC and NAc resulted in reduced accuracy on No Go trials. That is, the rats were not able to restrain their urge to press the lever even when it was disadvantageous to do so. These findings further strengthen the notion the communication between mPFC and NAc is necessary to retrain impulsive actions. Supported by DA027127.

A8 G

NMDAR PHOSPHORYLATION MUTANT *GRIN2ADELTAPKC* MICE SHOW ANXIOLYTIC BEHAVIOR

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Rapid regulation of neuronal proteins or their subunits by phosphorylation is one of the major mechanisms underlying activity dependent changes in synapses. Long-term potentiation (LTP) is an important phenomenon that was established as an electrophysiological correlation of learning and memory. Most of the molecular mechanisms of synaptic plasticity were understood based on studies involving NMDAR-activation dependent LTP. *In vivo*, these glutamatergic NMDA receptors are hetrotetramers, containing two GluN1 subunits and two of four different GluN2 subunits (A-D). A number of kinases and phosphatases interact with Serine and Tyrosine residues in the C-terminal domain (CTD) of the subunits. It was previously shown that phosphorylation of the Serines (S1291 and S1312) directly by Protein Kinase C (PKC) and Tyrosines (Y1292 and Y1387) indirectly via PKC activation of Src Tyrosine Kinase positively modulate the receptor currents. However, little is currently understood about the behavioral and physiological significance of C-terminal phosphorylation of those sites in the GluN2A subunit. In the present study, we employed a gene targeted replacement strategy to examine the role of the sites previously identified *in vitro*. We generated *Grin2adeltaPKC* mice with site directed mutations in two Serines and two Tyrosines (S1291A, Y1292F, S1312A and Y1387F) in the C-terminal domain of GluN2A. Expression levels of *Grin2a* mRNA normalized with GAPDH were similar between the *Grin2adeltaPKC* mice and their littermate controls. These mice exhibit normal locomotor behavior and spatial working memory on plus-maze spontaneous alternation test, and normal short-term recognition memory in novel object recognition test. However, these *Grin2adeltaPKC* mice show decreased alternation in a T-maze continuous alternation task. These mice also exhibit reduced anxiety-related behaviors such as increased time spent in the center of an open field, increased time in light side of light/dark box, and increased entries and dwell times in the open arms of an elevated plus maze. Interestingly, LTP induced by theta burst stimulation of Schaffer collateral-CA1 synapses in hippocampal slices from *Grin2adeltaPKC* mice was not impaired and in fact may have been enhanced. There were no significant differences in input-output curves and paired-pulse facilitation between the mutant and WT mice suggesting that presynaptic mechanisms are not involved. These data indicate that phosphorylation of at least one of those sites regulates NMDAR-mediated downstream signaling to modulate anxiolytic behaviors and regulate long-term plasticity. Supported by: NIH R03 NS-056321.

A9 G

THE EFFECTS OF DOPAMINE AGONISTS PRAMIPEXOLE AND ROPINIROLE ON MOTIVATED MOTOR FUNCTION AND MOTOR DEFICITS ASSOCIATED WITH PARKINSON'S DISEASE

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Dopamine receptors regulate multiple aspects of motor function, *via* particular neuronal circuits. For example, postural stability, a motor function dysregulated in Parkinson's disease (PD), is attributed to pathology in the putamen (humans) or the dorsolateral striatum (rats). Whereas actions governing motivated motor function, such as those that are involved in reward-driven behaviors (e.g., procuring food, money or an abused drug) are regulated by ventral striatal systems. Dopamine agonists that have a high affinity for D2/D3 dopamine receptors, e.g., pramipexole (PPX) and ropinirole (ROP), are commonly used to treat motor dysfunction in PD. These drugs are associated with several unwanted side effects including aberrant reward-driven motivated behaviors. In the current study, we determined if PPX and ROP differed with regard to postural stability and motivated motor function in laboratory rats. Postural stability was determined using the forelimb adjustment step test in a rat model of PD. A rotorod test was used to determine motivated motor behavior. To model PD, rats were injected with the neurotoxin 6-OHDA (or vehicle) into the dorsolateral striatum. Normal (unlesioned) rats were used in the rotorod tests. In all rats, baseline motor behaviors were quantified and tested with PPX (0.01-1mg/kg) and ROP (0.3mg/kg-30mg/kg) every 3-4 days. In PD-like rats, PPX and ROP improved stepping deficits dose-dependently with threshold being (0.1mg/kg) for PPX and (10mg/kg) for ROP. The agonists had no effect in sham controls. In the rotorod test, PPX and ROP dose-dependently decreased latency to fall, with threshold being (0.01mg/kg) for PPX and (6mg/kg) for ROP. Thus, doses that were subthreshold to improving stepping deficits significantly caused impairment in the rotorod test with both drugs. Due to the preferential activity for these drugs at the D3 receptor and the differential expression patterns of D2/D3 receptors in the brain we hypothesize that higher doses are activating both D2 and D3 receptors to improve motor symptoms, whereas the lower doses may be preferentially activating D3 receptors in the ventral striatum to influence reward-driven motivation. This study was supported by the Daniel F. and Ada L. Rice Fdn., and USPHSGs NS074014 and DA033121.

A10

PRECLINICAL CHARACTERIZATION OF A SELECTIVE α7 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST ABT-126: A NOVEL THERAPEUTIC AGENT FOR THE

TREATMENT OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE AND SCHIZOPHRENIA

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Enhancement of α7 neuronal nicotinic acetylcholine receptor (nAChR) activity is considered an attractive approach for ameliorating cognitive deficits associated with Alzheimer's disease and schizophrenia. Here, we describe the preclinical *in vitro* and *in vivo* profile of a novel α7 nAChR agonist, ABT- 126 ((1R, 4R, 5S)-4-(5-Phenyl-[1, 3, 4] thiadiazol-2-yloxy)-1-aza-tricyclo[3.3.1.1]decane). ABT- 126 displayed high affinity binding to α7 nAChRs (human, rat and mouse cortex, Ki = 12- 14 nM), but relatively lower affinity at other nAChR subtypes. Functionally, ABT- 126 activated human and rat α7 nAChR current responses in *Xenopus* oocytes, and enhanced current responses and synaptic activity in rat hippocampal slice preparations. *In vivo* administration of ABT- 126 in rodents modulated biochemical (pCREB phosphorylation) and neurochemical (ACh release) effects in hippocampal and cortical regions at the behaviorally effective dose range (0.01- 1 μmol/kg), as well as reduced tau hyperphosphorylation including in an *in vivo* model of tauopathy. Behaviorally, ABT- 126 demonstrated a broad spectrum of procognitive efficacy in rodent and primate models that captured domains of working memory, memory consolidation and recall, pre-attention and short- term memory. Repeated daily dosing or steady- state exposure of ABT- 126 did not result in attenuation of effects *in vivo* as revealed by both behavioral and biochemical measures. Our studies demonstrate that ABT- 126 is a selective α7 cholinergic receptor agonist that modulates cortical and hippocampal signaling mechanisms associated with cognitive functions, and exhibits broad-spectrum behavioral efficacy in preclinical models across domains implicated in Alzheimer's disease and schizophrenia. Based on these preclinical results, ABT- 126 was advanced into clinical development where positive signals of cognitive efficacy were observed in proof-of-concept studies. Disclosures: All authors are employees of AbbVie, and may own AbbVie Stock. This study was sponsored by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. These data were presented previously (AAIC 2013; nAChR SFN satellite 2013).

A11

AEROBIC EXERCISE IS THE CRITICAL VARIABLE IN A COMPLEX ENVIRONMENT THAT ACCELERATES THE EXTINCTION OF COCAINE CONDITIONED PLACE PREFERENCE

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Cocaine relapse is a growing issue worldwide. In the US alone, 4.5 million individuals reported cocaine dependency and many of these individuals relapse multiple times. Unfortunately, current treatments are limited which leads to the critical need to seek new and effective treatments to overcome relapse and maintain abstinence long-term. Exercise and environmental enrichment are under study to potentially provide effective treatments for relapse. Previous studies have reported that environmental enrichment can abolish cocaine conditioned place preference, however many of these protocols include exercise. The purpose of this study is to investigate if environmental enrichment alone can accelerate extinction. Eighty male C57BL/6J mice were exposed to either running, environmental enrichment, or sedentary conditions for 28 days. Running significantly accelerated extinction as compared to environmental enrichment and sedentary groups. Additionally, running displayed a trend toward protection against cocaine priming. The results suggest that exercise, in the form of running, is effective in decreasing drug-context associations problematic during relapse.

A12 UG

ALZHEIMER'S MODEL: MEMORY AND LEARNING IN SCOPOLAMINE-INDUCED RATS WITH ORAL ADMINISTRATION OF TURMERIC & BACOPA MONNIERI MIXTURE

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5.2 million people in the United States suffer from cognitive decline resulting from neurodegenerative diseases such as dementia and Alzheimer's disease. Unfortunately, there are few effective treatment options. However, ingredients found in traditional remedies may increase cognitive abilities. Turmeric (Tur) or bacopa monnieri (BM) have produced increased cognitive abilities in animal models of dementia and in humans. However, mixtures of Tur and BM have yet to be tested for their combined effects on cognitive decline. Thus, rats were given the muscarinic antagonist scopolamine in order to diminish cognitive abilities. The animals were split into four groups (control, Tur, BM, and Tur+BM) and examined using the Morris water maze memory test. During the acquisition trials, all of the rat groups learned the location of the platform similarly. During the probe trials, there was a significant increase in number of times rats crossed the previous location of the platform in the Tur and Tur+BM groups compared to the others groups. Further, there was a trend towards an increase of time the Tur and Tur+BM groups spent in the quadrant compared to the other groups. These results merit further research into combining novel, low side effect compounds like turmeric and bacopa to determine their mechanisms of action as well as see their true potential in fighting diseases like AD or age-related decline. This study is

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A13 UG

WHAT MAKES A GOOD LEARNER? NEURAL EVIDENCE FOR VARIATOPM IN ENCODING STRATEGIES

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Successful encoding is critical for long-term memory and is an important variable in understanding successful learning. In this study we used a retrieval practice paradigm in conjunction with EEG to examine the neural correlates of encoding throughout face-name association learning. For each of 108 unique faces, participants saw the face and then heard an assigned name. After studying several other face-name pairs participants 1) saw the face again while trying to recall the name, 2) made a prospective judgment of learning, and 3) saw the face and heard the correct name again, a sequence which repeated twice during a block of trials. Twenty four participants were divided into high and low performers based on final recall test performance after learning. We focused on neural differences during re-encoding (number 3 above), specifically calculating event related potentials (ERPs) when participants heard the name again. Presentation of the name served both as feedback for the previous recall attempt and also as an additional study opportunity. High and low performers showed a P300 (Cz) interaction with high performers showing a greater P300 with negative feedback, while low performers showing a greater P300 with positive feedback. Also of note high performers showed a much greater memory updating benefit than low performers as judged by the mean amplitude of the late positive complex (Pz) during re-encoding. These results suggest that the nature of feedback may be critical in appraising learning and allocating encoding resources during iterative learning opportunities may differ according to learning ability.

A14 UG

THE SIGMA-1 RECEPTOR: A UNIQUE TARGET FOR TREATMENT OF BEHAVIORAL CHANGES DURING METHAMPHETAMINE ADDICTION AND WITHDRAWAL

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Since its characterization, the sigma-1 receptor has been demonstrated to play a vital regulatory role in a plethora of neurobehavioral disorders and processes, including schizophrenia, anxiety, depression, learning, and addiction. A recent study found that non-selective antagonism of the sigma receptor alleviated the behavioral sensitization and neurotoxic effects of methamphetamine abuse; however, the resulting behavioral effects were not investigated. The present study was conceived to examine the effects of 4-methoxy-3-(2-phenylethoxy)-N,N dipropylbenzeneethanamine(NE-100), a selective sigma-1 antagonist, on the behavior changes induced by methamphetamine abuse and withdrawal and to biochemically analyze the resulting neuropharmacological changes. Behavioral tests were conducted on male Sprague-Dawley rats (*n*=45) after acute drug administration, once behavioral sensitization had been attained, and after 48 hours of withdrawal. Testing utilized a number of behavioral tests, including the elevated plus maze, open field, rotarod test, tail-flick test, and the forced swim test; a sucrose preference test was conducted throughout the study to examine anhedonia. Initial results have shown that co-administration of NE-100 (0.20 mg/kg) with methamphetamine (1.0 mg/kg) significantly decreases depression, anxiety, and impulsivity throughout testing and reduces withdrawal-induced anhedonia and altered pain-perception. These effects were not seen in a group that received NE-100 alone, suggesting a regulatory response by the sigma-1 receptor; however, NE-100 was found to profoundly and consistently decrease sucrose preference, suggesting baseline activity for the sigma-1 receptor in regulating hedonic behavior. Further biochemical analysis of sigma-1 receptor expression in the prefrontal cortex, nucleus accumbens, and ventral tegmental area may further elucidate the behavior findings. This study was funded by a research award from the Richter Memorial Trust.

A15 UG

PALLIAL VOLUME AND SOCIAL GROUP SIZE IN THREE CORVID SPECIES

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Certain brain regions are known to correlate with certain behavioral adaptations; for example, Dunbar's social brain hypothesis states that with an increase in social group size in primates, there is an increase in relative neocortex size. Many researchers have found similar homology in gene expression and circuitry between the mammalian neocortex and the avian pallium; thus, the pallium is a brain region that should be correlated with group size in corvids. We carried out a comparative study to test Dunbar's social brain hypothesis in corvids by measuring the area of the mesopallium, nidopallium, and hyperpallium of the pinyon jay (high sociality), Clark's nutcracker (low sociality), and azure-winged magpie (intermediate sociality). Brain sections were seen on a Leica MZ6 stereoscope, captured on a Sony ExwaveHAD digital color video camera, and measured using ImageJ software. No significant difference was found between the nutcrackers and pinyon jays of the pallium/telencephalon ratio (t-test, t = 1.9265, df = 4, p = 0.1263); however, the pinyon jays were found to have a relatively higher pallial/telencephalon ratio compared to nutcrackers (pinyon jay: 0.79135; nutcracker:

0.73487). Although no pallial volume data for the magpies are not yet available, the current results, based on only nutcracker and pinyon jay data, do not support Dunbar's social hypothesis. This research study is supported by the Paul K. and E.0valyn Elizabeth Richter Memorial Funds.

A16 UG

ROLE OF VENTRAL TEGMENTAL AREA AND ROSTROMEDIAL TEGMENTAL NUCLEUS MUSCARINIC CHOLINERGIC RECEPTORS IN OPIATE-INDUCED LOCOMOTION

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Cholinergic receptor mechanisms in the ventral tegmental area (VTA) are known to critically contribute to the stimulant and to the rewarding effects of opiates as well as to the ability of opiates to increase forebrain dopamine levels. The recently identified and adjacent rostromedial tegmental nucleus (RMTg) also critically contributes to the rewarding effects of opiates. The rates of intracranial self-administration of a μ-opioid receptor agonist are higher in the RMTg than in the VTA. Both the VTA and the RMTg receive input from the laterodorsal tegmental and pedunculopontine tegmental nuclei, each of which contain cholinergic neurons. We tested the contributions of muscarinic cholinergic receptors in the VTA and the RMTg to the stimulant effects of morphine induced by infusions of morphine (5nM) into either the VTA or the RMTg of mice. As expected morphine infusions into either the VTA or the RMTg increased locomotion. Consistent with previous reports on systemic morphine, the ability of VTA morphine to increase locomotion also depended on VTA muscarinic receptors; VTA co-treatment with atropine (3μg bilateral) strongly attenuated increases in locomotion induced by VTA morphine. By contrast, RMTg co-treatment with atropine increased locomotion induced by RMTg morphine. Thus, muscarinic cholinergic receptors in the VTA and the RMTg each contribute to the stimulant effects of opiates but do so in opposite ways. These data provide further support for an important role of VTA muscarinic receptors in the stimulant effects of opiate. Furthermore, these data suggest, for the first time, that the net effect of endogenous cholinergic input to the RMTg on morphine-induced locomotion is inhibitory. Supported by: Provost Fellowship Loyola University Chicago.

THEME B. DEVELOPMENT

B1

OPTIMIS: A HIGH SPEED SPECTRALLY RESOLVED FLOURESCENCE MICRSOCOPE UTILIZING LINE SCAN EXCITATION

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The Optical Micro-Spectrscopy (OptiMiS)[1] module is a microscopy system which delivers spectrally resolved fluorescent images (200 wavelength channels at 1 nm resolution; wavelength range between 420-650 nm) after a single excitation scan. In OptiMiS, fluorescence emission is projected through a transmission grating onto an electron-multiplying CCD (EM-CCD) camera with single-photon sensitivity. After passing through the transmission grating, the fluorescent signal is separated into its spectral components along a line, allowing the rows of the EMCCD to serve as different spectral channels. Acquiring fluorescent images with this level of spectral resolution has proven to be beneficial to *in vivo* studies of macromolecular interactions, e.g., the quaternary structure of membrane protein complexes was determined in living cells[2], and calcium signaling imaging[3]. Ideally, spectrally resolved fluorescence data would be acquired rapidly, at sub second frame rates, enabling the quantification of macromolecular interaction dynamics, e.g. ligand-induced changes to membrane protein oligomer conformations. This demand for high speed acquisitions led Aurora Spectral Technologies to develop OptiMiS TruLine, a multipoint excitation version of OptiMiS. In OptiMiS TruLine, the laser excitation region is spread from a diffraction limited voxel (point scan) to an entire line. The simultaneous excitation of multiple points along this line increases the sensitivity of the device in a manner proportional to the number of points sampled along the line. This increase in sensitivity (more than 100 times greater than typical PMT-based point scan systems) allows faster image acquisition speeds, thereby approaching frame rates where transient cellular mechanisms can be quantified[3]. In its most recent embodiment, OptiMiS allows the system to be configured for single-photon excitation, two-photon excitation, or both. Switching to the desired laser line is performed simply by rotating the filter cube turret to the position housing the appropriate dichroic beamsplitter and emission filter. Combining this flexibility in excitation choices with the ability to capture a full spectrum of available wavelengths at relatively high speeds makes OptiMiS an ideal microscopy instrument for use in real time imaging studies where simultaneous unveiling of multiple intracellular events is essential. This presentation will describe the details of the OptiMiS setup as well as various applications to biological samples of interest.

B2

CHARACTERIZATION OF TRANSCRIPTION FACTORS EXPRESSED DURING CHICKEN RETINAL DEVELOPMENT

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During retinal development, a group of multipotent progenitor cells give rise to six types of neurons and one type of glia. While numerous transcription factors that control this process have been identified and characterized, the details by which these genes regulate the process of cellular differentiation is still unclear. It is likely that many of these transcription factors represent only the first steps of genetic a cascades of differentiation, and that there are additional transcription factors that play a role in activating or repressing the genes necessary to convert a retinal progenitor cell into a functional neuron or glial cell. In previous studies we identified a number of genes that change after retinal conditional knockout of Dicer, an enzyme required for microRNA biogenesis (La Torre et al. 2013). On this list were numerous transcription factors whose expression and function in the retina has not yet been characterized. The aim of this study is to provide initial characterization of the expression of 6 of these transcription factors during chicken retinal development: Pawr, Pou6f2, Elk4, Jazf1, Nfil3, and Ncoa3. Using PCR, we show how expression of these genes changes across retina development and show expression of several splice forms identified using bioinformatics. Augustana College Faculty Research Grant, Augustana Research Foundation.

B3 G

APOPTOSIS IN ADULT RAT DORSAL ROOT GANGLIA FOLLOWING PERIPHERAL NERVE CRUSH LESION

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Clinical treatment of peripheral nerve injuries is considered inadequate with varying success. More information is needed to understand the overall repair process including cell death following a peripheral nerve lesion in order to improve current therapies. The aim of this study is to specifically focus on apoptosis of sensory neuron populations located in rat dorsal root ganglia (DRG) following axonotmesis. In this model the radial, ulnar, median, and musculocutaneous nerves of the brachial plexus are crushed in order to reproduce a mild peripheral nerve injury that is commonly seen in clinical settings. Multiple time frames were selected to sacrifice the animals, ranging from one to ten days post-injury, in order to investigate how the extent of apoptosis varies over time. The hypothesis is that as a consequence of a relatively mild axonotmesis lesion, a small population of neurons undergoes apoptosis and expresses markers involved in the associated cascade. This hypothesis is further supported with the idea that injury proximity correlates to cell death; in this model the crush lesion is performed distal to the effected DRG. Markers such as cleaved Caspase 3, BCL-2, and Annexin V that are involved in apoptotic mechanisms were analyzed using several techniques including Immunohistochemical staining, Western Blotting, and Flow Cytometry. Mass Spectrometry was also used to examine fluctuations of protein expression in the DRG between control sham animals compared to the crush groups. Current data resulting from these procedures has shown that many neurons respond to the crush lesion by upregulating apoptotic mechanisms; however, only a minimal number of these neurons fully undergo apoptosis. This data supports that a mild crush injury in rats does not lead to large scale neuronal cell death suggesting that most cells are able to repair and survive, which is promising from a clinical standpoint. This research is funded by Midwestern University's College of Health Sciences Master of Biomedical Sciences program.

B4 G

NEURONAL PROLIFERATION IN THE DORSAL ROOT GANGLIA FOLLOWING A PERIPHERAL NERVE CRUSH LESION

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Peripheral nerve injuries are fairly common resulting from causes such as trauma or disease and can vary in severity leading to problems with both motor and sensory functions. Treatments of these injuries are associated with varying degrees of success. Therefore, a better understanding of the mechanisms of neuronal regeneration is necessary to establish more efficacious therapies. In this scenario, recent findings of neurogenesis occurring in the peripheral nervous system open a new line of research. Changes in the neuronal population in terms of the number and size as a consequence of peripheral nerve damage has been hypothesized, but not fully addressed. The aim of this study is to investigate cell proliferation and progression through the neuronal lineage within the dorsal root ganglia (DRG) as a response to a peripheral nerve lesion. For this study, the DRGs, which house the neuronal bodies of the sensory afferents, were used. These tissues make a good model for studying changes in the neuronal population due to the fact that they are completely isolated from any postnatal cell migration, therefore any fluctuations should be the consequence of an internal factor. We hypothesize that various physiological changes including neurogenesis occur in the neuronal population associated with the DRG in response to a crush lesion of the radial, ulnar, median, and musculocutaneous nerves innervating the forelimb of a rat. Mass spectrometry, Western blotting, and immunohistochemistry were used to characterize changes in protein expression and localization of the assorted cell populations within the DRG of control, 1, 5, 10, and 30 days post-injury rats. To elucidate these cell populations many proliferation markers such as Ki67 as well as other markers of the neuronal lineage were analyzed. Results from this study suggest that injury to the nerves stimulates proliferation of new neuronal-like cells within the DRG. This study is

supported by the Department of Biomedical Sciences at Midwestern University.

B5 G

SCHWANN CELLS DEFICIENT IN MICRORNAS ARREST AT THE PROMYELINATING STAGE DURING DEVELOPMENT

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Schwann cells (SCs) play important roles in the peripheral nervous system. As demonstrated in many demyelinating neuropathies, proper differentiation of SCs is essential for producing myelin sheaths around axons to increase the speed of axon conduction and allow proper function of the nervous system. Since there are many human diseases and conditions, such as congenital hypomyelination, Charcot-Marie-Tooth disease and nerve trauma, that can be ameliorated through enhancing SC functions, it is imperative to understand the molecular mechanisms underlying SC differentiation. Recently, our group and others have found that microRNAs are crucial in the regulation of SC differentiation during development (Yun et al, J Neurosci, 2010; Perreira et al, J Neurosci, 2010; Bremer et al, PLoS ONE, 2010; Verrier et al, J Neurosci res, 2010). Mice with SCs lacking Dicer1 (Dicer1 cKOs), which is believed to be required for processing most of the miRNAs, resemble the phenotype of Egr2-deficient mice, both of which display a severe neurological impairment mimicking congenital hypomyelination. Interestingly, although the P0::Cre strain we used is active in the SC lineage from midgestational time points (13.5 d postcoitum) and the Dicer1 cKOs' movement is already visibly impaired between P7 and P14, we were surprised to find that only 25 out of 518 microRNAs tested in P7 Dicer1 cKOs sciatic nerves were reduced by greater than 10 fold by Taqman array microRNA cards. One possible explanation is that DICER1 or many microRNAs exhibit very long half-life in SCs. Methods: We obtained mice with SCs lacking Dgcr8 (Dgcr8 cKOs) by crossing P0::Cre strain to Dgcr8f/f strain. We have characterized Dgcr8 cKOs using behavioral tests and standard molecular biology methods, including electron microscopy, Taqman array microRNA cards, qRT-PCR, and immunohistochemistry. Results: Dgcr8 cKOs exhibit impaired myelin development and display severe neurological phenotypes that are similar to Dicer1 cKOs. Funding: This work was supported by NIH Grants 1R01NS071081-01.

B6 G

ZINC-FINGER PROTEIN INSM1 REGULATES NEUROGENESIS IN SPIRAL AND VESTIBULAR GANGLIA AND IS EXPRESSED IN NASCENT OUTER HAIR CELLS

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Discussion of the development and differentiation of inner ear neurons and hair cells has centered on the bhlh transcription factors. These factors, while necessary, cannot alone account for proper differentiation of these cells. Furthermore, no factor has been described that is expressed by outer hair cells (OHCs) and not inner hair cells (IHCs) during early embryonic stages of inner ear development. Insm1 is a zinc-finger protein that is expressed throughout the developing nervous system in late neuronal progenitors and nascent neurons. In the embryonic cortex and olfactory epithelium, Insm1 promotes the transition of progenitors from apical, proliferative, and uncommitted to basal, terminally-dividing and neuron producing. In the ear, not only is Insm1 expressed in neuronally committed progenitors and nascent neurons, but also in nascent OHCs. Insm1 expression pattern was assessed by *in situ* hybridization. Insm1 lineage analysis was conducted with Insm1 GFP-Cre mouse crossed with reporter mice AI9 and NZG (Jackson) which express tdTomato or nuclear localized lacZ behind a floxed STOP cassette. Insm1 function was analyzed by comparing wild type and Insm1 knockout (KO) embryos. Immunohistochemistry was used to identify delaminating progenitors, nascent neurons, cells in mitosis, and cells undergoing apoptosis. In the otocyst, delaminating and delaminated progenitors express Insm1, whereas, apically dividing progenitors do not. Lineage analysis confirms that nearly all of the auditory and vestibular neurons come from cells which have expressed Insm1. In the absence of Insm1, spiral and vestibular ganglia have a 40% reduction in neurons, and accordingly the ganglia are smaller. To account for the decrease in neurons, we observe delaminated progenitors undergoing fewer mitoses, but no change in apoptosis in the progenitors or nascent neurons. Furthermore, we see a novel role of Insm1 in the development of OHCs and not IHCs. Nascent, but not mature, OHCs express Insm1, whereas IHCs never express Insm1 nor are they derived from progenitors that have expressed Insm1. Thus far, we have not determined any abnormalities in the development of OHCs in the absence of Insm1. Insm1 is essential for the development of the inner ear. Insm1 is expressed in all neuronally committed progenitors and nascent neurons and is necessary for neurogenesis and survival of auditory and vestibular neurons. Insm1 is also uniquely expressed in nascent OHCs and not IHCs. As such, Insm1 can be used as a unique marker of OHCs for further inquiry into features of OHC differentiation. Furthermore, as a transcription factor, Insm1 may be an early factor in the unique differentiation of OHCs. R01-NS044363 (to JGA), 5T32-AG020418 and F31-DC012483-01 (to SML).

B7 G

COMPARISON OF BRAIN DEVELOPMENT IN SOW-REARED AND ARTIFICIALLY-REARED PIGLETS

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Provision of nutrients immediately following birth is critical for proper growth and development of the neonate, but the impact of nutritional composition of breast milk on neural maturation has yet to be determined. Using the piglet as a model for the human infant, our objective was to compare maternal sow's milk with artificial formula on postnatal neurodevelopmental patterns. Over a 25-day study, piglets (n=9-10 per treatment, 1.5 ± 0.2 kg initial BW) were either sow-reared (SR; control) with ad libitum intake, or artificially-reared (AR) receiving 285-325 ml/kg BW of milk replacer to mimic the nutritional profile and intake pattern of sow's milk. At study conclusion, piglets were subjected to a standardized set of magnetic resonance imaging (MRI) procedures to quantify structure and composition of the brain. Overall, SR piglets exhibited higher (P<0.05) body weight gain and heavier (P<0.05) extracted whole brain weights compared with AR piglets. Diffusion tensor imaging, an MRI sequence that characterizes brain microstructure, revealed that SR piglets had greater (P<0.05) average whole-brain fractional anisotropy (FA) values compared with AR piglets, suggesting differences in white matter organization. Tract-based spatial statistics revealed SR piglets had distinct areas of higher FA values along specific white matter tracts compared with AR piglets. Voxel-based morphometric analysis, a measure of brain region volumes, revealed differences (P<0.05) in bilateral development of grey matter clusters in the cortical brain regions of the AR piglets compared with SR piglets. Quantification of brain metabolites using magnetic resonance spectroscopy revealed SR piglets had higher (P<0.05) concentrations of myo-inositol, N-acetylasparate + N-acetylaspartylglutamate, glycerophosphocholine + phosphocholine, and creatine + phosphocreatine compared with AR piglets. Overall, increases in these metabolite concentrations, coupled with greater FA values in white matter tracts and volume differences in grey matter of specific brain regions, suggest greater myelin development and cell proliferation in SR piglets. This study is funded by Abbott Nutrition.

B8 UG

ROLE OF miR138 IN SCHWANN CELL PROLIFERATION

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Transcription factors have long been determined to play a role in the differentiation and proliferation of various cell types, but one field which has not yet received as much attention is the possible role of microRNAs in regulating cell development. Schwann cell proliferation and development is particularly important in demyelinating diseases such as Congenital Hypomyelination and Charcot-Marie-Tooth Disease. Determination of the factors which are responsible for controlling Schwann cell development and proliferation could lead to the development of more effective and efficient treatments for such diseases. It is suspected, based on previous research, that miRNA138 may play a role in the exit of Schwann cells from the cell cycle, decreasing Schwann cell proliferation by inhibiting cyclinD1, Sox2 and Jun (Yun et al, 2010). In this study, we tested this hypothesis using conditional knock-out and over-expression mouse models. We examined whether the conditional knock-out (cKO) or overexpression (cOE) of miR138 had a significant effect on the rate of Schwann cell proliferation, specifically in the sciatic nerve, and the parameters of this effect at different stages in the development of the mice. Methods of analysis included EdU labeling, histoimmunochemistry, and fluorescence microscopy. It was found that while there were no significant differences in measured proliferation rates in cKO and cOE mice at various stages in development, cKO mice had significantly greater numbers of Schwann cells at P14 than controls, possibly arising from subtle differences in proliferation which resulted in cumulative differences in the number of cells at P14, supporting the hypothesis that miR138 may play a role in suppressing Schwann cell proliferation. Further experiments are being conducted to examine this effect at P21 and to examine the effect of miR138 cKO on Schwann cell morphology using electron microscopy. This study is funded by a research grant from the National Institutes of Health (1R01NS071081-01).

B9 G

LOCAL PREFRONTAL SHRNA KNOCKDOWN OF PARVALBUMIN EXPRESSION IS SUFFICIENT TO REPRODUCE THE DEFICITS IN PREFRONTAL CORTICAL INHIBITION ELICITED BY EARLY ADOLESCENT TREATMENT WITH MK-801

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A developmental disruption of prefrontal cortical (PFC) inhibitory circuits is thought to contribute to the adolescent onset of cognitive deficits observed in schizophrenia. However, the mechanisms underlying such changes remain unclear. At the cellular level, changes in PFC function are dependent on local dopamine-glutamate interactions and the activity of parvalbumin-positive (PV^+) fast-spiking GABAergic interneurons, which exert feed forward inhibition over pyramidal output cells and enable synchronous firing in the PFC. Given the crucial role of N-methyl D-aspartate

(NMDA) receptors in the regulation of GABAergic transmission in the PFC, we examined how repeated administration of the NMDA antagonist MK-801 during early adolescence (postnatal days -P35-40-) impacts the normal development of local prefrontal GABAergic function. Electrophysiological analyses of PFC network activity *in vivo* indicated that early adolescent MK-801 exposure results in an enduring disinhibition of the prefrontal local field potential response to ventral hippocampal stimulation at 20 Hz and 40 Hz when measured in adulthood (P65-85). We found that acute local administration of the GABA-Aα1 positive allosteric modulator Indiplon into the PFC normalized the abnormal prefrontal disinhibitory state induced by early adolescent MK-801 exposure. *In vitro* whole cell patch-clamp recordings revealed that our *in vivo* observations are accompanied by a decrease in GABAergic transmission onto layer V pyramidal output neurons. In order to determine if a loss of PV^+ GABAergic interneuron function may be responsible for these deficits, we examined the effects of a local prefrontal shRNA-induced knockdown of PV expression in late adolescence (P50). Notably, the immature PFC state produced by early adolescent MK-801 is mimicked by the shRNA knockdown of PV expression resulting in attenuated suppression of the prefrontal local field potential response *in vivo* and reduced prefrontal GABAergic transmission *in vitro*. Together these results indicate a critical role of NMDA receptors in regulating the early adolescent maturation of prefrontal GABAergic circuits and point towards a mechanism of impaired PV^+ GABAergic interneuron function in the adult PFC following early adolescent exposure to MK-801. Supported by NIH Grant MH086507.

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 UG
EVIDENCE FOR THE ROLE OF ENDOCYTOSIS IN PARKINSON'S DISEASE: INSIGHTS FROM A BUDDING YEAST MODEL

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Parkinson's disease (PD) is a hypokinetic neurodegenerative disease that results from the death of dopaminergic neurons in the midbrain. This cell death has been linked to the misfolding and accumulation of α-synuclein, a brain protein. One of the suggested pathways for α-synuclein thought to contribute to its accumulation is impaired recycling and degradation. Therefore, increasing the degradation of α-synuclein is of therapeutic interest. A current hypothesis explains that endocytosis at the lysosome is one of the routes to α-synuclein degradation. Our lab has tested the hypothesis that α-synuclein uses endocytosis as a route to the lysosome for its degradation. We found genetic evidence that most of the proteins that form endocytosis pathway complexes (pre-ESCRT, ESCRT-I, ESCRT-II, ESCRT-III and post-ESCRT) on the endosome lumen alter one or more of these three PD-associated α–synuclein properties: cellular localization (causing loss of plasma membrane localization and increase perivacuolar aggregation), increase accumulation, and cellular toxicity. The deletion of the vascular sorting protein vps28 (an ESCRT-I gene) produced the strongest effect. To extend this work, I investigated if increasing the concentration of α-synuclein in yeast that lack vps28 would further increase α-synuclein accumulation and toxicity. I, specifically, found that increasing the concentration of α-synuclein in yeast that lack vps28 further enhances each of the three pathological characteristics I tested. Together, these studies illustrate the growing relevance of endocytosis in PD pathology

C2 UG
TWO STORIES ABOUT PARKINSON'S DISEASE PROTEIN, α-SYNUCLEIN: TRUNCATIONS AND AMINO ACID DETERMINANTS

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α-Synuclein is a protein implicated in Parkinson's disease (PD), the second most common neurodegenerative disease. Several questions about α-synuclein's role in PD pathology require more clarity, including: Which amino acids within α-synuclein govern its pathology-related properties? Are naturally occurring α-synuclein truncations relevant to PD? My senior thesis explored both questions. To evaluate the importance of specific amino acids within α-synuclein, I mutated five previously implicated amino acids and found each to be important for properties linked to PD. By truncating its c-terminus to differing lengths, I found that the C-terminus influences both α-synuclein membrane association and aggregation.

C3 UG
CREATION OF A-SYNUCLEIN SPLICE VARIANTS TO UNDERSTAND PARKINSON'S DISEASE

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Parkinson's disease (PD) is a hypokinetic neurodegenerative disorder characterized by the death of midbrain dopaminergic neurons. Misfolded proteins and aggregated α-synuclein leads to the accumulation of Lewy Bodies. While the full-length α-synuclein (which is 140 amino acids long) is the major Lewy body component, smaller versions of α-synuclein have recently been discovered, including splice variants (α-syn 126, α-syn 112, and α-syn 98; Beyer et al, 2008, McLean et al., 2011). The individual contributions of each such splice variant towards α-synuclein-based PD pathology is not clear. We hypothesized that these

splice variants likely contribute to PD as they lack the region that keep α-synuclein soluble (α-syn 112), or that which binds membranes (α-syn 126), or both regions (α-syn 98). In this study, we designed and created the three splice variants for yeast expression, attached each with and without a localization tag - green fluorescent protein (GFP). Here, we will describe the steps and data that led to creating the variants and transformation in yeast. This summer, we plan to evaluate their aggregation, localization, and toxicity properties, compared with the full-length α-synuclein.

C4

MONITORING PD-RELEVANT PHENOTYPES IN IPSC-DERIVED NEURAL STEM CELLS FROM A SPECTRUM OF PARKINSON'S DISEASE PATIENTS FOR DRUG SCREENING AND FOR UNDERSTANDING THE BIOLOGY OF PD

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Parkinson's Disease (PD) is a progressive neurodegenerative disorder that affects 1-2% of the population over age 65. Pathologically, PD is marked by a loss of dopaminergic neurons in the substantia nigra pars compacta region of the brain. Because of lack of access to such tissue, or availability of good animal models of PD, iPSC-generated neurons hold promise in the development of model systems to study PD. We have generated iPSCs from patients harboring mutations in the PARKIN and LRRK2 genes, as well as a rare case with mutations in both the LRRK2 and GBA genes, and a patient with Multiple Systems Atrophy (MSA)--a "Parkinson's Plus Syndrome" disease with no known genetic determinants. To eliminate line-to-line variations due to genetic background, we have set out to generate a set of isogenic iPSC lines that differ at a single point in the genome using the Transcription Activator-Like (TAL) effector nuclease technology. For instance, we have deleted the -synuclein gene from the MSA line in order to understand the impact of Lewy bodies, and reverted the LRRK2 and GBA mutations back to wild type in order to better understand any synergies between these mutations. These iPSC lines have been differentiated to neural stem cells (NSCs), and further into dopaminergic neurons and glial cells. Using the NSCs, fluorescence-based, high-throughput compatible assays have been developed to monitor phenotypes that are associated with PD, such as oxidative stress, metabolic activity, apoptosis, mitochondrial function, and autophagy. The long-term goal is to use these optimized assays to provide a platform that allows for the facile interrogation of small molecule compounds in "relieving" phenotypes associated with PD.

C5

RNA EDITING LEVELS OF 5-HT2C AND GLUA2 ARE INCREASED IN SUICIDES WITH MAJOR DEPRESSION

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The incidence of suicide is escalating in the US. The majority of suicides have major depression (MDD), and several studies, including our own, indicate that abnormal RNA editing is associated with suicide. RNA editing produces sequence changes in specific RNAs and we have recently reported increased ADAR1 expression in MDD suicide (Simmons *et al*., 2010), indicating that increased RNA editing in these patients may not be restricted to 5-HT2C receptors. We now present data from analyses of all three ADAR enzymes, 5-HT2C RNA editing and GluA2 RNA editing in a much larger cohort of postmortem subjects (n=114) to test the hypothesis that generalized increases in RNA editing occur in suicides with MDD. RNA was extracted from the gray matter of the DLPFC of 80 postmortem MDD cases and 34 control subjects and expression analyses were conducted by quantitative polymerase chain reaction (QPCR). QPCR data were normalized to the expression of three housekeeping genes and analyzed using the relative standard curve method. Subsequently, levels of RNA editing of the 5-HT2C receptor were measured using tagged next generation sequencing in these subjects. GluA2 RNA editing was assessed using RT-PCR followed by restriction enzyme analysis. Data were analyzed by ANCOVA, covarying for age at death and postmortem pH of the brain. ADAR expression and 5-HT2C RNA editing but not GluA2 RNA editing were associated with the presence of antidepressants in postmortem toxicological screens. In the antidepressant-free MDD suicides, there were increased levels of 5-HT2C RNA editing, resulting in increased levels of RNA editing at the 5-HT2C 'B' site ($F_{2, 73}=3.8$, $p=0.02$) relative to controls. The expression of all three ADAR enzymes was correlated with GluA2 RNA editing ($F_{3, 74}=24.6$, $p<10^{-10}$) and also 5-HT2C RNA editing at the B site ($F_{3,74}=6.2$, $p=0.001$). *Post-hoc* tests showed that GluA2 RNA editing was also increased in the MDD suicide group ($F_{2, 112}=5.1$, $p=0.008$). Multivariate analyses revealed a gender by diagnosis effect of all three ADAR enzymes with MDD ($F_{3, 68}=10.4$, $p<10\text{-}4$). In addition, a gender by diagnosis interaction was detected between the expression of the three ADAR enzymes and MDD. These data indicate that the RNA editing of 5-HT2C and GluA2 are increased in MDD suicide cases. Increases in the editing of these RNA targets would be predicted to lead to reduced 5-HT2C signal transduction (Niswender *et al*., 1999) and also reduced cell surface trafficking and altered conductance of the AMPA

receptor ion channel (Greger *et al*., 2006). In addition to identifying potential biomarkers of suicide, these molecular changes may also facilitate the development of improved antidepressant drugs. Supported by: American Foundation for Suicide Prevention.

C6

THE INFLUENCE OF SECRETASE-DEPENDENT APP-CTF ACCUMULATION ON AXODENDRITIC DEVELOPMENT AND ASSOCIATED SIGNALING

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Mutations in *PSEN1*, which encodes presenilin 1 (PS1), cause familial Alzheimer's disease (FAD). PS1 is an essential component of γ-secretase, the enzyme responsible for intramembraneous cleavage of amyloid precursor protein (APP) to generate β-amyloid peptides and APP intracellular domain (AICD). Our recent findings show that accumulation of APP C-terminal fragments (APP-CTF) following γ-secretase inhibition or targeting AICD at the membrane (mAICD) stimulates axodendritic arborization, enhances cAMP/PKA activation and GSK3β inhibition in primary cortical neurons. Our goal is to examine whether accumulation of APP-CTF through various secretase activities could influence axodendritic outgrowth and associated intracellular signaling in neurons. We expressed mAICD and APP-C99 (β-secretase cleavage product) in primary cortical neurons generated from wild-type (wt) and knock-in (KI) mice harboring FAD-linked *PSEN1* M146V mutation to investigate the contribution of APP-CTF accumulation on axon vs dendrite outgrowth. We examined intracellular signaling events associated with APP-mediated neurite formation using antibodies that recognize phospho-PKA substrate Ser/Thr epitopes (pPKA) and phospho-GSK3β Ser9 epitope (pGSK3β□). mAICD and APP-C99 constructs lacking the G-protein binding motifs within the cytoplasmic tail of APP were used to establish the requirement of G-protein interacting motifs in intracellular signaling. In wt neurons, we observe that APP-CTF accumulation through APP-C99 expression or mAICD expression induces similar increases in axodendritic arborization, accompanied by cAMP/PKA activation and GSK3β inhibition. Mutating the G-protein binding motifs in mAICD or APP-C99 abolished these morphological and signaling events. In KI neurons, axodendritic outgrowth and PKA activity were stimulated in naïve cells, whereas GSK3β activity was increased. We are presently characterizing how FAD-linked mutation in PS1 influences G-protein-mediated intracellular signaling associated with APP-CTFs. Our results suggest that neuronal accumulation of APP-CTFs generated through β- and γ-secretase activities could selectively impact neurite outgrowth and associated signaling pathways. Our findings also highlight the importance of the G-protein interaction motif in APP as a mediator of axodendritic development. Supported by NIH R01NS055223.

C7

PALMITOYLATION OF SUPEROXIDE DISMUTASE 1 (SOD1) IS INCREASED FOR FAMILIAL ALS-LINKED SOD1 MUTANTS

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Mutations in Cu/Zn superoxide dismutase (mtSOD1) cause familial amyotrophic lateral sclerosis (FALS), a neurodegenerative disease resulting from motor neuron degeneration. Here we demonstrate that wild type SOD1 (wtSOD1) undergoes palmitoylation, a reversible post-translational modification that can regulate protein structure, function, and localization. SOD1 palmitoylation was confirmed by multiple techniques including acyl-biotin exchange, click chemistry, cysteine mutagenesis and mass spectrometry. Mass spectrometry and cysteine mutagenesis demonstrated that cysteine residue 6 (C6) was the primary site of palmitoylation. The palmitoylation of FALS-causing mtSOD1s (A4V and G93A) was significantly increased relative to that of wtSOD1 expressed in HEK cells and a motor neuron cell line. The palmitoylation of FALS-causing mtSOD1s (G93A and G85R) was also increased relative to that of wtSOD1 when assayed from transgenic mouse spinal cords. The function of SOD1 palmitoylation is not yet clear. We found that the level of SOD1 palmitoylation correlated with the level of membrane-associated SOD1, suggesting a role for palmitoylation in targeting SOD1 to membranes. We further observed that palmitoylation occurred predominantly on disulfide-reduced as opposed to disulfide-bonded SOD1, suggesting that immature SOD1 is the primarily palmitoylated species. Increases in SOD1 disulfide bonding and maturation with increased CCS expression caused a decrease in wtSOD1 and mtSOD1 palmitoylation. These findings suggest that SOD1 palmitoylation occurs prior to disulfide bonding during SOD1 maturation and that palmitoylation is increased under conditions when there is more immature disulfide-reduced SOD1. Supported by: NIH NRSA award (F32NS077609) to SEA and NIH grants (NS043782, DA019695, MH081251) to WNG.

C8 PD

THE HISTONE DEACETYLASE HDAC3 IS ESSENTIAL FOR PURKINJE CELL FUNCTION, POTENTIALLY COMPLICATING THE USE OF HDAC INHIBITORS IN SCA1

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Spinocerebellar ataxia type 1 (SCA1) is an incurable neurodegenerative disease caused by a pathogenic glutamine repeat expansion in the protein ataxin-1 (ATXN1). One likely mechanism mediating pathogenesis is excessive transcriptional repression induced by the expanded ATXN-1. Because ATXN1 binds HDAC3, a class I histone deacetylase that we have found to be required for ATXN1-induced transcriptional repression, we tested whether genetically depleting HDAC3 improves the phenotype of the SCA1 knock-in mouse ($SCA1^{154Q/2Q}$), the most physiologically relevant model of SCA1. Given that HDAC3 null mice are embryonic-lethal, we used for our analyses a combination of HDAC3 haplo-insufficient and Purkinje cell-specific HDAC3 null mice. Although deleting a single allele of HDAC3 in the context of SCA1 was insufficient to improve cerebellar and cognitive deficits of the disease, a complete loss of Purkinje cell HDAC3 was highly deleterious both behaviorally, with mice showing early onset ataxia, and pathologically, with progressive histological evidence of degeneration. Inhibition of HDAC3 may yet have a role in SCA1 therapy, but our study provides cautionary evidence that this approach could produce untoward effects. Indeed, the neurotoxic consequences of HDAC3 depletion could prove relevant wherever pharmacologic inhibition of HDAC3 is being contemplated, in disorders ranging from cancer to neurodegeneration. This work was funded by U.S. National Institutes of Health grant R01 NS062051 and 1R01NS082351; with additional funding from the National Ataxia Foundation and the Brain Research Foundation (P.O.).

C9 PD

LOSS OF THE PARKINSONS'S DISEASE-ASSOCIATED PROTEIN DJ-1 (PARK7) RESULTS IN PATHOGENIC PHENOTYPES IN HUMAN MIDBRAIN DOPAMINERGIC NEURONS

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Parkinson disease (PD) is the second most common chronic progressive neurodegenerative disorder, and the clinical features of PD likely result from the loss of dopaminergic (DA) neurons in the substantia nigra (SN) pars compacta. Although "idiopathic" PD is more common, 2–3% of PD cases can currently be linked to a single genetic factor, and over the last several years, the discovery of these genes has provided insights into the cellular and molecular pathogenesis of PD. Loss of function mutations in the PD-associated gene *DJ-1* are a rare cause of neurodegeneration in early-onset PD. Reduced levels of physiological DJ-1 have been found in the cerebrospinal fluid and SN of idiopathic PD patients suggesting that DJ-1 may play a role in the pathogenesis of more common forms of PD. DJ-1 has an important role in cellular response to oxidative stress and protects neurons from mitochondrial damage and cell death. While studies in DJ-1 knockout mice suggest that mitochondrial dysfunction contributes to degeneration of midbrain DA neurons in the SN, the underlying cause of selective vulnerability in PD is not well understood. We used human midbrain DA neurons generated from induced pluripotent stem cells (iPSC) to further investigate the mechanisms of DJ-1-mediated neurodegeneration. Western Blot analyses revealed that the homozygous c.192G>C mutation in the *DJ-1* gene leads to an almost complete loss of the protein. This results in increased oxidative stress, accumulation of alpha-synuclein in iPSC-derived neurons and elevation of toxic DA quinones in an age-dependent manner. These results suggest that midbrain DA neurons serve as a useful model for studies of age-dependent changes in vulnerable neuronal populations. This study is funded by a postdoctoral research scholarship from the German Academic Exchange Service (DAAD) as well as NINDS and MJFF.

C10 PD

CHARACTERIZATION OF INNATE AND ADAPTIVE IMMUNE RESPONSES IN THE $HSOD1^{G93A}$-MCP1-CCR2 TRIPLE TRANSGENIC ALS MOUSE

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Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease characterized by progressive degeneration of the motor neuron circuitry. Multiple studies have revealed the involvement of innate and adaptive immune responses in both the spinal cord and motor cortex of ALS patients, and in mouse models of ALS. However, their role in ALS pathology, and specially their association to motor neuron death are not completely elucidated. Secretion of the cytokine MCP1 (monocyte chemoattractant protein-1) has been detected in both cerebrospinal fluid and spinal cord of ALS patients and mouse models of ALS. Additionally, MCP1-mediated recruitment of CCR2 (CC chemokine receptor 2) + monocytes is supported by decreased levels of CCR2 + monocytes in the blood

of ALS patients. The purpose of this study is to understand the cellular components and the molecular basis of innate and adaptive immune response in ALS using a novel hSOD1^{G93A}-MCP1-CCR2 triple transgenic ALS mouse model. In this model, MCP1+ and CCR2+ cells are genetically labeled with mRFP (monomeric red fluorescent protein) and eGFP (enhanced green fluorescent protein), respectively. This allows for visualization and isolation based on their fluorescent character. Our intent is not to characterize the MCP1 and CCR2 system in ALS, but rather to use their expression pattern as a bait to genetically label cells of interest. For this purpose, we evaluate MCP1+ and CCR2+ expression at different stages of disease in different regions of the cerebral cortex and spinal cord where neurodegeneration is observed. Our results reveal high levels of MCP1+ cells that belong to microglia lineage in the motor cortex at pre-symptomatic stage, and Interestingly, CCR2+ cells express markers of infiltrating monocytes. Furthermore, fluorescence-activated cell sorting (FACS) has allowed us to isolate MCP1+ and CCR2+ cells from the complex and heterogeneous structure of the brain and spinal cord for microarray analysis. Evaluating the cellular identity together with their transcription profile has the potential to reveal details of the molecular controls over initiation and progression of immunity in ALS. Identification of cellular mechanisms involved in the immunologic response to vulnerable motor neurons will help reveal novel therapeutic targets for building effective treatment strategies. This work was supported by The Milton Safenowitz Post-Doctoral Fellowship from the ALS (JHJ), Les Turner ALS Foundation (PHO), and Wenske Foundation (PHO).

C11 PD

REORGANIZATION OF NUCLEUS ACCUMBENS PROPERTIES IN TRANSITION TO CHRONIC PAIN IN RAT

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Chronic pain is an enormous problem facing society, and many imaging studies in humans have demonstrated major reorganization primarily in regions of the limbic system. Recent fMRI data in humans has implicated the nucleus accumbens (NAc) as causally involved in the transition to chronic pain; however, underlying mechanisms of this involvement remain entirely unknown. Here we use fMRI, gene expression, and behavior in a rat model of neuropathic pain (spared nerve injury, SNI) to elucidate mechanisms of NAc reorganization, both longitudinally and cross-sectionally. We observed inter-related changes: 1) In resting-state fMRI, functional connectivity of the NAc to dorsal striatum and cortex was reduced 28 days (but not 5 days) after SNI; 2) contralateral to SNI injury, gene expression of NAc dopamine 1A, 2, and κ-opioid receptors decreased 28 days after SNI; 3) In SNI (but not sham) covariance of gene expression was upregulated at 5 days and settled to a new state at 28 days; and 4) NAc functional connectivity correlated with dopamine receptor gene expression and with tactile allodynia. Moreover, interruption of NAc activity (via lidocaine infusion) reversibly alleviated neuropathic pain in SNI animals. Together, these results demonstrate macroscopic (fMRI) and molecular reorganization of NAc and indicate that NAc neuronal activity is necessary for full expression of neuropathic pain-like behavior. Follow up studies have revealed reduction of a major transcription factor in the NAc at the 5 day post SNI timepoint, and experiments aimed at restoring this factor in the NAc of SNI rats are underway.

C12 PD

EARLY DEFICITS IN SYNAPTIC, CELLULAR, AND NETWORK-LEVEL HIPPOCAMPAL CA1 FUNCTION IN PRESYMPTOMATIC ALZHEIMER'S MICE

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An important goal in Alzheimer's research is to identify early, presymptomatic changes in neuronal and network properties that could provide novel treatment strategies for preventing the emergence and progression of cognitive decline. Here we utilized 2-photon calcium imaging in single CA1 hippocampal neurons together with large-scale voltage sensitive dye imaging to examine hippocampal network function and plasticity in 3xTg-AD mice, which develop neurofibrillary tangles, amyloid plaques and cognitive disorders beginning at several months of age. In these and other AD mouse models, we recently described markedly increased ryanodine receptor (RyR) mediated calcium release within dendritic spines of CA1 pyramidal neurons at presymptomatic disease stages. Yet, synaptic transmission and long term plasticity appear normal, despite an underlying tendency towards synaptic depression only upon RyR manipulation. This surprising maintenance of synaptic function in the face of profound dysregulated synaptic calcium handling suggests the presence of compensatory homeostatic mechanisms operating early in disease development that preserves normal function for a period of time. The present study again used acute hippocampal brain slice preparations from presymptomatic (2-3 month) animals. Using 2-photon imaging and patch clamp electrophysiology, we found that calcium responses in dendritic spines of CA1 pyramidal neurons evoked by an LTP-inducing stimulus were 3-fold greater in 3xTg-AD mice compared to NonTg animals, yet LTP expression appears normal under these conditions. In contrast, post-tetanic potentiation, a shorter-term form of calcium-dependent synaptic plasticity, was severely disrupted in the 3xTg-

AD mice. To measure responses to the same stimuli throughout the entire CA1 subfield, a 128x128 pixel CMOS camera was used with the fast voltage sensitive absorbance dye RH155 to image CA1 responses to Schaffer collateral stimulation in brain slices from the same cohort of 3xTg-AD and NonTg mice. Here, synaptic stimulation elicited a reduced voltage response in the CA1 hippocampal region of the 3xTg-AD mice compared to NonTg mice. These findings of aberrant synaptic calcium responses, reduced short term plasticity, and blunted CA1 responsiveness in early AD animals reveal an integrated set of dysfunctions ranging from the molecular to the network level in early stages Alzheimer's disease pathology. Furthermore, our results are consistent with the existence of additional, compensatory homeostatic mechanisms that operate to preserve normal network function prior to the onset of detectable cognitive impairment. Supported by: Rosalind Franklin University of Medicine & Science Pilot Award.

C13 PD

PROGRESSIVE DEGENERATION OF THE RETINAL AND SUPERIOR COLLICULUS NEURONS IN MICE WITH SUSTAINED OCULAR HYPERTENSION

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Glaucoma, often associated with elevation of intraocular pressure (IOP), is characterized by retinal ganglion cell (RGC) degeneration and death. Using a combination of laser photocoagulation of the trabecular meshwork and injection of polystyrene microbeads into the anterior chamber of mouse eyes, we were able to induce significant and sustained IOP elevation for several months. We then characterized the functional degeneration of the retina and the superior colliculus (SC), where most RGCs project to. Using full-field electroretinogram (ERG), we showed that the dysfunction of the inner retina was first detected at 4-5 weeks, and then progressed into the outer retina. Furthermore, with Multi-Electrode Array (MEA) recordings to examine the light response properties of RGCs, we demonstrated that the RGC degeneration was subtype-dependent. The subpopulations of ON and OFF RGCs, which responded to light onset and offset, respectively, had smaller receptive fields in glaucomatous eyes compared to age-matched control eyes. In contrast, ON-OFF cells, which responded to both light onset and offset, exhibited no significantly changes. In addition, focal ERG showed that different locations of the retina exhibited different susceptibility to the insult of ocular hypertension. We next assessed physiological consequences of RGC degeneration in the higher visual center, specifically, the Superior Colliculus. We characterized the functional deficits of SC neurons by *in vivo* extracellular single-unit recording. The SC neurons exhibited irregular RF structure with disrupted pattern of ON-OFF subfield overlap. Together, our findings provide the foundation to further characterize the mechanisms underlying the progressive degeneration of the retina and the higher visual centers in glaucoma. This work was supported by National Institutes of Health (NIH) grants R01EY019034 (X.L.), EY018621 (J.C.) and EY020950 (J.C.), and R21EB004200 (J.B.T.), William & Mary Greve Special Scholar Award from the Research to Prevent Blindness (X.L.), Northwestern Memorial Foundation/Brinson Foundation (X.L.), and Dr. Douglas H. Johnson Award for Glaucoma Research from BrightFocus Foundation (X.L.) and the Illinois Society for the Prevention of Blindness (H.C.).

C14 PD

CDC42 AND RALA GTPASES FACILITATE TNF-A MEDIATED RELEASE OF MCP-1 FROM PERIPHERAL NERVE MICROVASCULAR ENDOTHELIAL CELLS

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Inflammatory peripheral neuropathies constitute one of the largest and least understood spectrums of neurologic disorders. Inclusive among these disorders is acute inflammatory demyelinating polyradiculopathy (AIDP), a debilitating inflammatory autoimmune disease. While the mechanisms that govern disease onset and progression are not completely understood, cytokine-mediated trafficking of autoreactive leukocytes across the blood-nerve barrier and into peripheral nerves is an early pathological hallmark. Our group previously reported that migration of autoreactive leukocytes during experimental autoimmune neuritis, a well-characterized animal model of AIDP, is dependent on active GTPase signaling. In this study, we determined the mechanism by which GTPases facilitate transendothelial leukocyte migration across the blood-nerve barrier using a novel rat peripheral nerve microvascular endoneurial endothelial cell line (PNMECs). TNFα (10 ng/ml, 0-4h) elicited marked increases in MCP-1 mRNA and intracellular protein content in PNMEC cultures while enhancing release of MCP-1 into the culture media. Pretreating PNMEC cultures (16h) with a selective inhibitor of geranylgeranyltransferase-I (GGTI-298; 10 μM), but not farnesyltransferase (FTI-277; 10 μM), attenuated TNF-α mediated MCP-1 release without altering levels of MCP-1 mRNA or intracellular protein content. PNMEC cultures treated with GGTI-298 (10 uM, 16h) exhibited marked changes in the intracellular distribution of MCP-1 protein. Pretreating PNMEC cultures with C3 exoenzyme or NSC23766, selective inhibitors of Rho or Rac1 GTPases, respectively, did not prevent TNF-α mediated release of MCP-1. Pretreatment with ML141, an inhibitor of Cdc42 GTPase, however, significantly

attenuated TNF-α mediated MCP-1 release. Knockdown of individual GTPases with siRNA confirmed the involvement of Cdc42 GTPase and also revealed a role for RalA GTPase in TNF-α mediated MCP-1 release. Together, these findings suggest that TNF-α mediated trafficking and release of MCP-1 from the blood-nerve barrier during inflammatory autoimmune disease occurs, in part, by a Cdc42 and RalA dependent mechanism. Individual GTPases may represent novel therapeutic targets for the management of inflammatory peripheral neuropathies, including AIDP. This work was supported by grants from the Department of Veterans Affairs and NIH.

C15

INCREASED MTDNA MUTATIONS WITH AGING PROMOTES AMYLOID ACCUMULATION AND BRAIN ATROPHY IN THE APP/LD TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

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The role of mitochondrial dysfunction has long been implicated in age-related brain pathology, including Alzheimer's disease (AD). However, the mechanism by which mitochondrial dysfunction causes neurodegeneration in AD is unclear. To model mitochondrial dysfunction *in vivo*, we utilized mice that contain knock-in mutation, inactivating the proofreading function of mitochondrial DNA polymerase γ (*PolgA* D257A), so that these mice accumulate mitochondrial DNA mutations with age. *PolgA* D257A mice rapidly develop a myriad of mitochondrial bioenergetic defects and physical phenotypes that mimic premature ageing, with subsequent death around one year of age. We crossed the D257A mice with a well-established transgenic AD mouse model (APP/Ld) that develops amyloid plaques. We hypothesized that mitochondrial dysfunction would affect Aβ synthesis and/or clearance, thus contributing to amyloidogenesis and triggering neurodegeneration. Initially, we discovered that Aβ42 levels along with Aβ42 plaque numbers were increased in D257A; APP/Ld bigenic mice compared to APP/Ld alone given that these mice expressed similar levels of APP transgene. An Aβ production increase appeared an unlikely explanation for the higher Aβ42:APP/Ld ratio, because the levels and activity of Aβ generating enzymes such as b-and g-secretase were unchanged in these mice. However, the levels of a major Aβ removal enzyme, insulin degrading enzyme, were lower with the D257A mutation than without, indicating a potential mechanism for increased amyloid load via reduced Aβ clearance from the brain. In the presence of the APP transgene, D257A mice also suffered from significant brain atrophy with apparent cortical thinning attributable to neuron loss. These bigenic mice had increased levels of activated caspase-3 and nuclei characteristically similar to apoptotic cells when compared to mice with either D257A mutation or APP transgene alone. Overall, our results suggest that there might be synergism between the effects of the *PolgA* D257A mutation and Aβ in causing neurodegeneration. These findings shed insight on how mitochondrial dysfunction may contribute to the pathogenesis of AD via decreased clearance of Aβ. Mechanisms of Aging and Dementia Training Grant T32 AG20506 and by NIH grant R01AG030142.

C16

ENVIRONMENTAL ENRICHMENT ENHANCES AKT/GSK3B, NEUROTROPHIN-3 AND CREB SIGNALING PATHWAYS IN WILD-TYPE MICE, BUT NOT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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The enriched environment is a well-established experimental paradigm known to enhance learning and memory in wild-type (WT) mice. In the APPswe/PS1de9 (FAD) mouse model of Alzheimer's disease (a disease characterized by memory deficits), the enriched environment has been shown to rescue impairments in hippocampal neurogenesis and synaptic plasticity. However, the molecular signals responsible for these effects have not been fully elucidated. Here, we show that in the hippocampus of both WT and FAD mice, the enriched environment enhances brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase B, as well as nerve growth factor (NGF). The enriched environment also increases Akt signaling which results in a decrease of glycogen synthase kinase 3B (GSK3B) in wild-type mice, but not in FAD mice. In addition, we found that mRNA for cAMP response element-binding protein (CREB) is increased following the enriched environment in both WT and FAD mice. However, the phosphorylated form of CREB (pCREB), an important component of gene transcription related to learning and memory, was increased in WT mice only. In summary, we show that in WT mice, signaling related to learning and memory is enhanced following enrichment, but in FAD mice some of these pathways are not rescued by environmental enrichment. Therapeutic interventions aimed at improving learning and memory in Alzheimer's disease may therefore require pharmaceutical targeting of these pathways in addition to life-style modification.

C17

REDUCED LEVELS OF PRESENILIN-1 IN NEURAL PROGENITOR CELLS IN THE ADULT HIPPOCAMPUS INDUCES LEARNING AND MEMORY DEFICITS

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Presenilin-1 (PS1) is the catalytic core of the aspartyl protease γ-secretase, which cleaves numerous membrane proteins, including amyloid precursor protein, notch-1 and other proteins involved in neurogenesis. Mutations in *PS1* cause familial Alzheimer's disease (FAD), a progressive neurodegenerative disease characterized by loss of memory and cognitive decline. We previously showed that PS1 regulates neural progenitor cell differentiation in the adult brain. New neurons are thought to play a role in aspects of learning and memory. However, it is not clear if PS1 plays a role in neurogenesis-dependent learning and memory. To determine that, we injected lentivirus expressing small interfering RNA (siRNA) to knockdown PS1 expression in neural progenitor cells in the dentate gyrus of adult mice and evaluated their learning and memory performance 3 months and 6 months following the injection. Here we show that down-regulation of PS1 in hippocampal neural progenitor cells causes progressive deficits in hippocampus-dependent learning and memory function. These results support a role for neurogenesis in learning and memory and provide a mechanism by which dysfunction of PS1 in Alzheimer's disease compromises learning and memory.

C18 G

CAV1.3 CHANNEL INHIBITORS FOR NEUROPROTECTION IN PARKINSON'S DISEASE

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Parkinson's disease (PD) is the second most common neurodegenerative disease, in which the primary motor deficits are the result of selective degeneration of mesencephalic dopaminergic neurons (DA) in the substantia nigra pars compacta (SNc). We have shown that SNc DA neuronal physiology engages a low-threshold, high-conductance, *long-lasting* voltage-dependent calcium channel with a $Ca_V1.3$ pore-forming subunit. $Ca_V1.3$ L-type calcium channels (LTCCs) are engaged throughout the pacemaking cycle of adult SNc DA neurons, allowing extraordinary amounts of calcium into SNc DA neurons -- manifested as phasic dendritic calcium oscillations. As a consequence of increased intracellular free calcium, mitochondrial oxidative phosphorylation in SNc DA neurons increases to enable ATP-dependent calcium buffering mechanisms. These active buffering mechanisms are metabolically expensive -- leading to increased reactive oxygen species production. Inhibiting $Ca_V1.3$ LTCCs non-selectively via 1,4-dihyropyridines (DHPs) attenuates these dendritic calcium oscillations, relieves mitochondrial oxidant stress, and is neuroprotective in PD animal models. DHPs are a class of FDA approved anti-arrhythmic and anti-hypertension small organic molecules, which have nanomolar affinities to *all* neuronal LTCCs. Thus, chronic treatment of DHPs for PD preventive purposes might have unintended physiological consequences. Using whole-cell voltage-clamp electrophysiology, we present the first $Ca_V1.3$ LTCC isoform selective small molecule 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-trione (PYT), which selectively inhibits $Ca_V1.3$ LTCCs in a voltage-dependent and reversible manner. In addition, using two-photon laser scanning microscopy (2PLSM), we show PYT attenuates dendritic calcium oscillations and reduces mitochondrial oxidant stress. In conclusion, PYT represents a novel pharmacological tool in calcium channel physiology and potential therapeutic measure in slowing the progression of SNc DA neuronal degeneration in PD. Supported by NIH/NINDS.

C19 G

DIRECT CONVERSION OF ADULT SPINAL CORD-DERIVED OLIGODENDROCYTE PROGENITOR CELLS TO A NEURONAL FATE

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The lack of cell replacement following neurological injury, limits the regenerative response of the CNS. Progress in understanding the biology of neural stem cells has raised interest in using stem cells for replacing neurons lost to injury or to disease. As existing committed and uncommitted cells in the CNS do not naturally progress to a neuronal fate, it will be necessary to engineer a conversion to a neuronal fate. Advances in cellular reprogramming provide new tools for re-specification of cell fate and provide a potential alternative to cell transplantation, namely the direct in vivo conversion of resident CNS cell populations for neuronal replacement. Success in this approach will require the generation of relevant neuronal subtypes. The aim of this study was to evaluate the effect of various neurogenic transcription factors, including sox2, mash1, olig2, pax6, and neurogenin2, that are related to cell specification during development on fate induction and subtype specificity on resident glia in the spinal cord. We have used cultures of adult- spinal cord derived oligodendrocyte progenitor cells (OPCs) to evaluate the potential for their engineered conversion to neurons. OPCs are the most abundant cycling population in the adult CNS and their isolation provides an ideal in vitro assay for screening neuronal determinants. Our results show that retroviral delivery of neurogenin2 or the combination of sox2 and mash1 to

adult spinal cord OPCs in vitro can directly convert these cells into neurons through transcription factor mediated reprogramming and provide an alternative therapeutic strategy for neuronal replacement in the adult spinal cord. This work is supported by NIH AG20047.

C20

DECREASED VIRAL VECTOR TRANSDUCIBILITY IN THE AGED RAT MIDBRAIN

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Viral vector-mediated gene delivery to the brain is an experimental therapeutic intervention aimed at replenishing diminished proteins or overexpressing neuroprotective factors that may alleviate symptoms or alter disease progression. Currently, clinical trials are examining the efficacy of viral vector-mediated gene delivery for treating age-related neurodegenerative diseases such as Parkinson's disease (PD). While viral vector strategies have been successful in preclinical studies employing animal models, to date, human clinical trials have disappointed. This may be partially due to the fact that preclinical studies fail to account for aging as an important covariate. In fact, aging is the single greatest risk factor for developing PD. Cellular processes that are needed by viral vectors for gene transduction are also altered with age. Therefore, we hypothesized that the aged rat brain would be relatively resistant to viral vector transduction when compared to the young adult rat brain. We examined recombinant adeno-associated virus serotype 2/5 mediated green fluorescent protein (rAAV2/5 GFP) expression in young adult (3 month) and aged (20 month) Sprague-Dawley and Fischer 344 rat nigrostriatal system. Overexpression of GFP occurred in both young adult and aged rats. However, aged rats displayed significantly less (~50%) striatal GFP protein expression. These decreases occurred regardless of rat strain or duration of gene expression. In addition, aged rats exhibited fewer (~60%) total numbers of cells transduced throughout the midbrain. Furthermore, GFP mRNA levels were decreased in the aged rat as compared to the young adult rat, indicating the presence of deficiencies in steps of viral transduction prior to protein synthesis. Collectively, our results demonstrate that the efficacy of viral vector mediated gene therapy is diminished in the aged rat brain and that transduction deficiencies leading to signficantly less mRNA encoded by the transgene are primarily responsible for the diminished protein expression observed in the aged rat mesencephalon. These findings are important in light of ongoing clinical trials using gene therapy to treat neurodegeneration in an aged population. Future studies will explore the generalizability of this age-related transduction deficiency to other species and viral vector constructs to determine whether these deficiencies are at play in the human brain and if they can be circumvented. This research was supported by the Michael J. Fox Foundation (CES), the Graduate School of Michigan State University (NKP), Mercy Health Saint Mary's (FPM) and the Morris K. Udall Center of Excellence Fox Foundation, MSU Graduate School, Mercy Health Saint Mary's and the MSU Udall Center.

C21 G

ATTENUATION OF ALPHA-SYNUCLEIN INDUCED NEUROINFLAMMATION AND MICROGLIOSIS VIA RHO-KINASE INHIBITION: A POSSIBLE MECHANISM BEHIND FASUDIL-MEDIATED NEUROPROTECTION

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No treatments exist to halt or slow the progression of nigrostriatal degeneration in Parkinson's disease (PD), and many existing treatments exacerbate dyskinesias after prolonged use. The approach of repurposing drugs with known safety profiles in humans can accelerate new developments for PD treatment. Previous studies in our lab have shown that fasudil, a rho-kinase (ROCK) inhibitor, provides neuroprotection from recombinant adeno-associated virus (rAAV) α-synuclein-mediated toxicity. However, the mechanisms behind fasudil-mediated neuroprotection remain unknown. Recent studies have shown α-synuclein to be a direct mediator of neuroinflammation via upregulation of phagocytic microglia. ROCK regulates microglial polarization and motility. In the present study we examined whether fasudil treatment to rats attenuated neuroinflammation associated with intranigral injection of rAAV α-synuclein. We hypothesized that neuroprotective fasudil treatment would be associated with attenuation of microglial polarization and motility via ROCK inhibition. Nigral tissue sections from rAAV α-syn injected animals treated orally with 1) neuroprotective high dose fasudil chow (25 mg/kg/day), 2) low dose fasudil chow (10 mg/kg/day, non-neuroprotective) or 3) control chow were utilized. Sections were double-labeled for tyrosine hydroxylase (TH, dopamine neurons) and Iba-1 (microglia) immunofluorescence and analyzed using near infrared imaging to quantify Iba-1 signal intensity. Stereological quantification of phagocytic marker CD68 was also performed. While there was a dramatic increase in CD68 immunoreactive cells ipsilateral to rAAV α-syn injection, there were no differences in CD68 immunoreactive cells between treatment groups. rAAV α-syn was associated with a marked increase Iba-1 immunoreactivity. High dose fasudil resulted in a significant decrease in Iba-1 immunoreactivity in the rAAV α-syn substantia nigra (SN), intact SN, and tectum (used as a control) suggesting that fasudil

attenuates α-syn-mediated microgliosis. These findings, along with previous findings from our lab, demonstrate that fasudil may protect SN dopamine neurons against α-syn-mediated inflammation via inhibition of ROCK, ultimately attenuating microgliosis. Given that orally administered fasudil has an established safety profile in humans and is, to our knowledge, the first orally available drug to provide neuroprotection in the rAAV α-syn model of PD, it demonstrates potential for development as an effective therapeutic agent to slow progressive nigrostriatal degeneration in Parkinson's disease. Supported by the Michael J. Fox Foundation for Parkinson's Research (JPM/CES), the Michigan State University Neuroscience Program T32 NS44928 (CLS), and the Morris K. Udall Center of Excellence for Parkinson's Disease Research at Michigan State University (TJC).

C22

ROLE OF trkB SIGNALING IN NEUROPROTECTIVE AND BEHAVIORAL EFFECTS OF LONG-TERM, HIGH-FREQUENCY SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

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High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is the most common neurosurgical treatment for the alleviation of Parkinson's disease (PD) motor symptoms. Beyond symptomatic efficacy, our laboratory and others have demonstrated that high-frequency DBS of the subthalamic nucleus (STN) provides neuroprotection for dopaminergic neurons of the substantia nigra pars compacta (SNc) and increases brain-derived neurotrophic factor (BDNF) in the SNc in the 6-hydroxydopamine (6-OHDA) rat model of PD and in the striatum of unlesioned rats (Spieles-Engemann et al., Neurobiol Dis, 2010; Spieles-Engemann et al., J Parkinsons Dis, 2011). However, whether BDNF participates in either the neuroprotection or behavioral effects or if BDNF is an epiphenomenon remains unknown. In the present study we investigated the impact of ANA-12, an antagonist for the trkB BDNF receptor in the brain (Cazorla et al., J Clin Invest, 2011), using our STN DBS paradigm. We conducted long-term, STN DBS in male, Sprague Dawley rats that received unilateral, intrastriatal 6-OHDA. Stimulation was initiated ten days following 6-OHDA (~25% loss of SNc DA neurons) with rats randomly assigned to receive ACTIVE or INACTIVE continuous stimulation for eighteen days. Within each cadre, rats were randomized to receive ANA-12 (0.5 mg/kg) or vehicle twice per day for the remainder of the study. Forelimb use asymmetry measured via the cylinder task was used to evaluate functional efficacy of STN DBS. Electrode placement in the STN was verified post mortem. Tyrosine hydroxylase immunoreactive (THir) neurons of the SNc were quantified using unbiased stereology. Preliminary data suggest that ANA-12 treatment: (1) abolishes the neuroprotective effect of ACTIVE STN DBS and (2) attenuates the functional effects of ACTIVE STN DBS. These results highlight the importance of BDNF-trkB signaling in the functional and morphological effects of STN DBS. Supported by Spectrum Health (DLF), the Edwin A. Brophy Fund (TJC) and the Morris K. Udall Center of Excellence for Parkinson's Disease Research at Michigan State University (TJC).

C23 G

FLAVONOIDS AS POTENTIAL THERAPEUTICS FOR NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the leading cause of age-related memory loss and the ϵ4 allele of the apolipoprotein E (*APOE*) gene is its greatest genetic risk factor, compared to the more common ϵ3 allele. Pathologically, AD is characterized by neurofibrillary tangles (aggregated tau) and amyloid plaques composed of the amyloid-□ peptide (A□). Importantly, AD and other neurodegenertative diseases exhibit early signs of chronic neuroinflammation, likely the result of activated glial cells. Soluble oligomeric aggregates of A□ (oA□) are thought to be the neurotoxic form of the peptide, but *in vitro* data also demonstrates that oA□ induces an inflammatory response similar to that seen with lipopolysaccharide (LPS), a bacterial endotoxin routinely used to induce inflammation in a variety of experimental models. This pro-inflammatory phenotype is consistently greater with *APOE4* compared to *APOE3*. Nutraceuticals targeting this early neuroinflammatory response are one option as an inexpensive and effective treatment. Indeed, recent studies indicate that flavonoids, a class of plant-derived compounds, act as potent anti-inflammatory agents. Thus, the goal of this study was to identify plant extracts that would attenuate or prevent neuroinflammation. To increase flavonoid content, mutants of Arabidopsis seedlings were UV-irradiated for flavonoid production, and three best candidates were quantified by LC-MS. Mutant genotypes *prn1, xpf3, cop1* and a wild type (WT) control were selected. Metabolism of these potential botanical supplements was mimicked using mouse liver microsomes to ensure hydroxylation and oxidative demethylation of the flavonoid compounds by cytochrome P450s. Primary glial cultures (~95% astrocytes 5% microglia) from transgenic (Tg) mice expressing human *APOE3* or *APOE4* were treated with the metabolized plant extracts, and inflammation was induced with LPS or oA□. The anti-inflammatory effect

of the mutants and WT plant extracts were assessed by measuring the levels of the pro-inflammatory cytokine TNF□□by ELISA in the cell culture media. Extracts from all three plant mutants significantly reduced TNF□ levels by 40-50% in the glial cultures expressing *APOE3*, whereas extracts from only *xpf3* mutant decreased TNF□ in *APOE4* cultures, suggesting a differential effect of the plant extracts based on the *APOE* genotype. Future *in vivo* testing in AD-Tg mouse models expressing human *APOE* will address their use as novel therapeutics in both treatment and prevention paradigms, particularly for the at-risk *APOE4* populations, who often fail to respond or respond negatively in clinical trials. This study is funded by the OVCR Ignite award (200250/387005).

C24 G

CAMKII A MECHANISM FOR PAIN IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. Pain is a common and severe symptom in MS. The mechanism for MS pain has not been well studied. In this study, we tested the hypothesis that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKIIα) plays a critical role in the development and maintenance of pain and neuropathy in MS. We established an experimental autoimmune encephalomyelitis (EAE), a widely used animal model to study pathological mechanism of MS, in mice for the study. We found that spinal CaMKIIα activity were increased, correlating with the development of mechanical allodynia and thermal hyperalgesia, in EAE mice. Prophylactic administration of KN93, an inhibitor of CaMKII, significantly reduced the clinical scores of EAE and attenuated mechanical allodynia and thermal hyperalgesia in EAE mice. Moreover, KN93 was effective in reversing established mechanical and thermal hypersensitivity in EAE mice. Furthermore, CaMKIIαT286A point-mutation mice showed significantly reduced signs of disease and pain severity when compared with littermate wildtype mice. Taken together, these data implicate a critical role of CaMKIIα as a cellular mechanism in pain and neuropathy in multiple sclerosis.

C25 G

THE GLO1/METHYLGLYOXAL PATHWAY AS A THERAPEUTIC TARGET FOR THE TREATMENT OF ANXIETY AND DEPRESSION

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Higher Glyoxalase 1 (*Glo1*) expression is associated with greater anxiety-like behavior in mice. GLO1 is a ubiquitous cellular enzyme responsible for the detoxification of methylglyoxal (MG), which is a byproduct of glycolysis. Previous studies in the lab showed that overexpression of *Glo1* results in reduced concentrations of MG and increased anxiety-like behavior in the open field test (OFT), whereas IP injections of MG reduced anxiety-like behavior in the OFT. We have recently shown that MG is a competitive partial agonist at GABA-A receptors, which likely explains GLO1's effects on anxiety-like behavior. Given the high comorbidity of anxiety and depression, the studies performed here investigated the therapeutic potential for MG/*Glo1* modulation on anxiety and depression-like behavior.

These studies first aimed to determine whether the effects of *Glo1*/MG on anxiety-like behavior are peripherally or centrally mediated, and if central, to elucidate the neuroanatomical systems responsible for regulating the anxiolytic effects of MG. As *Glo1* and MG are expressed throughout the brain and MG activates GABA-A receptors that are highly expressed within amygdala-prefrontal cortex circuitry, our hypothesis was that the *Glo1*/MG pathway exerts control over anxiety-like behavior through this circuitry. Anxiety-like behavior was assessed in the OFT in either mice with region-specific overexpression of *Glo1* (achieved through genetic manipulations; FLOX-CRE) or in mice receiving bilateral injections of MG directly into the basal-lateral amygdala (BLA). Overexpression of *Glo1* in neurons was sufficient to increase anxiety-like behavior, while direct injection of MG into the BLA reduced anxiety-like behavior in the OFT. Secondly, we investigated the effects of both pharmacological and genetic inhibition of GLO1 on depression-like behavior in mice. We found that both acute and chronic pharmacological inhibition of GLO1 reduced depression-like behavior across multiple behavioral assays and in multiple mouse strains. The studies presented here provide evidence for the therapeutic potential of *Glo1*/MG modulation for the treatment of anxiety and depression. They also suggest that the effects of *Glo1*/MG on anxiety-like behavior are centrally mediated and work through typical circuitry. This knowledge will aid in the development of novel therapeutics targeting this pathway. Research was supported by NIDA grant T32DA007255 and NIMH grant R01MH079103.

C26 G

***S*-PALMITOYLATION MEDIATES DENDRITIC SPINE LOCALIZATION OF THE ALZHEIMER'S DISEASE BETA-SECRETASE, BACE1**

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Alzheimer's disease (AD) is a devastating neurodegenerative disease, and the number of cases of AD is expected to increase in the next 30 years; however, there is currently no effective therapy or cure. The pathological hallmark of AD is the presence in the

brain of extracellular plaques composed of the amyloid-beta (Aβ) peptide. Accumulating evidence strongly suggests that increased cerebral Aβ burden is directly responsible for synaptic dysfunction, neuron death, and ultimately cognitive decline in AD. Beta-site APP Cleaving Enzyme 1 (BACE1) is the transmembrane aspartyl protease that initiates proteolytic processing of Amyloid Precursor Protein (APP) to produce Aβ. This processing is thought to occur during transit of APP and BACE1 in endosomal compartments, and during axonal transport of APP. One strategy for preventing Aβ over-production is to influence BACE1 trafficking away from compartments in which APP resides. Therefore an understanding of the mediators of BACE1 intracellular transport, specifically in the neuron, will be instructive for developing novel AD therapeutics. In this study, we examined how *S*-palmitoylation of BACE1 regulates its localization and trafficking in neurons. *S*-Palmitoylation is a dynamic, reversible post-translational modification that mediates neuronal protein targeting to neuron-specific compartments. We expressed YFP-tagged BACE1 in primary hippocampal neurons and employed confocal fluorescence microscopy to analyze BACE1 targeting. We found that BACE1 WT localizes to dendritic spines in cultured hippocampal neurons, where it co-localizes with markers of early and recycling endosomes. Interestingly, a palmitoylation-deficient mutant was mostly absent from spines, despite normal transport to dendrites, suggesting that spine localization largely depends on BACE1 S-palmitoylation. Further characterization of dynamic BACE1 localization in dendrites and axons will provide a better understanding of the neuronal mechanisms that regulate in Aβ production, and will contribute to therapeutic strategies for the treatment of AD. This study is funded by grants from the National Institutes of Health and Cure Alzheimer's Fund. CGF was supported by The University of Chicago Lebo Endowment.

C27 G

SEX DIFFERENCES IN AGED RATS ON SENSORIMOTOR TASKS AND POST-STROKE RECOVERY

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Sex-based differences in learning and recovery from stroke are an area of research not yet fully explored, especially with regard to aged rats performing sensorimotor tasks. In the human population, females have been shown to recover from stroke less successfully than males, and therefore studying sex differences in rat models of stroke is clinically relevant. 18 month-old Fischer 344 male and female aged rats were used for these studies. Rats were divided into four groups: ovarectomized (OVX) females, intact females, sham OVX males, and intact males. Pre-stroke, animals were trained in the skilled forelimb reaching task and skilled ladder walk test. The rats then underwent focal ischemic stroke via middle cerebral artery occlusion (MCAO) to affect the sensorimotor cortex associated with the preferred forelimb. Rats were then tested on the behavioral tests for eight weeks to assess post-stroke recovery. At the end of the eight weeks, rats were sacrificed for Golgi-Cox staining and dendritic characterization. Our results show that pre-stroke, in the skilled forelimb reaching task, intact females began reaching sooner ($\bar{x}$=2±1 days vs. male $\bar{x}$=7±1 days, $p < 0.05$), had their first successful reach sooner ($\bar{x}$=3±1 days vs. male $\bar{x}$=8±1 days, $p < 0.05$), and reached baseline success scores sooner than their aged male counterparts ($\bar{x}$=14±2 days vs. male $\bar{x}$=18±1 days, $p < 0.05$). OVX females had slower times in all categories. In the skilled ladder walk task, intact females reached baseline faster than males ($\bar{x}$=4±1 days vs. male $\bar{x}$=8±2 days, $p < 0.05$) and faster than OVX females. Following stroke, all males recovered faster than all females, with the OVX females recovering worse, in both the skilled forelimb reaching and skilled ladder walk tests. Following stroke, histological lesion analysis revealed that there was no significant difference in lesion size, therefore lesion size did not account for the post-stroke difference in recovery. In conclusion, our results show that aged intact female rats learn sensorimotor tasks faster than aged males and aged OVX females pre-stroke. Post-stroke recovery was worse in females, with OVX females performing worse than all other groups in the skilled reaching task. Neuronal dendritic branching with Golgi analysis is currently underway. This study was funded by the Loyola Neuroscience Research Institute and the Department of Veterans Affairs.

C28 G

BEHAVIORAL RESPONSES TO ETHANOL ARE REGULATED BY THE LIM ONLY PROTEIN LMO3

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The LIM only protein LMO3 is a transcriptional regulator that has primarily been characterized for its developmentally-regulated expression in the brain and role in neuroblastoma. We previously determined that Lmo3 expression in the brains of transgenic mice expressing a short hairpin RNA (shRNA) targeting Lmo3 is significantly correlated with ethanol-induced loss of righting reflex (LORR) and 2-bottle choice ethanol consumption. To further characterize the role of Lmo3 in behavioral responses to ethanol, we tested Lmo3 knockout (Lmo3KO) mice for several ethanol-related behaviors. Lmo3KO mice showed significantly increased LORR sedation time at doses of 3.2 and 3.6 g/kg ethanol. These data are similar to previous findings with the Lmo3 shRNA transgenic mice. In contrast, we

observed no effect of genotype between wild-type and Lmo3KO mice in 2-bottle choice ethanol consumption, whereas previous studies in shRNA transgenic mice suggested a positive correlation between Lmo3 expression and ethanol consumption. Interestingly, in a model of binge drinking behavior (drinking in the dark, DID), Lmo3KO mice consumed significantly more ethanol than wild-type mice. To understand where Lmo3 might function to regulate these behaviors, we used the Lmo3KO mice, which contain an insertion of the β-galactosidase (β-gal) gene in the Lmo3 locus, to examine expression of β-gal under the control of the Lmo3 promoter in the adult brain. Strong β-gal activity was evident in the caudate putamen, nucleus accumbens, cortex, hippocampus, septum, habenula, hypothalamus, superior colliculus, substantia nigra, ventral tegmental area, interpeduncular nucleus, periaqueductal gray, and amygdala. Several of these regions have been implicated in alcohol use disorders. In addition, expression of Lmo3 in the nucleus accumbens of male C57BL/6J mice was significantly negatively correlated with ethanol consumed in the DID test. These data suggest that Lmo3 might act in the nucleus accumbens to inhibit binge drinking behavior. This study is supported by the NIH/NIAAA INIA Consortium (AA029012 and AA016654).

C29

LONGITUDINAL NEUROANATOMIC AND COGNITIVE TRAJECTORIES IN SCHIZOPHRENIA

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Schizophrenia is a neurobiological disorder associated with abnormalities in brain structure that have shown to progress over certain phases of the illness. Cognitive dysfunction is another consistent feature that is increasingly being conceptualized as a core factor in the expression of the disease. The exact longitudinal course of these features continues to be a focus of inquiry as their relationship may hold clues to the nature of the behavioral and pathophysiological process of schizophrenia. The overall aim of this study was to understand the relationship between longitudinal courses of neuroanatomical decline and cognitive/clinical stability in schizophrenia. Clinical, neuropsychological and MRI structural data were collected from a sample of schizophrenia (n=30) and healthy subjects (n=26) at baseline line (T1) and 24 month follow-up (T2) time points. Surface-based cortical thickness mapping using a General Linear Model was utilized to determine the differences in cortical thickness between groups. The resulting cortical thickness map from T2 was then utilized to create a region of interest (ROI) for longitudinal analysis using Repeated Measures ANOVA. Results revealed significant thinning of the cortical mantle for the schizophrenia group relative to healthy subjects at both time points. Differences in thinning across time were also observed, with areas of the precuneus and superior frontal gyrus demonstrating significant group-by-time interactions indicating greater rates of thinning in these regions. The cognitive profile of the schizophrenia group, while significantly impaired relative to healthy participants, did not evidence any effect for time. Results from this study suggest longitudinal trajectories of neuroanatomic and clinical/cognitive changes vary and are not linked in a consistent manner. Whether a direct relationship between these constructs exists, or secondary factors are the mechanism of change is unclear. Further exploration would focus on these relationships at different illness stages.

C30

AN ANTISENSE OLIGONUCLEOTIDE THAT TARGETS SPLICING TO TREAT USHER SYNDROME IN MICE

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Usher syndrome (Usher) is the leading genetic cause of combined deafness and blindness. Type 1 Usher (Usher 1) is the most severe form of the disease and is characterized by hearing impairment and vestibular dysfunction from birth, and the development of retinitis pigmentosa (RP) in early adolescence. A 216G>A (216A) mutation in *USH1C*, accounts for all Usher 1 cases in Acadian populations of the United States and Canada. The *USH1C* gene codes for the protein harmonin which is essential for development of hair cells in the ear and survival of retinal cells. The 216G>A mutation creates a cryptic splice site that is used preferentially over the authentic splice site. Use of the cryptic site gives rise to a frame-shift that results in the production of a truncated, non-functional protein. We developed an antisense oligonucleotide called ASO-Ush, which binds to the 216A mutation in *USH1C* RNA, blocks it from being recognized by the cellular splicing machinery and redirects splicing to the authentic splice site. In this way, the deleterious effects of the mutation are subverted and harmonin expression restored. The chemistry of ASO-USH makes the molecule very stable and easily deliverable to different cell types in the body. The specificity of the molecule eliminates harmful side-effects that can arise from treatment with small-molecule drugs. ASO-USH was tested for its ability to block the 216A mutation and restore harmonin expression in a mouse model of Usher syndrome. These mice were engineered to have the identical *Ush1c*.216G>A mutation (216AA) as humans. These Usher mice are deaf, exhibit circling behavior indicative of severe vestibular dysfunction, and have retinal dysfunction by 1 month of age and begin to lose photoreceptors between 6 and 12 months of age. We

found that mice treated with a single dose of ASO-USH shortly after birth had normal vestibular function and could hear for up to six months of age. The treated mice also had a modest improvement in visual function at one month of age. Our results demonstrate that ASO-USH can effectively correct an *Ush1c* mutation and suggest the therapeutic potential of this class of molecule in Usher syndrome and other diseases of the eye and ear. Supported by: NIH R01DC012596, Foundation Fighting Blindness Wynn-Gund Translational Research Award.

C31 UG

TRANSPLANTED NEUROSPHERES DERIVED FROM GENETICALLY MODIFIED ADULT BONE MARROW MESENCHYMAL CELLS FOLLOWING CONTROLLED CORTICAL IMPACT (CCI): EFFECTS ON INJURY SIZE AND TRANSPLANT SURVIVAL

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Traumatic brain injury (TBI) affects millions of people annually, causing 138 deaths every day in the United States alone. Even so, treatment availabilities are limited. A potential treatment is transplantation of adult bone marrow-derived mesenchymal stem cells (BMSC). Although previous studies have transplanted undifferentiated BMSC following TBI, our lab transplanted neurospheres derived from BMSC genetically modified with the intracellular domain of Notch1 (NICD) and neo-resistance genes. These NICD-induced BMSC were transduced with a GFP lentivirus and grown under non-adherent conditions to promote formation of neurospheres that were transplanted one-week post-controlled cortical impact (CCI) in the rat. These transplants were placed either in the injured cortex or in the striatum below the cortical injury. Our previous data demonstrated that transplanted neurospheres decreased sensorimotor behavioral deficits out to one month post-transplant. However, behavioral enhancement was better in rats with striatal transplants vs. cortical transplants. The current study examined whether these behavioral results could be explained by differences in stem cell survival or neuroprotection of tissue post-TBI. Brain tissue from animals injected with neurospheres, either in the injured cortex or striatum was analyzed one month post-injury. Survival of stem cells was measured qualitatively using the computer program Neurolucida, using a rating scale for presence of GFP positive cells. To examine whether transplants resulted in neuroprotection or replacement of cells post-injury, remaining cortical area (μm^2) was measured in sections containing the forelimb sensorimotor cortex using Neurolucida. The volume of remaining cortex was obtained by taking the total area and multiplied by the distance between sections, 0.24 mm^2, to obtain volumes in mm^3. Data analysis with ANOVA demonstrated that striatal neurosphere transplants showed better survival (i.e. presence of more GFP positive cells) than cortical neurosphere transplants ($p<0.05$). One-way analysis of variance of cortical volume indicated that there was no significant difference between striatal neurosphere transplants and cortical neurosphere transplants in remaining cortical volume ($p>0.05$ compared to CCI only). Results indicated that striatal neurosphere transplants following TBI have better survival than cortical neurosphere transplants, but the neurosphere transplants in either region have no effect in reducing contusion size through neuroprotection, suggesting that the behavioral enhancement seen is due to other factors besides neuroprotection.

C32 UG

A ROLE OF OVEREXPRESSED ALPHA-SYNUCLIEN IN ORGANIZATION OF THE PRESYNAPTIC AXONAL TERMINALS IN *C. elegans*

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Parkinson's disease is a non-treatable neurological disorder that affects mainly people over the age of 50. It can lead to an inability to control one's own muscles, causing rigidness and lack of movement. Parkinson's disease follows its mechanism through some disruption that reduces the ability to produce dopamine as a signal for synaptic terminals. In order to prevent and treat this disease we need to understand the pathogenesis mechanism underlying neuronal cell death. Alpha-synuclein is a protein that has been found in aggregate forms in a number of Parkinson's disease patients and seems to bind synaptic vesicles membranes as well as aid in vesicle transporting. It has also been shown that increased levels of alpha-synuclein have caused its aggregation in vitro. Our research focuses on the effect that over-expressed forms of alpha-synuclein have on *C. elegans* neuronal organization. This research will take into account how alpha-synuclein can cause an effect on presynaptic axon terminals of *C. elegans*. In order to examine this relationship we constructed a transgenic animal expressing alpha-synuclein throughout the nervous system of wild type *C. elegans*. We then integrated the mCherry-tagged *rab-3* gene, which highlights the active zones of presynaptic terminals with red florescence, into the alpha-synuclein transgenic *C. elegans*. We compared the localization patterns of the *rab-3* in wild type and alpha-synuclein transgenic animal. The images captured between the two strains showed some difference in the expression of the marker. The strain without alpha-synuclein showed steady expression of puncta along the axon of the *C. elegans*. While the strain with alpha-synuclein

had disruption of the puncta resulting in areas with increased spacing and fewer puncta being present along the axon. This supports that the disruption taking place in the synaptic terminals is caused by the presence of alpha-synuclein. If alpha-synuclein is affecting active zone organization it would cause a loss of neuron signaling. When signals between neurons is lessened or lost it would cause symptoms like lack of motor control which is seen from Parkinson's disease. We will determine the localization pattern of additional subcellular proteins in alpha-synuclein transgenic animals in the future. This research is supported by NIH grant (R21NS077018).

C33 UG

SPECIFIC TRANSDUCTION OF CORTICOSPINAL MOTOR NEURONS BY AAV2 AFTER DIRECT INJECTION INTO THE MOTOR CORTEX

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The application of adeno-associated virus (AAV) in gene therapy has multiple advantages due to its long-term expression in the central nervous system (CNS) and low immunoreactivity in humans. Gene therapy strategies in CNS include Canavan's disease, Alzheimer's disease and motor neuron diseases such as amyotrophic lateral sclerosis (ALS). Targeting only specific neuron populations without affecting other neuron types within the cerebral cortex is a major obstacle for translational neuroscience. This applies to ALS where in the cerebral cortex corticospinal motors neurons (CSMN; a.k.a upper motor neurons) progressively degenerate. In this study, we investigated whether different AAV serotypes showed selective tropism for CSMN. Seven different AAV serotypes that harbor the eGFP gene were tested after direct injection into the layer V of the motor cortex. CSMN transduction was confirmed by immunocytochemistry to CTIP2 and with red fluorescent microsphere labeling of CSMN after injection into the corticospinal tract (CST). Large pyramidal neurons located in layer V showed higher tropism for AAV2-2. In an effort to increase the selective transduction of CSMN by AAV, we used capsid proteins that are engineered, and different promoters to drive the eGFP expression. Our ongoing studies suggest that the choice of the promoter is critically important to enhance selectivity of gene expression in CSMN. Identification of AAV serotypes that transduce only a select set of neuron populations, even upon direct cortical injection is critically important to develop effective and long-term gene therapy approaches in the cerebral cortex. Such discoveries will allow gene delivery into the neurons that are vulnerable, without affecting other cortical neurons or other circuitries. This work was supported by Northwestern Weinberg Grant (MJS), The Milton Safenowitz Post-Doctoral Fellowship from the ALS (JHJ), Les Turner ALS Foundation (PHO), and Wenske Foundation (PHO).

C34 UG

RXR AGONISTS EFFECTS ON SOLUBLE LEVELS OF Aβ42 AND OLIGOMERIC Aβ DIFFERENTIALLY REGULATED BY HUMAN APOE GENOTYPES

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Alzheimer's disease (AD) is the most common form of dementia, and amyloid-β42 (Aβ42) in soluble, oligomeric (oAβ) forms, is purported to be the primary neurotoxin. As current clinical trials attempting to lower Aβ levels are failing, there is a critical need to develop novel therapeutic targets. *APOE4* is the greatest AD genetic risk factor, increasing risk up to 15-fold compared to *APOE3*. Apolipoprotein E (apoE) represents a promising target for modulating Aβ levels. Indeed, bexarotene (Bex), a retinoid X receptor (RXR) agonist, was shown to reduce soluble and insoluble Aβ levels via increasing mouse apoE (m-apoE) levels *in vivo*. However, the effect of modulating the human apoE isoforms on Aβ levels is unclear. Concern centers on whether apoE4 represents a toxic-gain of function, which would predict an increase in Aβ levels with Bex treatment, or loss of function. Recent reports have also raised concerns over the activity and mechanism of action of Bex, even in the context of m-apoE. In this study, novel EFAD mice (overexpressing human Aβ42 with human *APOE3 or APOE4*) were treated with Bex and LG268, a more selective RXR agonist. In brain regions with low Aβ levels at time of treatment, RXR induced no changes in soluble levels of Aβ42 and oAβ in E3FAD or E4FAD mice. In brain regions with intermediate Aβ levels, RXR agonist treatment resulted in increased soluble Aβ42 and oAβ, while markers of synaptic viability (PSD95) were decreased in both E3FAD and E4FAD mice. Critically, in the hippocampus, with high Aβ levels at time of treatment, RXR agonist treatment of E4FAD mice decreased soluble Aβ42 and oAβ levels and increased markers of synaptic viability. In addition, total apoE levels were unaffected for all treatment groups, indicating an alternate mechanism of action for RXR agonists. Accordingly, our data indicate that the beneficial effects of RXR agonists in E4FAD mice are mediated via: increased ABCA1 and ABCG1 expression, increased apoE lipidation, and increased apoE/Aβ complex levels, thereby reducing oAβ levels and enhancing synaptic viability. Collectively, our data demonstrate that the levels of Aβ pathology at time of treatment determine

RXR agonist efficacy. Specifically, RXR agonists may have no effect, or even increase neurotoxic Aβ levels in prevention paradigms i.e. low/sub-pathological Aβ levels at time of treatment. However, RXR agonists may address a loss of function of apoE4, exacerbated by increased Aβ levels, lower apoE lipidation and apoE/Aβ complex levels. Future studies are vital to determine whether this pathway is relevant for *APOE3* carriers with high Aβ pathology, or if RXR agonists are an *APOE4*-specific AD therapeutic. Supported by Alzheimer's Drug Discovery Foundation.

C35 G

NIEMANN-PICK DIESEASE TYPE C2 PROTEIN (NPC2; HE1) IS A CSF BIOMARKER OF MACROAUTOPHAGY

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Macroautophagy (MA) is an inducible process for the cellular clearance of proteins, macromolecules and organelle. Perturbations in neuronal MA have been implicated in several neurodegenerative disorders, and the induction of this mechanism to clear toxic protein aggregates is a potential therapeutic approach to protein misfolding disorders. Since MA is an entirely intracellular process, monitoring disease or drug-induced alterations in MA in the CNS poses a dilemma. Therefore, we identified a secreted marker of this process computationally and confirmed our findings *in vitro* and *in vivo.* We constructed an interaction network of autophagy-associated genes/proteins. Using a network building algorithm to discover neighboring interactions with proteins that were known or predicted to be secreted by two different methods (PSORT and Sec-HMMER), we identified Niemann-Pick disease type C2 protein (NPC2: HE1). To verify that NPC2 is a secreted biomarker of MA, we induced MA in human H4 neuroglioma cells by treatment with rapamycin (RAP), amitryptaline (AMI: a brain-penetrant inducer of autophagy) or nutrient (serum) starvation, and monitored LC3 -II maturation. 3-methyladenine (3MA) treatment was used to inhibit nutrient deprivation-induced MA. In order to verify that NPC2 levels are modulated in vivo by autophagy inducers, we treated rats with AMI and monitored levels of NPC2 in the CSF. Induction of MA by RAP, AMI or nutrient deprivation as monitored by LC3 II maturation resulted in increases in NPC2 levels in conditioned media (CM). Nutrient-deprivation induced MA was inhibited by 3MA, and caused corresponding reductions in NPC2 levels in CM. CSF levels of NPC2 increased in response to AMI treatment in rats. Our data suggest that NPC2 is a secreted CSF biomarker of MA.

THEME D. HISTORY AND TEACHING NEUROSCIENCE

D1

CONCUSSION EDUCATION AS AN UNDERGRADUATE STUDENT ORGANIZATION AT DEPAUL UNIVERSITY

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Concussions have received significant media attention lately due to the rise in reports about the devastating effects of repeat concussion in contact sports and in the military. Sports Legacy Institute (SLI) is a non-profit whose goal has been to educate the community about concussions and how to play sports safer. One mechanism by which this is done is through concussion education presentations to elementary, middle and high school students. These presentations were first conducted by medical students in Boston who created SLICE - Sports Legacy Institute Community Educators. DePaul University in Chicago became the first institution outside of Boston to develop a chapter of SLICE. Undergraduates in the College of Science and Health developed a student organization, recognized by the university, and together with SLI marketed the presentations to Chicago area schools. This is an entirely student-run organization with a faculty sponsor. The students go through a concussion education training, which may or may not result in academic credit. They learn how to give the presentations and then they travel the city offering 30-40 minute presentations to schools. In addition they have events on campus both for students and the general public about concussions and have a network of students that are passionate about neuroscience and health education. All together SLICE has reached over 1000 students in one year. This is an easy to implement, student run, educational program in Neuroscience that increases public awareness of a public health epidemic-brain injury. Supported by DePaul University & Sports Legacy Institute.

D2 UG

EFFECTIVENESS OF THE "SLICE CONCUSSION EDUCATION PROGRAM" FOR CHICAGO YOUTH

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The Center for Disease Control and Prevention states that between 1.6 and 3.8 million student athletes experience concussions each year. Sports Legacy Institute Community Educators (SLICE) is a student-run organization that teaches elementary, middle school, and high school students around the country about symptoms, associated risks, and appropriate responses to concussions. In the present Chicago study, students in participating schools, ranging in age from 9-19 years (*N* = 299), were given an interactive presentation complete with demonstrations, discussions, and case studies. SLICE presenters gave participants surveys before (*n* = 299) and immediately after (*n* = 272) the program to assess knowledge of concussion symptoms

and appropriate responses to a concussion. A one-tailed t-test showed a significant difference in mean survey scores between groups before and after the SLICE presentation ($p < 0.0001$). A significant improvement in scores was observed such that scores increased by 17% after the presentation, from an average failing score (<50%) to an average passing score (>50%). Additionally, a binomial distributions test revealed that there was a significantly higher overall passing rate on the post surveys than on the pre surveys ($z = 6.86$, $p < 0.05$). Preliminary results suggest that the SLICE program in Chicago is effective in promoting concussion knowledge for students between the ages of 9 and 19 years. Further analysis will include the examination of differences across age group, gender, and geographical location.

THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1

SEX-SPECIFIC EFFECTS OF REPEATED RESTRAINT STRESS ON NEURONAL ACTIVITY IN FEMALE AND MALE BASOLATERAL AMYGDALA

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Females are more likely to suffer from stress-related affective disorder such as anxiety or depression in their lifetime, and tend to display differences in their symptomotology compared to males. This difference between males and females may occur as a result of sex differences in limbic function. The basolateral amygdala (BLA) is a stress sensitive limbic structure integral to the generation of emotions and emotional learning. Despite all that is known regarding sex differences in BLA-dependent behaviors in humans and rodents, very little is known about female amygdala physiology. In this study, we examined BLA neuronal activity in control handled and stressed urethane anesthetized cycling female and male rats using *in vivo* extracellular single unit recordings. The estrous cycle was monitored daily for a minimum of 3 weeks before electrophysiological recordings. Females were recorded in the diestrus (low estrogen) or proestrus (high estrogen) phases of the estrous cycle. Animals were control handled or stressed (restraint) for 7 out of 9 days and recorded 1-3 days post-stressor. Our experiments revealed a sex difference in BLA neuronal activity in both control handled and stressed rats. Control handled females displayed a higher firing rate compared to control males. There was no difference in female BLA activity between diestrus and proestrus phases of the estrous cycle, however, both diestrus and proestrus females showed significantly higher BLA neuronal firing rate compared to males. Neuronal activity in the lateral and basal nuclei of the BLA did not differ between diestrus and proestrus females. However, the basal nucleus was more active in proestrus females compared to the lateral and basal nuclei in males. The number of active neurons per electrode track and the coefficient of variation were similar in both sexes. Similar to control handled animals, stress also had a sex specific effect on BLA neuronal activity. Stressed females displayed lower BLA neuronal firing rate compared to control females. In contrast, stressed males displayed greater BLA activity compared to control males. Similar to control animals, the number of active neurons per electrode track and the coefficient of variation were similar in both sexes following stress. The relationship between action potential (AP) width and BLA neuronal firing rate was more variable in the female (control) BLA compared to males (control), suggesting that females have a more diverse population of spontaneously firing neurons. Collectively, our experiments demonstrate that there are sex differences in BLA neuronal physiology and that these differences may render females more vulnerable to stress-related affective disorders. This study is funded by research award MH100536.

E2

17B-ESTRADIOL REGULATES THE BIOSYNTHESIS OF MATURE MICRORNA AT MULTIPLE LEVELS IN THE AGED FEMALE RAT HYPOTHALAMUS

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Menopause is characterized by the rapid age-related decline in circulating 17β-estradiol (E_2) levels, which can result in cognitive disorders such as impaired memory and increased anxiety. Hormone therapy (HT), such as E_2 supplementation, is widely used as a treatment for the adverse effects associated with menopause. However, data from the Women's Health Initiative (WHI) showed that HT failed to provide any benefit for women who were 10 years post menopause. Previous data from our lab have shown that E_2 treatment can regulate microRNA (miRNA) expression in the hypothalamus of ovariectomized (OVX) rats in an age dependent manner. miRNAs are a class of small RNAs that regulate gene expression at the post-transcriptional level by binding to the 3' untranslated region (UTR) of an mRNA target and inducing its degradation. miRNAs are transcribed from the genome in a RNA polymerase II dependent manner to produce a long primary miRNA (pri-miRNA), which is sequentially cleaved to form the small (~22 nucleotides) mature miRNA. We hypothesized that E_2 treatment after a period of extended ovarian hormone deprivation differentially regulates mature miRNA expression. Fischer 344 female rats were OVX and then received 3 consecutive days of E_2 treatment (s.c. 2.5μ/kg) at either 1, 4, 8, or 12 weeks post-OVX. 24 hours after their last treatment, animals were sacrificed and the hypothalamus from the right side of the brain was

removed for RNA extraction. Our qRT-PCR results showed that E_2 treatment significantly increased let-7i, miR-9, and miR-7a after 8 weeks of ovarian hormone deprivation. Interestingly the expression of the pri-miRNA forms did not correspond to the mature miRNA expression, suggesting that E_2 might regulate miRNA processing. E_2 has two intracellular mediators: estrogen receptor (ER) α and β. To understand how E_2 regulates miRNAs we analyzed the expression levels of ERα and ERβ by qRT-PCR. Our results showed that ovarian hormone deprivation did not alter ERα mRNA expression in the hypothalamus; however 8 weeks of deprivation significantly increased ERβ expression. We also showed that E_2 and ovarian hormone deprivation had no effect on mRNA expression levels of miRNA processing enzymes, drosha and dicer, and did not alter argonaute 2. Finally we examined mRNA expression levels of two potential gene targets of miR-9 and miR-7a; sirtuin1 (SIRT1) and glucocorticoid receptor (GR). We observed that GR expression significantly decreased after 8 weeks of ovarian hormone deprivation, corresponding to increased miR-9 and miR-7a expression. Together our data demonstrate that prolonged periods of ovarian hormone deprivation, as occurs following menopause, alters E_2-mediated regulation of miRNA expression profiles, which could result in altered gene expression. These results support the possibility that miRNAs might contribute to the observed differential age-related effects of HT. Supported by NIH.

E3 G

FUNCTIONAL IMPLICATIONS OF ESTROGEN RECEPTOR β POSTTRANSLATIONAL MODIFICATIONS IN NEURONS

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Estrogens have pleiotropic effects on brain physiology, yet the results of clinical studies on the beneficial neurobiological effects of estrogen therapy (ET) in older women are contradictory. We hypothesized that declining levels of estrogens at the time of menopause alters cellular kinase activity, thereby altering estrogen receptor (ER) phosphorylation and downstream target gene activation. The effects of estrogens are mediated by two high-affinity nuclear receptors: ERα and ERβ. Phosphorylation of ERα has been implicated in nearly every aspect of ERα signaling, yet ERβ phosphorylation in the brain is less understood. Importantly, there are two serine residues in the N-terminal region of ERβ, S87 and S105, that can be phosphorylated by Mitogen Activated Protein Kinases (MAPK) p38 and ERK1/2 (Extracellular-signal-Regulated Kinases). Therefore, in this study we determined how ERβ phosphorylation at S87 and S105 affects transcriptional activity in a hypothalamic-derived neuronal cell line. Cells were transiently co-transfected with an expression vector containing full length ERβ wild type, phosphomimetic (S87E, S105E), or phosphonull (S87A, S105A), and a Firefly luciferase reporter construct containing ER binding elements (ERE or AP-1) upstream of a minimal thymidine kinase (tk) promoter. Cells were treated with 17β-estradiol (E2) or vehicle 24 hours following transfection. The results showed that site-dependent phosphorylation of ERβ affected both estrogen-independent and estrogen-dependent ERβ transcriptional regulation. These data demonstrate that phosphorylation of ERβ could differentially alter downstream gene expression, possibly by altering receptor dimerization or interactions with coregulatory proteins. To address this possibility, we used bioluminescence resonance energy transfer ($BRET^2$) to measure protein:protein interactions between ERβ wildtype and phosphomutant receptors, as well as their interactions with coregulatory proteins, such as NCor and SRC3. Overall these data demonstrate that phosphorylation of ERβ has important functional consequences for ERβ-mediated gene expression, and that disruption of coregulatory protein interactions is a potential mechanism for how ERβ phosphorylation alters downstream gene expression. Clinical studies show benefits of ET during early menopause but detrimental effects later, which might be reflective of changes in ERβ phosphorylation status as a result of increased age-related kinase activity. Supported by NIH R01AG033605 TRP.

THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG

STRESS, SEX, AND BRAIN: FUNCTIONAL NEUROANATOMY OF KCa CHANNELS IN THE BASOLATERAL AMYGDALA

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Females are at a higher risk for developing stress and anxiety disorders than males. In previous studies, female rats showed a heightened fear response, which is linked primarily to the basolateral amygdala (BLA), the brain structure associated with regulation of emotion. Despite a trend of sex differences in stress disorders and the knowledge that BLA activity is modulated via small-conductance calcium-activated potassium (K_{Ca}) channels, it is unclear what influence gender has on K_{Ca} channels in the BLA. The purpose of this thesis was to examine the hypothesis that neurons in female rat amygdalae are more excitable than those of males due to decreased expression of K_{Ca} channels. To test this hypothesis, we characterized K_{Ca} channel expression in the BLA, using immunohistochemistry in-situ hybridization for protein and gene expression, respectively. We compared results between females at

varying stages of their estrous cycle to males. Our preliminary data, not yet statistically analyzed, shows a trend consistent with our hypothesis that females with decreased estrogen exhibit similar K_{Ca} channel expression to males, and both exhibit less than females with elevated levels of estrogen. Once completed, these studies will aid in understanding mechanisms for sex differences in anxiety disorders.

F2

MODULATION OF $CA_V2.1$ CHANNELS BY CHOLESTEROL LEVELS

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Calcium channels (Ca_V) show different compartmentalization on neuronal plasma membranes where they form clusters, involving both cytoskeletal elements and microdomains within the lipid bilayer. $Ca_V2.1$ channels are distributed in lipid microdomains.We showed an acute effect of pregabalin (PGB, a α2δ-binding drug) on the cellular function and distribution of $Ca_V2.1$ channels transfected in HEK293t. The system allowed us to visualize the internalization of subunits within cells after PGB treatment by means of fluorescence microscopy, while recording barium-mediated currents (I_{Ba}). We studied how the cytoskeleton and the lipid rafts organization might modulate the calcium channels. For this purpose, we treated transfected cells with methyl-cyclodextrin (MβCD, 5-10 min.), a cholesterol sequestering drug, and determined the internalization of the fluorescent subunits, and the distribution of microtubules. MβCD (10 mM, 10-20min) increased α1 internalization (with a membrane/interior ratio 10% lower compared to untreated cells) and reduced I_{Ba}, similarly as after PGB treatment. Moreover, addition of cholesterol (10 mM, 10min) to the membrane decreased the currents. In addition, MβCD and PGB exerted an effect on the microtubule cytoarchitecture evidenced by a diffuse tubulin staining. The implications on the importance of this modulation lies on the fact that lipids change in the aged brain which could in turn modulate the levels of functional channels at the plasma membrane.

F3

MODULATION OF NEURONAL VOLTAGE-GATED CALCIUM CHANNELS BY KELCH-LIKE-1 PROTEIN

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Kelch-like 1 protein (KLHL-1) is an actin-binding protein specific to the nervous system, constitutively expressed throughout the cytoplasm, axons and dendrites in neurons and in glia. The KLHL1 gene locus is closely localized to ATXN8 and in antisense to ATXN8OS, two genes implicated in the neurodegenerative disease Spinocerebellar ataxia type 8. This disease is characterized by the presence of trinucleotide expansions in the ATXN8OS and ATXN8 loci. It is not yet clear whether ATXN8OS alters KLHL1 expression or if the presence of expansions in this region affects KLHL1 function, however the expression pattern of the KLHL1 antisense strand is suggestive of a regulatory role of KLHL1, and also correlates with the pathology of SCA8. Moreover, trans-RNA interference assays in HEK 293 cells also suggest ATXN8OS may function as a negative regulator of KLHL1; furthermore, the conditional knockout model of KLHL1 exhibits loss of post-synaptic structures, mild cerebellar atrophy and loss of motor coordination and gait abnormalities, confirming a role of KLHL1 in normal cerebellar function. KLHL1 has various functions, including the modulation of neurite outgrowth and of ion channel activity *in vitro*. The positive modulation of voltage-gated calcium channels by KLHL-1 known to date includes $Ca_V2.1$ (P/Q-type, α_{1A}), 3.2 (T-type α_{1H}) but not 3.1 (T-type α_{1G}). *In vitro* studies revealed the ABP interacts with and up-regulates T-type α_{1H} calcium channel function by altering its kinetics of deactivation and by increasing the number of active channels present at the plasma membrane. The latter is achieved by the interaction of α_{1H} with KLHL-1 and with the polymerized actin cytoskeleton, which results in altered endosomal recycling, increased trafficking of α_{1H} back to the membrane and subsequent surface expression. Here we probed the endogenous effect of KLHL1 in KLHL1 KO mice, and compared it to the acute down-regulation using adenoviral delivery of shKLHL1 (gene knockdown) in WT neurons. Our results confirm that KLHL1 is a voltage-gated calcium channel modulator in cultured hippocampal and hypothalamic neurons, and shows that KLHL1 physiological role is not restricted to the cerebellum, where it is most abundant but it contributes to cellular function in all neuronal regions where it is expressed. Our data also suggests possible alterations in ion channel expression and/or compensatory changes may occur in the KLHL1.

Supported by NSF.

F4

LONG-TERM POTENTIATION OF EXTERNAL GLOBUS PALLIDUS-SUBTHALAMIC NUCLEUS SYNAPSES FOLLOWING ACTIVATION OF MOTOR CORTICAL INPUTS

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The frequency and pattern of activity in the subthalamic nucleus (STN) are intimately related to motor function and dysfunction and are influenced in large part by the

STN's major glutamatergic afferent, which arises from the motor cortex and its major GABAergic afferent, which arises from the external globus pallidus (GPe). In order to understand how the balance of cortical excitation and pallidal inhibition is regulated in the STN, the effect of optogenetic activation of motor cortical inputs on GPe-STN inputs was studied in *ex vivo* brain slices using patch clamp recording. Repeated optogenetic activation (300 ms trains of 50 Hz stimulation repeated 30X at 0.2 Hz) of motor cortical inputs led to heterosynaptic long-term potentiation (hLTP) of GPe-STN inputs. hLTP was associated with a reduction in the coefficient of variation (CV) of IPSC1 and a reduction in the ratio of IPSC2:IPSC1, indicating an increase in the initial probability of GPe-STN transmission. Furthermore, following stimulation of M1-STN axon-terminals the frequency but not the amplitude of spontaneous IPSCs (sIPSCs) increased, consistent with an enhanced probability of GPe-STN transmission. hLTP was blocked by intracellular loading of the exocytosis inhibitor tetanus toxin, but not heat-inactivated tetanus toxin, indicating that $GABA_A$Rs are inserted into the membrane of postsynaptic STN neurons during hLTP. hLTP was prevented by blockade of NMDARs but not by blockade of group 1 mGluRs and mimicked by bath application of NMDA. NMDA also increased $GABA_A$R current evoked by uncaging of RuBi-GABA (10 □M) at soma of STN neurons, confirming increased expression of postsynaptic $GABA_A$Rs during hLTP. Stimulation of M1-STN inputs failed to induce hLTP when postsynaptic Ca^{2+} was chelated by intracellular infusion of BAPTA via the patch pipette and led to LTD when postsynaptic CaMKII was inhibited by autocamtide-2-related inhibitory peptide (AIP). Moreover, hLTP was prevented by inhibition of nitric oxide synthase (NOS), scavenging of nitric oxide (NO), inhibition of guanylate cyclase (GC) or inhibition of PKG. hLTP was not mimicked by application of the NO donors SNAP, suggesting that NO/GC/cGMP/PKG signaling is necessary but not sufficient for hLTP. Additionally, the density of gephyrin in the STN, the postsynaptic scaffolding protein at GABAergic synapses, was significantly increased by NMDA application or photostimuaiton of M1-STN inputs, suggesting that hLTP is mediated by an increase in the number of GPe-STN synapses. More interestingly, both the frequency and amplitude of mIPSCs in STN neurons were significantly decreased after *in vivo* knockout of NMDARs in STN. We are currently investigating the relationship between this form of plasticity and the proliferation of GPe-STN synapses following loss of dopamine in experimental Parkinson's disease. This work was supported: NIH-NINDS (2R37NS041280 and P50NS047085) and the Parkinson's Disease Foundation (PDF-IRG-1101).

F5 PD

REGULATION OF SYNAPSE STRUCTURE BY AN AUTISM-ASSOCIATED CADHERIN

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The correct regulation of synapse structure and function is essential for cortical development and plasticity, and dysregulation of these processes can result in cognitive dysfunction, demonstrated in diseases such as autism spectrum disorders (ASDs). There is an urgent need to fully understand the neurobiology that underlies ASDs, due to their growing prevalence in the population. At the cellular level, ASDs are strongly associated with synaptic dysfunction, dendritic spine abnormalities. This is supported by evidence from genetic-association studies that point to a number of genes associated with ASDs, many of which encode synaptic proteins, suggesting that ASD has a major synaptic pathology component. However, the molecular mechanisms underlying synapse structure and function in ASDs remain unknown. Recent genetic studies have identified a member of the cadherin family of adhesion proteins as a significant ASD risk gene. The study of this new candidate protein may shed light on the mechanisms leading to pathogenic synapse alterations observed in ASD brains. Here we examine the expression and localization of this cadherin in cortical neurons, and explore its role in regulating synapse structure and function. Using a combination of confocal imaging, electron microscopy and super-resolution microscopy we have characterized the subcellular localization of this autism-associated cadherin in both rat cortex and cultured cortical neurons. Furthermore we show that genetic manipulation altering cadherin expression levels causes abnormal dendritic spine morphology and altered synaptic function, thereby disrupting synaptic transmission. Together, these data provide further insight into the molecular mechanisms that regulate dendritic and synaptic structure, the disruption of which may contribute to ASD pathology. This study was funded by a Marie Curie Outgoing Postdoctoral Fellowship.

F6 G

NEURAL STEM CELL AND MICROGLIAL RESPONSES AFTER TRAUMATIC BRAIN INJURY AND REPEATED BINGE ALCOHOL

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We have previously found that a repeated dose of binge ethanol prior to TBI leads to worse recovery on a sensitive test of skilled forelimb function. One means by which the brain is able to compensate for injury is in the mobilization of neural precursor cells. We therefore sought to determine the effect of binge ethanol at the time of TBI on subventricular zone (SVZ) and

perilesional neural precursor cells. Adult, male rats were given three injections of ethanol (2gm/kg/i.p/per day). One hour after the final injection, animals were given a TBI directed to the forelimb sensorimotor cortical area and sacrificed three weeks after TBI. Brains were immunostained for proliferating cell nuclear antigen and doublecortin. In animals receiving binge ethanol there was a significant reduction in PCNA-positive cells in the SVZ. Ethanol also reduced the number of double labeled PCNA-positive/DCX-positive cells on the side of the TBI, but not contralateral to the cortical lesion. Furthermore, binge ethanol significantly reduced the number of PCNA-positive cells as well as double labeled PCNA-positive/DCX-positive cells in the cortical perilesional area. Thus, a relatively short repeated dose of binge ethanol prior to TBI reduced the proliferation of neural precursor cells in the SVZ and perilesional area as well as decreased the differentiation of these cells into neurons. Additionally, we are in the process of determining microglial activation immediately following TBI and binge ethanol. Furthermore, we are using gastric gavage of ethanol as a more clinically relevant method of administration. Supported by NIH.

F7 G

CHARACTERIZING SOMATOSTATIN+ INTERNEURONS OF THE STRIATUM AND THEIR INHIBITORY INPUTS ONTO STRIATAL PROJECTION NEURONS

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The basal ganglia are a group of subcortical nuclei known for their central role in coordinating and executing movement. The neostriatum is the largest of these individual nuclei and composed almost exclusively of GABAergic striatal projection neurons (SPNs, ~95%). These SPNs are parsed into two populations based on the type of dopamine (DA) receptor (DAR) they express (D_1R or D_2R) and their projection site. Canonically, D_1R-expressing cells promote movement whereas D_2R-expressing cells inhibit it; the activity of both is modified by DA, the release of which provides the striatum 'feedback' regarding the outcome of the chosen action. Neurons of the substantia nigra pars compacta provide the striatum with this dopaminergic input. Perturbations in levels of this striatal DA are thought to contribute to a plethora of costly pathologies including schizophrenia, drug addiction and Parkinson's disease (PD). It has been long appreciated that the striatum undergoes reorganization following DA depletion in rodents, a model of PD. This observation may help to explain why simply replacing DA is not an adequate therapy. Therefore, the development of novel medications will require a more complete understanding of intrastriatal dynamics as well as the processes governing reorganization. One of the biggest unknowns of striatal physiology is what role various interneuron subtypes play in modulating striatal networks. Until now, most work has focused on cholinergic (ChI) and fast-spiking (FSI) interneurons. However, there exists another much less well characterized interneuron population that is anatomically poised to exert great influence on SPN activity; these are the GABAergic *plateau and low-threshold spike (PLTSIs).* Because of their rarity (<5%) and morphological similarity to SPNs, PLTSIs have been difficult to study with conventional methods. The advent of transgenic animals, pharmacogenomics and optogenetics has made these difficulties surmountable. We will use these tools, in tandem with traditional patch-clamp electrophysiology and two-photon light scanning microscopy (2PLSM) to: 1.) Explore the role of PLTS interneurons in regulating SPN excitability; 2.) Characterize the role of PLTS itneneurons in regulating dedritic excitability in SPNs in mouse models of PD. This study is funded by the General Motor Control Mechanisms and Disease Training Program (NS041234) and Northwestern University's Medical Scientist Training Program (GM008152).

F8 G

THE INTEGRATED STRESS RESPONSE IN PERINATAL WHITE MATTER INJURY: TARGETING AN ENDOGENOUS STRESS RESPONSE TO PROTECT AGAINST NEONATAL BRAIN INJURY

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Perinatal white matter injury (PWMI) is a disorder associated with premature birth, which is increasing in prevalence and leads to cognitive and behavioral deficits in 40-50% of preterm infants. PWMI is caused by hypoxic and ischemic insults that damage oligodendrocyte precursor cells (OPCs) leading to reduced myelination. We are currently exploring the integrated stress response (ISR) in PWMI. The ISR is a conserved cellular stress response activated by a variety of stresses that protects cells by both decreasing protein synthesis and increasing expression of cytoprotective genes, including anti-oxidant genes. The ISR is activated by hypoxia and ischemia in non-neuronal cells, and importantly activation of the ISR is protective. Here, we present data showing that the ISR is activated in OPCs following oxygen-glucose deprivation (OGD), an *in vitro* model of hypoxia and ischemia. Moreover, inhibition of the ISR sensitizes OPCs to OGD and enhancement of the ISR provides increased protection. Additionally, we present data demonstrating that genetic enhancement of the ISR protects myelin in an intermittent hypoxia model of white matter damage in mice. This study addresses the role of the ISR in survival of OPCs during hypoxia and ischemia and introduces the ISR as a potential therapeutic target for PWMI.

F9

α-SYNUCLEIN EXPRESSION DEFINES INTRINSIC MOSSY FIBERS OF UNIPOLAR BRUSH CELLS

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α-synuclein (α-Syn) has been shown to play a crucial role for synaptic vesicle release and synaptic membrane recycling in physiological condition. Interestingly, □-Syn is intensely expressed in the cerebellar lobule IX and X [Allen Brain Atlas] in which type I and type II unipolar brush cells (UBCs) are enriched. To answer whether □-Syn plays a role in synaptic function of cerebellar neurons, we used □-Syn immunohistochemistry in adult mice cerebellar sections. We found that □-Syn labels mossy fibers in granule cell layer, in lobule IX and X in particular; no cytoplasmic labeling was observed in neuronal somata. To elucidate whether □-Syn-positive (□-Syn+) mossy fibers belong to UBCs, we double labeled cerebellar sections with antibodies to □-Syn and UBCs type specific markers [calretinin for type I and metabotropic glutamate receptor 1 □ (mGluR1□) for type II]. We found that □-Syn colocalizes with calretinin in type I UBC axons, specifically in their terminals. >50% of □-Syn+ fibers, however, were not labeled by calretinin. This suggests that □-Syn is expressed by some, if not all, type II UBCs. The presence of extrinsic mossy fibers [that might be also □-Syn+] makes it difficult to assign these □-Syn+/calretinin-negative (calretinin-) mossy fibers to type II UBCs; moreover, no specific type II UBCs axon marker is available. To circumvent these problems, we prepared long-term cerebellar organotypic culture [24 days *in vitro* (DIV24)] in which only the intrinsic UBCs mossy fibers survive; the extrinsic mossy fibers degenerate within DIV2-3. In these organotypic cultures, both type I and II UBCs survived and displayed extensive axonal branching and terminals, that were labeled with □-Syn. Immunolabeling of □-Syn and calretinin recapitulated our observation from brain sections; colocalization of □-Syn and calretinin in a subset of mossy fibers. The absence of calretinin from the □-Syn+ intrinsic mossy fibers is an indirect proof of □-Syn expression in type II UBCs. Our data show that □-Syn is enriched in type I and type II UBCs and is exclusively localized to axonal and presynaptic compartments. This study is funded by National Institutes of Health (NIH) NS09904.

F10 UG

HCO_3^--DEPENDENT, K^+-INDUCED INCREASE IN PROTON FLUX AT THE ENDFOOT OF ISOLATED MULLER CELLS OF THE TIGER SALAMANDER

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Within the retina and the broader CNS, synaptic transmission is extremely sensitive to minute changes in pH. A growing number of studies suggest that regulation of extracellular pH may play an important role in shaping neuronal communication. In the outer synaptic layer of the retina, light-induced visual signals can be abolished with tenths of a unit changes in pH. Tightly regulated levels of HCO_3^- are an understated contributor to extracellular pH. Levels of this extracellular pH buffer are impacted by blood flow, CO_2 levels, as well as the expression and activity of HCO_3^- transporters and the enzyme carbonic anhydrase. Previous work (Newman, 1996) detected the presence of HCO_3^- transporters and carbonic anhydrase on radial glia (Müller cells) that span much of the overall thickness of the retina. The Müller cell plays a primary role in regulating many aspects of the retinal environment, such as ion, H^+, and neurotransmitter levels, and an active role in the release of gliotransmitters. Newman's observations suggested a HCO_3^--dependent mechanism by which high extracellular K^+ acidified the extracellular environment at their endfoot. This mechanism could be important for H^+ clearance to the vitreal surface of the retina during times of increased neuronal activity. Our findings, using a novel ultrasensitive H^+-selective self-referencing system in combination with a newly develop CO_2 chamber, corroborate these previous studies. The self-referencing system utilizes a H^+-selective microelectrode that records measurements from a near and a far point from a cell in order to obtain a differential pH value 1000 times more sensitive than a stationary pH electrode. Our work suggests Müller cells, isolated from tiger salamander retina, respond to increased K^+_o with an extracellular acidification, at the endfoot. This acidification can be abolished when extracellular Na^+ or HCO_3^- is removed or in the presence of the HCO_3^- transport antagonist, DIDS. These findings extend previous work strongly implicating an important role for HCO_3^- in shaping extracellular pH by Müller cells in the retina. They warrant future studies to characterize other pH regulatory mechanisms mediated by Müller cells, and to see their impact in the overall pH state of the retina and their contribution to the processing of visual signals. This study is funded by a research award from the National Science Foundation (Grant no. 0924383 and 0924372) and an Indiana Wesleyan University institutional award (Hodson Research Fellowship).

F11

CHARACTERIZATION AND FUNCTIONAL APPLICATIONS OF HUMAN IPS CELL-DERIVED MIDBRAIN DOPAMINERGIC NEURONS

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A major challenge in the field of neuroscience drug discovery has been the lack of robust and

physiologically relevant systems for cellular analysis and disease modeling. Human induced pluripotent stem (iPS) cells have emerged as a promising source of material from which tissue-specific cell types can be derived. In particular, neuronal subtypes from specific regions of the brain can be generated and are proving to be more predictive of the human condition as compared to immortalized cell lines or primary rodent cultures. The controlled differentiation of human iPS cells into either forebrain neurons or midbrain dopaminergic (DA) neurons – and not into cardiomyocytes or hepatocytes, for example – is a complex process that is tightly regulated. In addition, the ability to repeat the method of differentiation consistently at a scale sufficient for drug discovery efforts has proven to be very difficult. We have previously presented on the derivation and characterization of human forebrain neurons. Here, we demonstrate how a midbrain DA neuron differentiation was adapted from published literature, and then further optimized, resulting in the ability to produce commercial quantities of cryopreserved midbrain DA neurons. Using methods of gene expression, flow cytometry, and high content imaging, we were able to monitor the development of these neurons during differentiation. The final product displays typical neuronal morphology, with long and branching processes, and expresses key markers for this midbrain DA neuron population, including Lmx1, FoxA2, tyrosine hydroxylase (TH), and Map2. Moreover, this differentiation method yields a highly pure population of cells (>80% for TH and FoxA2; negative when stained for Nestin). Functionally, these cells reveal typical electrophysiology including spontaneous and evoked action potentials and excitatory post-synaptic currents. Lastly, as a proof of concept for scaling out the process, a panel of pure (>90%) iPSC-derived neurons from 15 donors was produced. The data presented here underscore the value of using iPS cell-derived cell types and highlight the use of different neuronal subtypes in various applications.

THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1 PD

AIMING FOR THE LESION: EXPLORING NEW DRUGS AND TRACERS SPECIFIC FOR DEMYELINATED AXONS

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Multiple sclerosis (MS) is a crippling neurological disease that typically strikes people in their twenties. Diagnosing and monitoring the disease and even testing new therapies are challenging because there is no direct way to visualize the lesions in the brain. MRI is the most commonly used tool, and while it offers excellent spatial resolution, it lacks specificity. Thus, a molecular imaging tracer, such as for positron emission tomography (PET), is critically needed. In this project we hypothesized that 4-aminopyridine (4-AP) –a K^+ channel blocker recently approved by the FDA to improve walking in people with MS– would only bind to K^+ channels on axons that have become demyelinated and could serve as a tracer. Thus we evaluated the distribution of C-14 labeled 4-AP in mouse models of MS and found that this molecule only localizes to white areas when there is demyelination. We also show that addition of fluorine to 4-AP does not affect its biological activity (binding to K^+ channels and enhancing action potentials) indicating that F18-labeled 4-AP could serve to image demyelinating lesions in MS patients using PET. In addition, we show that fluorinated 4-APs have better stability and permeability than 4-AP and have potential as therapeutics.

Support: National Multiple Sclerosis Society and NIH NINDS R21.

G2 PD

A RAPID METHOD FOR EVALUATING RISK/REWARD DECISION-MAKING IN THE RAT USING INTRACRANIAL SELF-STIMULATION

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Suboptimal risk/reward decision-making is common to a number of behavioral pathologies. Risk/reward decision-making can be assessed using probability discounting paradigms in which subjects choose between small, certain reinforcers, and larger reinforcers delivered with varying probabilities. Preference for the larger, uncertain ("riskier") reinforcer at low probabilities of delivery indicates risky decision-making. In studies with non-human animals, food commonly serves as the reinforcer. This procedure often requires that animals are food restricted, which may affect impulsivity itself. To circumvent this problem, we implemented intracranial self-stimulation (ICSS) of the medial forebrain bundle as the reinforcing stimulus for probabilistic discounting tasks (ICSS directly activates the neural circuitry involved with natural reinforcers) (Rokosik and Napier: J Neurosci Meth 198:260, 2011; Neuropsychopharm 37:1397, 2012). Our protocol consisted of nine phases that incrementally trained rats to perform in a final test that measured risk/reward decision-making. The present study aimed to streamline this protocol. Following recovery from surgically implanting the bipolar stimulating electrodes, the rats were trained to associate the positively reinforcing electrical stimulation with a lever press using a forepaw (phase 1). Next, rats were required to show stable responding for stimulation on an FR-1 schedule of reinforcement (phase 2). Our prior studies had verified that 50Hz and 100Hz could

serve as small and large reinforcers, respectively. Thus, rats underwent a discrimination task in which they could respond on one of two simultaneously presented levers. A press on one lever resulted in a 50Hz stimulation while a press on the other resulted in a 100Hz stimulation (phase 3). Once rats distinguished between the two (>%80 selection of the 100Hz stimulation over 3 consecutive sessions), they were trained in the discounting task (phase 4). We determined that rats quickly acquired the task, omitted fewer trials, and discounted the larger reward at lower probabilities, suggesting that this abbreviated protocol retains the construct validity of the previous procedure, with the advantage of expedited data collection. This procedure may accelerate preclinical research examining the role of suboptimal risk/reward decision-making in psychiatric disorders, as well as a means to screen compounds for liability to enhance impulsivity. Acknowledgements: USPHSGs NS074014 and DA033121, Daniel F. Ada L Rice Fdn., and the Center for Compulsive Behavior and Addiction, Rush University.

G3 UG

A COMPARISON OF HIPPOCAMPAL SUBFIELD MEASURE METHODS ABILITY TO DIAGNOSE EMCI PATIENTS

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Individuals diagnosed with amnestic mild cognitive impairment (MCI) are at high risk of developing Alzheimer's dementia (AD). Early mild cognitive impairment (EMCI), a recent designation within the Alzheimer's Disease Neuroimaging Initiative (ADNI2), describes individuals with a milder degree of memory impairment than MCI who may progress into MCI. The ability to detect neuroimaging changes in early stages of AD in a more timely and accurate manner is crucial to a greater understanding of the disease's progression. In this study, we compared classification performance between an improved hippocampal subfield measure with previously developed measures of subfields in EMCI subjects. MRI scans of normal controls (NL) and EMCI (n = 9) patients were obtained from the ADNI 2 add-on project. The hippocampus and its subfields were mapped using multi-atlas, FreeSurfer-initiated large-deformation diffeomorphic metric mapping (MA-FSLDDMM). The quality of the maps was rated on a four point quality scale: 1 being of the highest quality and 4 of the lowest. Only those scans deemed 1s and 2s were then used for statistical analysis. As a result, 66 NL and 9 EMCI subjects were included the final analysis. Hippocampal subfields boundaries were defined based on mapping of the template. For the CA1 and subiculum subfields, a previously published measure – mean subfield deformation – was calculated. A new shape measure based on principal component analysis (PCA) was also calculated. Classification was performed on subfield PC scores and mean subfield deformation values between EMCI and NL subjects using logistic regression procedures. Compared to the mean subfield deformation measures, the subfield PC scores showed better classification performance for all subfields of interest. The mean deformation model had a 0% sensitivity toward EMCI patients for all categories, while the PC scores ranged from a 77.8% sensitivity based on CA1 PC scores to a 55.6% sensitivity for subiculum PC scores. Overall, findings suggest PC scores are a better predictor for diagnosing patients with EMCI. Further analyses are needed to demonstrate and validate subfield PC shape measures as a marker for early-stage AD.

G4 UG

AUTOMATED SEGMENTATION OF MOUSE MAGNETIC RESONANCE IMAGES INTO 568 REGIONS OF INTEREST

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Manually delineating neuroanatomical structures from mouse magnetic resonance (MR) images is time-consuming, laborious, and subject to inter-rater reliability. Developing an algorithm that could automatically segment regions of interest (ROI) not only increases consistency by limiting human error but also dramatically decreases the time required. In working with Dr. Ali Khan from Simon Frasier University, we have taken his algorithm used to align human brain images and adapted it to use with mouse brain images. T1 anatomical images with 80µm resolution of were collected from five mice. The automated pipeline first removes the skull from the anatomical dataset. Then, the individual skull-stripped anatomical datasets are aligned to the common anatomical and ROI template using affine and diffeomorphic warping. The algorithm uses an iterative process to converge on the best alignment to the template image. In order to determine the volume of 568 anatomical regions, the ROI template is back projected to the subject's native space image. The segmentations are of good quality by visual inspection. An algorithm that can automatically segment ROIs would be useful for analyzing large datasets efficiently. This pipeline can be adapted to work on any species, including rabbit or human, making it applicable for research analyzing the volume of ROIs. However, the algorithm can still be used without a common template. A new template is made by averaging all of the subject images. All of the images are put into approximately the same space during the first iteration. The algorithm continues through iterations until the created template becomes steady.

G5 UG

FOURIER TRANSFORM SPECTROSCOPIC INFRARED IMAGING FOR LABEL-FREE CELL-TYPE IDENTIFICATION IN NEURAL TISSUE

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Neuropathology is the study of cell types and tissue structures in the brain. Changes in these are implicated in a number of brain disorders. In this study we set out to use a label-free chemical imaging approach called Fourier Transform Infrared (FT-IR) spectroscopy. To start the study it was necessary to distinguish various regions, layers and cell types in the brain before proposing a diagnostic tool. We addressed the utility of FT-IR spectroscopic imaging as a tool for the identification of the different cell types and tissue structures. The objective was to apply identified signatures for brain cell types and structures to gain insight into disease processes where tissue, cell types, and architecture were deregulated. We used FT-IR imaging to obtain biochemically rich spectral information from cells residing in the brain which allowed us to identify cell types and tissue structure in an entirely label-free and non-perturbing manner. Our ultimate goal is to apply this technology to identify adult neural stem cells and for the tracking of cell types as part of brain disease processes.

G6 UG

THE RAT P3 ERP IN BEHAVIORAL CHAINS AS A FUNCTION OF CUE DURATION AND CUE SEPARATION.

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The P3 Event Related Potential (ERP) is a time locked, averaged EEG to task relevant stimuli. Previous research in our laboratory has suggested that the robust P3 ERP, recorded in freely behaving rats, is a correlate of the brains recognition of a conditioned reinforcer, and a decremental function of its proximity to the primary reinforcer in backward behavioral chaining. Because many of the stimuli in behavioral chains occur in close temporal proximity, the ERPs may overlap and interfere with each other. In this paradigm, a tone cues the insertion of a lever on which the rat must meet a VR-6 schedule requirement that produces a different tone that is followed by food reinforcement. By manipulating the tone to lever insertion, and tone to pellet delivery delays, and the tone durations, we found that P3 ERP latencies moved proportionate to the delays while the P1 and P2 ERPs were unchanged. The latency of the P3 also demonstrated that the ERP was a function of stimulus onset, and relatively unaffected by stimulus offset. Normally, the click of the food dispenser and food delivery are practically simultaneous, making the separation of the P3 ERP to each difficult to isolate. Here we found that early in training the P3 ERP to the click and appearance of the food pellet gradually merge across training sessions, but are distinguishable early in training. The establishment of a robust animal model of the human P300 ERP would be an excellent tool for conducting pharmacological investigations of the substrates of the P300 ERP. Our data strongly suggest that the rat P3 ERP is the equivalent of the human P300 ERP. In humans, alterations in the P300 ERP are trait markers for schizophrenia and early onset Alzheimer's disease. Since rat models of schizophrenia and Alzheimer's disease exist, the rat P3 ERP may also be a useful tool for research on these diseases.

G7 UG

DIFFERENTIAL ABERRANT GENE EXPRESSION IN HETEROTOPIC:ORTHOTOPIC GLIOBLASTOMA MULTIFORME XENOGRAFTS AND CELL LINES USING A FOCUSED MICROARRAY APPROACH

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Glioblastoma multiforme (GBM) is the most common primary brain cancer in adults. Multimodal therapy for these tumors is currently the cornerstone of treatment but largely ineffective, as the majority of patients experience progression or recurrence. Therefore, developing an effective therapeutic strategy for patients with high-grade gliomas is desired. A growing body o f literature has focused on the molecular characterization of GBM, and recent studies have shown that identification of tumor-associated biomarkers followed by subsequent manipulation of gene expression to inhibit tumor invasivity present a novel approach to therapeutic development. In an effort to guide the choice of an appropriate model system to evaluate such an approach, these studies focused on comparing *in vivo* and *in vitro* GBM models in order to identify potential gene targets. Our work used *in vivo* heterotopic:orthotopic xenografts compared to the corresponding *in vitro* propagated cell lines from a panel of 16 heterogeneous, clinically-defined human glioblastomas. Dye-coupled aRNA was created and hybridized to oligonucleotide microarrays expressing a panel of 2,576 glioma-associated genes. Ontological analysis of the transcriptomic data to identify relevant gene families utilized GoMINER algorithms. Although a large proportion of expressed genes did not differ between the xenografts and the respective cell lines, the data identified a number of significantly differentially expressed genes that fell into defined ontological categories, including those related to the regulation of transcription and translation, glycosylation, energy metabolism, and endocytosis. Taken together, this large repository of differential gene expression data underscores the need to strategically and selectively choose appropriate GBM xenografts/cell lines for

pharmaceutical studies specifically aimed at drug development. The appropriate cell line model(s) selected must both mimic the expression of the parental tumor as well as demonstrate the desired transcriptomic profile relevant to the pharmaceutical activity tested. This study is funded by an undergraduate research grant from the Office of Undergraduate Research at Northwestern University and a grant from the Falk Foundation (Chicago, IL).

THEME H. SENSORY AND MOTOR SYSTEMS

H1

FUNCTIONAL COOPERATIVITY BETWEEN CANONICAL AND NON-CANONICAL SIGNALING PATHWAYS IN TGF-B2 MEDIATED ET-1 EXPRESSION

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Analysis of aqueous humor (AH) from patients with primary open-angle glaucoma (POAG) reveals marked and potentially pathologic increases in the content of endothelin-1 (ET-1) and transforming growth factor (TGF)-β2. Using cultured primary human trabecular meshwork (TM) cells, we previously demonstrated for the first time that TGF-β2 markedly enhances ET-1 synthesis and secretion. Here, we examined the molecular mechanisms by which TGF-β2 mediates ET-1 expression. Primary human TM cells (passages 3-5) were conditioned in serum-free media (x24h) and then incubated in the absence or presence of TGF-β2 (5 ng/ml; x24h). Human TM cells treated with TGF-β2 exhibit a marked (>15-fold) increase in ppET-1 mRNA content compared with vehicle-treated controls, as quantified by RT-PCR. Similarly, TGF-β2 elicits a marked induction of mature ET-1 peptide secretion, as quantified by ELISA. Specific inhibition of either canonical (TGFβRI/Smad) or non-canonical (Rho GTPase subfamily) signaling pathways completely prevented TGF-β2 mediated increases in ET-1 expression. To determine cooperativity between Smad and Rho GTPase signaling pathways, primary human TM cells were incubated x24h with GGTI-298 (a selective inhibitor of protein geranylgeranylation) prior to TGF-β2 treatment (x30 min). Unexpectedly, TGF-β2 mediated phosphorylation of Smad3 was significantly (40%) reduced in GGTI-298 pretreated TM cells. This suggests for the first time a novel role for Rho GTPase signaling in facilitating Smad phosphorylation. We conclude that elevated levels of TGF-β2 present in AH of POAG patients may promote aberrant ET-1 synthesis and secretion through activation of non-canonical (Rho GTPase) signaling, which promotes canonical Smad phosphorylation. This work was supported by the Department of Veterans Affairs, the Illinois Society for the Prevention of Blindness, the Midwest Eye Banks, and the Richard A. Peritt Charitable Foundation. Dept. of Veterans Affairs, Illinois Society for Prevention of Blindness, Midwest Eye-Banks.

H2 PD

EFFICIENT CODING OF VISUAL MOTION SIGNALS IN THE SMOOTH PURSUIT SYSTEM

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Performance in sensorimotor behaviors guides our understanding of many of the key computational functions of the brain: the representation of sensory information, the translation of sensory signals to commands for movement, and the production of behavior. Eye movement behaviors have become a valuable testing ground for theories of neural computation because the circuitry has been well characterized and eye movements can be tightly coupled to cortical activity. Here we show that the pursuit eye movements, and the cortical sensory signals that mediate them, demonstrate the hallmarks of efficient coding. Barlow proposed that neurons should adapt their sensitivity as stimulus conditions change in order to maintain efficient representation of sensory inputs. Evidence for efficient coding of temporal fluctuations in visual contrast has been observed in the retina. We asked whether adaptation to stimulus variance generalizes to higher cortical areas whose neurons respond to features of visual signals that do not drive adaptation in the periphery and whether such adaptation impacts performance of visually-driven behavior. We recorded eye movements of monkeys pursuing moving targets with an added stochastic perturbation. We found that the amplitude of the linear filter relating eye to target movement rescaled in proportion to target motion variance, consistent with the efficient coding hypothesis. Steps in target motion variance created a transient decrease in the information capacity of pursuit. To test whether this behavioral adaptation arises in the visual system, we recorded unit responses in middle temporal cortical area (MT). We found that MT responses echo those of pursuit: neural filters between firing rate and target motion scale with variance, the stimulus-response distribution rescales rapidly -- within 20ms of a variance change -- and some units display a rapid recovery of motion information after a step. Furthermore, these gain changes cannot be accounted for by saturation - they occur when the highest observed firing rate is below the peak firing rate of the neuron (or eye velocity), however this work does not identify a mechanism. These data suggest that feature selective cortical areas are themselves capable of efficient sensory coding and that efficiencies in cortical coding can be relevant to behavioral performance.

H3 PD

CORTICAL CATEGORIZATION AND CONTEXT OF SPEECH SOUND PRODUCTION

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Decoding of phonemes during speech production from cortical signals provides hope for restoring function to those who have lost the ability to speak. To better decode speech, we must first determine the exact cortical representation and functional dynamics during speech production. Prominent theoretical models of speech production in the literature differ in their hypothesized functional organization of speech motor cortex. Using electrocorticography (ECoG), we analyzed the spatial and temporal cortical dynamics during complex speech execution. We evaluated whether speech motor cortex has a predominantly phoneme-based (Hickok) or articulator-based (Browman & Goldstein) functional representation. Four subjects with intractable epilepsy, who required electrocorticographic monitoring prior to epilepsy surgery, participated our experiment. Subjects read words aloud presented on a screen at a rate of 1 word every 4 seconds. Words included all speech sounds used in the General American accent of English. We recorded simultaneous cortical activity (1 kHz) and speech audio (44.1kHz). For analysis, we labeled audio data according to the onset time of each speech sound, and we aligned these times to cortical data. We extracted the power in several pertinent frequency bands in sliding 150-ms bins from cortical activity to use as features for classification. We further investigated the contextual independence of these representations as they relate to speech sounds within the context of a word. We compared phoneme and articulator models by performing linear discriminant analysis (LDA) on these features, evaluating the classification success based upon speech sound and based upon motor articulator. To evaluate context-dependent vs. -independent functional representations, we performed LDA separately on each occurrence within the data set, as well as with respect to their context within a word (e.g. \k\e\t\ vs \t\e\k\). Degree of successful classification and cross-validation results using LDA determined affirmation of a tested organizational model. The highest classification results occurred using the articulator-based model. Our results support functional organization that closely mimics the articulator-based distinctions of phonology. This suggests the articulator-based model's hypothesized organization may be dominant within cortical representation. By determining the functional representation of speech motor cortex, we can better design a neural interface that accesses these control signals for speech. This work was supported in part by the Doris Duke Charitable Foundation (Grant No. 2011039) and the National Science Foundation (Grant No. 0549489 and 0718558).

H4 PD

INVESTIGATION OF THE TIMING AND EXTENT OF SENSORY NERVOUS SYSTEM DEGENERATION IN ALS

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Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of the motor neuron circuitry. However the spatial and temporal degeneration of sensory nervous system with respect to disease progression has not been studied in detail. We recently generated a novel ALS mouse model reporter line, in which corticospinal and spinal motor neurons, together with sensory neurons, are genetically labeled with enhanced green fluorescent protein (eGFP) expression under the UCHL1 promoter. This mouse model offers, for the first time, a comparative study of peripheral neurons together with motor neurons and allows investigation of the sensory nervous system involvement in motor neuron disease pathology. In this study we investigated the timing and extent of potential sensory nervous system degeneration, using one of the most characterized mouse models of ALS. Sensory neurodegeneration was studied by quantification of epidermal nerve density using eGFP+ distal peripheral nerves in the footpads of the hSOD1G93A- UeGFP mice at postnatal days (P) 30, 60, 90, and 120. Our preliminary results show a significant decrease in epidermal nerve density by P120. Similar decrease in epidermal nerve density has previously been reported in skin biopsies from ALS patients.

H5 PD

DIFFERENT ROLES OF AXON GUIDANCE CUES AND PATTERNED SPONTANEOUS ACTIVITY IN ESTABLISHING RECEPTIVE FIELDS IN THE MOUSE SUPERIOR COLLICULUS

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Visual neurons in the superior colliculus (SC) respond to both bright (On) and dark (off) stimuli in their receptive fields. This receptive field property is due to proper convergence of On- and Off- centered retinal ganglion cells to their target cells in the SC. In this study, we have compared the receptive field structure of

individual SC neurons in two lines of mutant mice that are deficient in retinotopic mapping: the ephrin-A knockouts that lack important retinocollicular axonal guidance cues and the nAChR-β2 knockouts that have altered activity-dependent refinement of retinocollicular projections. We find that even though the receptive fields are much larger in the ephrin-A knockouts, their On-Off overlap remains unchanged. These neurons also display normal level of selectivity for stimulus direction and orientation. In contrast, the On-Off overlap is disrupted in the β2 knockouts. Together with the previous finding of disrupted direction and orientation selectivity in the β2 knockout mice, our results indicate that molecular guidance cues and activity-dependent processes play different roles in the development of receptive field properties in the SC. This work was supported by US National Institutes of Health (NIH) grants (EY018621 and EY020950) and a Klingenstein Fellowship Award in Neurosciences to J.C.

H6

A NON-CANONICAL PATHWAY FROM COCHLEA TO BRAIN DETECTS TISSUE-DAMAGING NOISE AND MEDIATES AUDITORY NOCICEPTION

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Loud noise damages the cochlear organ of Corti, particularly the outer hair cells, but these are not innervated by nociceptors of somatosensory ganglia, which detect damage elsewhere in the body. The only afferents that innervate this organ are type I and II neurons of the cochlear spiral ganglion. Type I afferents exclusively innervate inner hair cells and mediate sound perception. Type II afferents send processes under the outer hair cells, but have no known function, as they do not respond to sound. We measured neuronal activity in the cochlear nucleus (where these afferents terminate) of *Vglut3*$^{-/-}$ deaf mice in which the canonical auditory pathway (inner hair cell and type I afferents) is silent and found response to harmful (i.e., that damages and kills hair cells), but not innocuous, noise. This response originates in the cochlea and not in other areas also stimulated by loud noise (middle ear and vestibule) as it was absent in mice with selective cochlear degeneration but normal vestibular and somatosensory function. Hence, an alternative pathway between cochlea and brainstem communicates tissue-damaging noise, serving a novel form of sensation we term auditory nociception. Funded by: 1F31DC012013 (ENF), R01NS044363 and R21DC006089 (JG-A).

H7 G

NEURAL SYNCHRONY IS IMPORTANT FOR LANGUAGE LEARNING: LINKS BETWEEN BEAT ENTRAINMENT AND NEURAL CONSISTENCY FOR SPEECH ENCODING IN PRESCHOOLERS

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Beat entrainment, although a seemingly simple task, places stringent demands on the temporal processing and sensorimotor integration capabilities of the auditory system. Recent work has demonstrated links between the consistency of beat entrainment, the consistency of subcortical speech encoding, and reading abilities, suggesting neural synchrony is necessary for forming stable representations of sound important for relating phonology and orthography during reading. Here, we demonstrate this relationship between beat entrainment consistency and neural consistency of speech processing for the first time in a preschool population, in children who have not yet begun to read. Given previously established links between auditory neural consistency and reading ability, we suggest consistency and integration of auditory and motor systems is crucial for language acquisition and development. These findings indicate beat entrainment abilities may serve as a behavioral marker of auditory function in preschoolers and may inform strategies for early detection of auditory-based language skills such as reading. This work was supported by the National Institutes of Health (RO1 HD069414 to NK, T32 DC009399 to KWC) and the Hugh Knowles Hearing Center of Northwestern University (to NK).

H8 G

MOLECULAR GENETICS OF PAIN IN SICKLE CELL DISEASE: ROLE OF THE MONOAMINE SYSTEM

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Pain is a hallmark symptom of sickle cell disease (SCD) that is characterized by the presence of both acute and chronic pain. Since effective pain control in SCD is suboptimal while pain severity and frequency is heterogeneous, identifying genetic variation may elucidate pain variation and aid in new therapeutic advances and management. We employ pathway libraries and data mining to identify genetic variants within the monoamine system. Candidate gene polymorphisms such as single nucleotide polymorphisms, copy number variation, and variable number tandem repeats are captured within monoamine receptor, transporter, and enzyme genes. A systems biology approach is taken to understand the interrelatedness of genetic variation within this system. Adult and pediatric sickle cell patients have been

recruited during routine outpatient clinic visits where blood and buccal samples were collected for DNA extraction and genotyping. Association studies are performed for candidate gene polymorphisms by using phenotype data gathered from PAINReportIt®, a pain assessment tool. Composite pain index (CPI) score is a marker for baseline pain and represents the multidimensional pain experience. Utilization is defined as admissions to the emergency department and/or the acute care center resulting from a sickle cell pain crisis and is a surrogate marker for acute pain in SCD. *In vitro* studies are utilized to validate association analyses. Variants in the monoamine system have been identified to associate with utilization in our patient population such as rs4680 (catechol-O-methyl transferase) and rs6280 (dopamine receptor D3). A SNP in the tyrosine hydroxylase gene has been associated with CPI. In addition, several other pain markers have been identified in the monoamine system and we predict that the contribution of several subtle effects of each variant will play a cumulative role in this complex disease phenotype.

H9 G

KAINATE RECEPTOR COMPOSITION IN SENSORY NEURONS

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Kainate receptors (KARs), one of three families of ionotropic glutamate receptors, are expressed throughout the peripheral and central nervous system, including in those pathways comprising the pain neuraxis. Both human and animal studies support a role for KARs, and in particular GluK1-containing receptors, in the mediation of aggravated pain rather than acute pain. KARs are expressed in dorsal root ganglion (DRG) neurons, and in the spinal dorsal horn neurons that comprise the targets of DRG innervation. In DRG, KARs are expressed predominantly in IB4-positive C-fiber nociceptors and serve at least two functions: (i) peripheral chemosensing and (ii) presynaptic modulation of glutamate release from afferent terminals in the dorsal horn of the spinal cord. We hypothesize that KAR auxiliary subunits impact the aforementioned receptor functions in peripheral sensory neurons by functionally assembling into DRG KARs. Recently, the auxiliary subunits neuropilin and tolloid-like 1 (Neto1) and Neto2 were shown to profoundly modulate recombinant and endogenous KARs in receptor subunit- and Neto isoform-dependent fashions, and therefore could be important but poorly characterized constituents of KAR function in sensory pathways. We find that KAR kinetics are altered in Neto2-null DRG neurons, suggesting functional assembly of Neto2 with native receptors in peripheral sensory neurons. Additionally, deletion of Neto2 reveals KAR kinetics similar to heteromeric receptors containing GluK1 and GluK5, an interpretation consistent with changes we find in receptor kinetics in GluK5-null DRG neurons. Interestingly, adult DRG neurons have KAR kinetics distinct from neonatal DRG neurons but incorporate Neto2 into KARs over time in culture. Despite the demonstrated importance of GluK1 in formalin-induced spontaneous pain and hypersensitivity, we find these pain modalities to be unaffected by genetic deletion of Neto proteins and are investigating the role of Neto in other pain behaviors. Elucidation of how Neto proteins shape KAR function in sensory signaling pathways is key for developing a clear mechanistic understanding of the relevance of KARs to sensory transmission and their potential utility as therapeutic targets. Supported by NINDS.

H10 UG

TWO ODOR RECEPTORS CONTRIBUTE COMPLEX AND DISTINCT SIGNALS THAT UNDERLIE ODOR CODING IN *DROSOPHILA* LARVAE

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A prominent question in the study of olfaction is how a repertoire of odor receptors allows detection and discrimination of odors. We used electrophysiological responses of *Drosophila* larval odor receptors to test predictions of behavior, with the hypothesis that strongly activating odors are salient for behavior. We tested behavioral responses to odors that strongly activate two odor receptors, *Or42a* and *Or42b*, using mutants of these respective odor receptors. We found odor receptor activity to be modestly predictive of behavior, and we suggest that odor coding is weakly combinatorial, where some odor receptors are differentially weighted. We also tested three odors that are weak activators of *Or42a* and *Or42b*. We found that the *Or42b* mutant had unaltered responses to these odors as expected. However, the *Or42a* mutant showed reduced attraction to these three weakly activating odors. One explanation for these data is that modest odor receptor responses are important for gain control of the neuronal circuits. A second type of test included a behavioral arena that was divided into four concentric circle regions. The results of these tests indicated that some mutants are unable to smell some odors, rather than being repelled by the odors. Finally, we found that robust and heritable differences in behavioral responses to ethyl acetate between wild type strains are not explainable by clear polymorphisms in either the coding regions of *Or42a* or *Or42b*. Taken together, our data indicate the existence of complex odor coding mechanisms in the numerically simple *Drosophila* larval olfactory system. Supported Dominican Universite.

H11 UG

MAPPING A HEDONIC HOTSPOT IN INSULAR CORTEX

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Insular cortex has been implicated in a wide array of functions, including integrating multiple sensory modalities, coding disgust for unpleasant foods, and processing reward and motivation. Specifically, anterior insula appears to be involved in mediating disgust while posterior insula may produce positive affect and may code for palatable food reward, such as sucrose. The current known regional functions within insular cortex support the prediction of a hedonic hotspot and coldspot in anatomically localized areas. To determine whether such pleasure/displeasure-generating zones actually exist in the region, we selectively stimulated anterior and posterior regions within insular cortex with DAMGO (mu-opioid agonist) or orexin-A, a peptide that is only produced in lateral hypothalamus. Posterior insular stimulation with either agonist amplified “liking” reactions to sucrose by two-fold. In contrast, preliminary results from anterior insula stimulation with DAMGO or orexin shows suppressed “liking” of sucrose. Taken together, these results support the discovery of a hedonic hotspot in posterior insula, and a potential hedonic coldspot in anterior insula. These results provide the first direct evidence for any cortical region amplifying or suppressing pleasure, and have important evolutionary implications on social and economic rewards in humans. This research was supported by National Institutes of Health grants (MH63649 and DA015188).

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