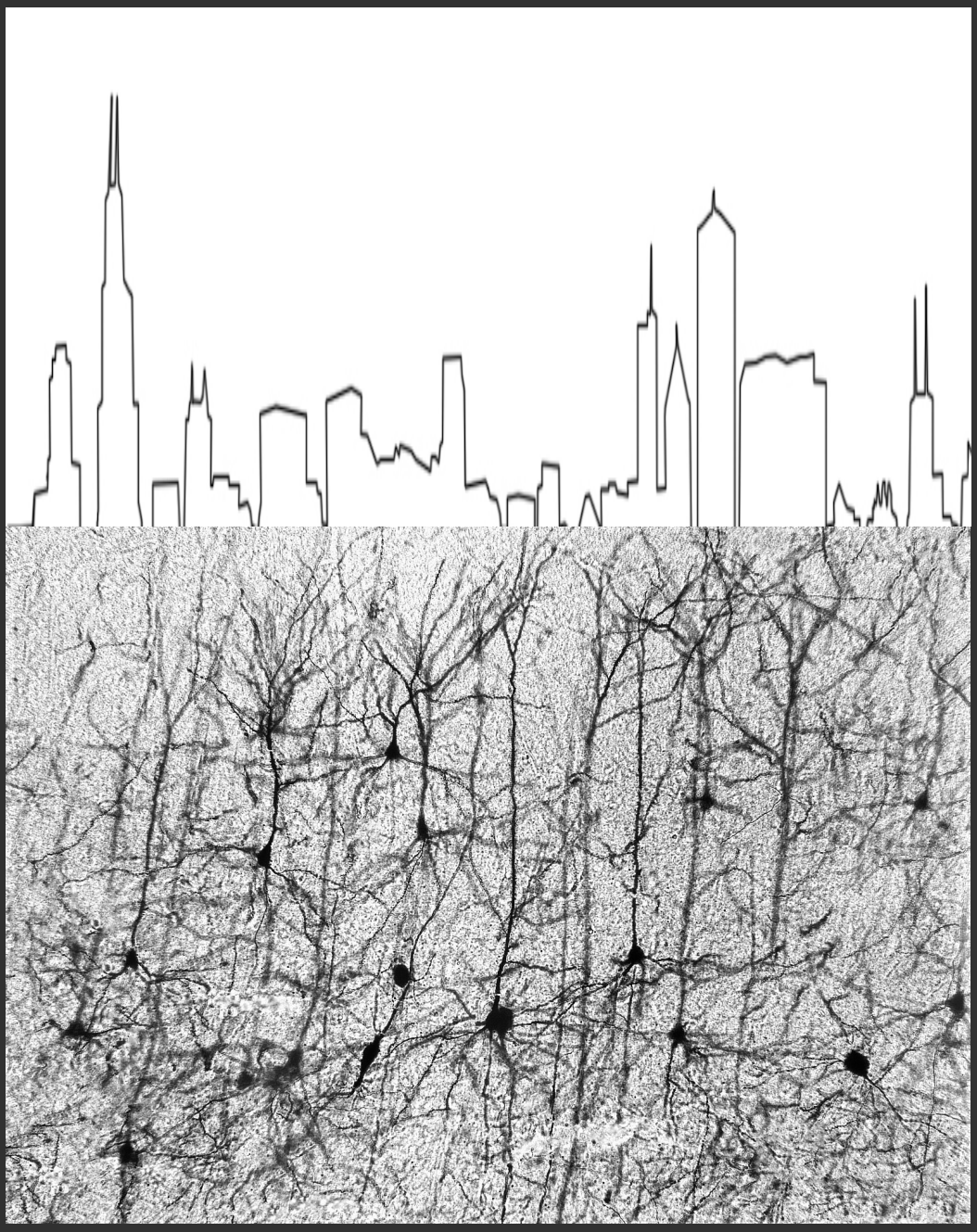
Chicago Chapter of the Society for Neuroscience 2015 Scientific Meeting



Friday, March 20th, 2015

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 SfN

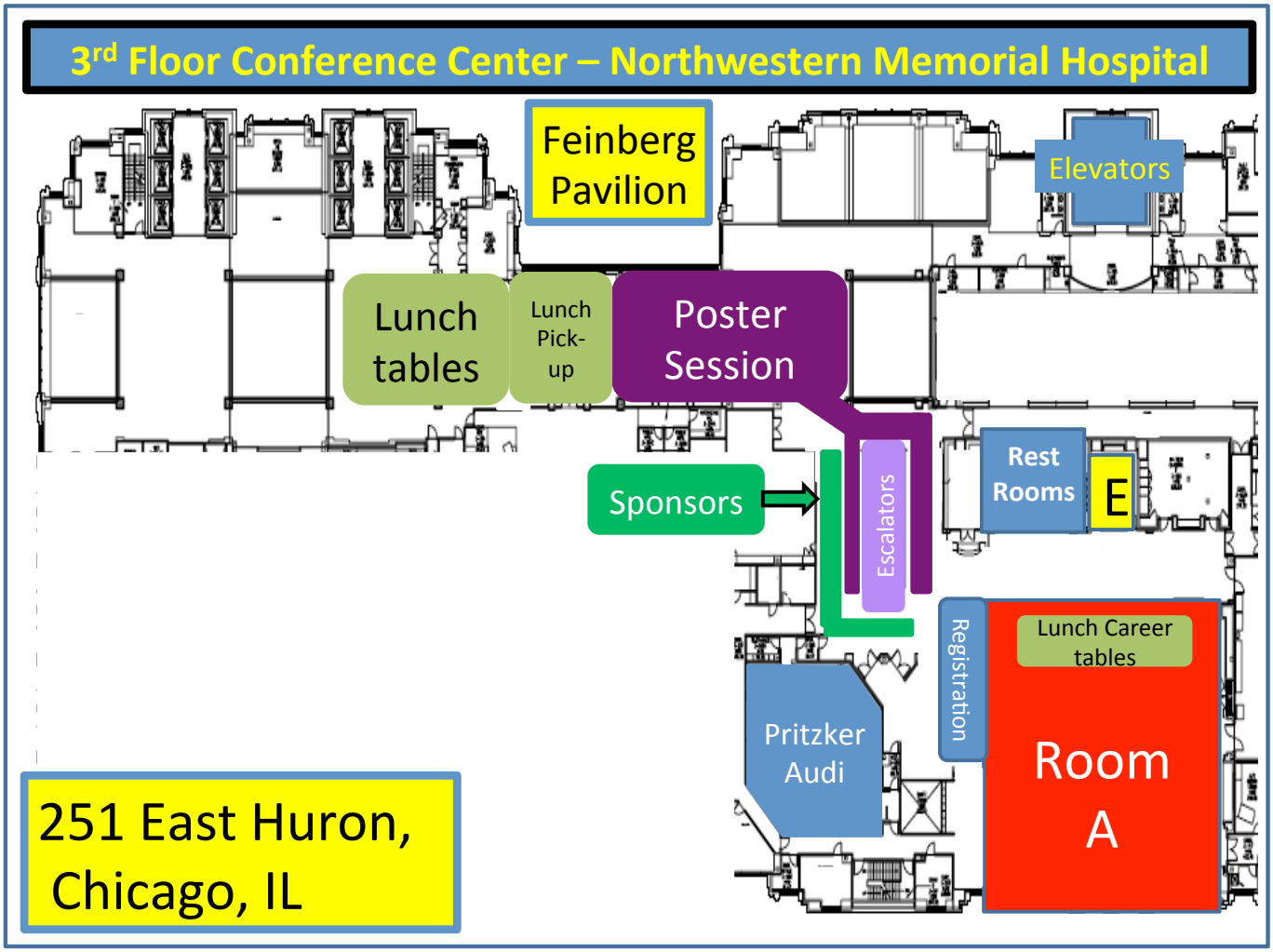
Atrium, 3rd floor

- **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 today.**
- **Vote for next year's Chicago Chapter SfN 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: Brightfield image of Golgi stained neurons in the cerebral cortex of a rat. Photomicrograph taken by Maria Bompolaki working with Dr. Janice H. Urban (Rosalind Franklin University of Medicine and Science, Department of Physiology and Biophysics).


3rd Floor Conference Center – Northwestern Memorial Hospital
Feinberg Pavilion
Elevators
Lunch tables
Lunch Pick-up
Poster Session
Sponsors
Escalators
Rest Rooms
E
Registration
Lunch Career tables
Pritzker Audi
Room A
251 East Huron, Chicago, IL

2015 CSfN Keynote Speaker

Joshua Sanes, Ph.D.

Paul J. Finnegan Family Director, Center of Brain Science, Harvard University

Dr. Joshua Sanes studies the formation of synapses, the connections that transmit information between nerve cells. For many years, he used the neuromuscular junction to elucidate the intercellular communication systems that lead to formation and maturation of the synapse. More recently, he has focused on how specific connections form in the visual system to generate the complex circuits that underlie the processing of information. He and his colleagues have also pioneered new ways to mark and manipulate neurons and the synapses they form. Their work has been published in over 350 papers. Dr. Sanes received a BA from Yale and a PhD from Harvard. He served on the faculty of Washington University for over 20 years, before returning to Harvard in 2004 as Professor of Molecular and Cellular Biology and founding Director of the Center for Brain Science. He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He has served on the editorial board of several scientific journals, including Cell and Neuron; as a member of the Board of Scientific Counselors and the National Advisory Council of the National Institute of Neurological Diseases and Stroke (NIH), the Council of the Society for Neuroscience, and the NIH planning committee for the BRAIN Initiative; and on advisory panels for the Max-Planck Institute, Wellcome Trust, National Academy of Sciences, Howard Hughes Medical Institute and NIH.

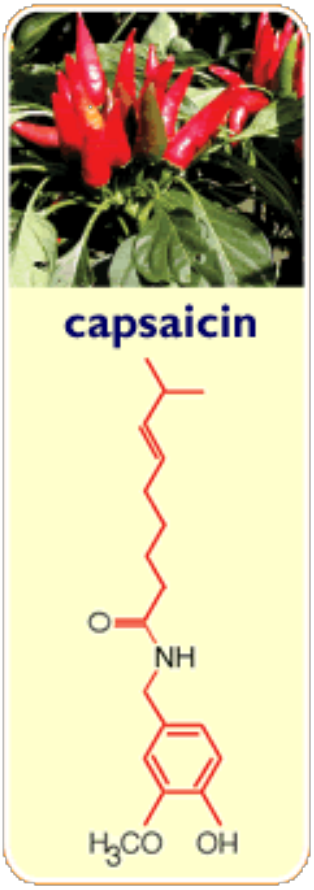
Save the Date – April 8, 2016
Chicago SFN Annual Meeting

Keynote Speaker:

DAVID JULIUS Ph.D.

Professor and Chair, Department of Physiology
University of California-San Francisco

http://physio.ucsf.edu/julius/

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BIOSCIENCE


Cellular
Dynamics
international


IDT
INTEGRATED DNA TECHNOLOGIES


SUTTER INSTRUMENT

INDEX

Chicago Society for Neuroscience
2015 Career Achievement in Neuroscience Award

Celeste Napier, Ph.D.

Dr. Napier has dedicated her academic career to making outstanding contributions to neuroscience education, the advancement of neuroscience research, and public communication and outreach in the greater Chicago community and beyond. Dr. Napier is a Professor in the Department of Pharmacology at Rush University and the Director of both the Center for Compulsive Behaviors and Addiction and HIV/AIDS Substance Use Disorders CoMorbidity Scientific Working Group. Her research on the reward system, drug abuse and its interaction with disorders such as Parkinsons disease and HIV have resulted in over a hundred publications and support from the NIH and Michael J. Fox Foundation. She is a media expert on the neuroscience of addiction and has provided her expertise to local and national organizations focused on drug abuse prevention. She has mentored dozens of undergraduate and graduate students and post-doctoral fellows, many of whom received prestigious grants and awards. She has served as both the secretary and the president of the Chicago Society for Neuroscience (1993-1997) as well. Dr. Napier has been an asset to the Neuroscience community in Chicago and we are pleased to honor her with this inaugural award.

Schedule of Events

7:30-10:00 AM	**Registration/Continental Breakfast**	**3rd floor**
8:00-8:40 AM	**Mentoring Panel** (with Keynote Speaker and Presidential Symposium Speakers)	***Pritzker Auditorium***
	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***
9:00-9:15 AM	**2015 Chicago Career Achievement in Neuroscience Award** Presented by Dr. Shubhik DebBurman & Dr. Dorothy Kozlowski	***Room A***
9:15-11:00 AM	**Presidential Symposium (Presented by Takeda)** ***"Synaptic and Circuit Dysfunction in Brain Diseases"*** Chaired by Dr. Shubhik DebBurman	***Room A***
11:00-12:00 PM	**Keynote Lecture** **Assembling Neural Circuits in the Retina** Joshua Sanes, Ph.D., Harvard University	***Room A***
	Lunch Break	
12:00-2:00 PM	Poster Competitions Viewing/Judging Presidential Symposium Speakers Table	***Atrium, 3rd floor***
12:15-1:15 PM	Dr. Sanes and Graduate Student Symposium participants lunch	***Room E***
12:30-1:30 PM	**Themed Lunch Tables: *"Diversity in Careers"***	***Room A***
12:00-4:00 PM	**Chicago Public Schools Teachers Workshop**	**Diebold Building**
2:00- 3:45 PM	**Plenary Afternoon Symposium** ***"Neural Circuits and Behavior"*** Chaired by Drs. Shreaya Chakroborty and Michelle Hastings	***Room A***
4:00- 5:45 PM	**Graduate Student Symposium** Selected Graduate Student Talks Chaired by Drs. Monsheel Sodhi and Sara Weisenbach	***Room A***
6:00-7:00 PM	**Reception and Business Meeting** Announcement of awards, recognition and election results immediately followed by Social Meeting	***Atrium, Room A***

Morning Program

Mentoring Panel — *Pritzker Audi*

8:00-8:40 AM Breakfast and discussion with Keynote and Presidential Symposium Speakers
Moderated by Drs. Sarah London and Dr. Dan Nicholson

2015 Chicago Career Achievement in Neuroscience Award — *Room A*

9:00-9:15 AM Inaugural Recipient: Dr. T. Celeste Napier, Rush University
Presented by Dr. Shubhik DebBurman & Dr. Dorothy Kozlowski

Presidential Symposium (Presented by Takeda) — *Room A*

9:15-9:30 *Welcoming Remarks by* Dr. Shubhik DebBurman

"Synaptic and Circuit Dysfunction in Brain Diseases"
(For abstracts, see page 24)

9:30-10:00 **PSA**
Brain Wiring and Brain Disorders
Mriganka Sur, Ph.D.
Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, M.I.T.

10:00-10:30 **PSB**
Receptors, Synapses and Memories
Richard Huganir, Ph.D.
Professor and Director, Solomon H. Snyder Department of Neuroscience
Johns Hopkins University School of Medicine and H.H.M.I.

10:30-11:00 **PSC**
Developing Disease Modifying Therapies for Fragile X Syndrome and Autism
Mark Bear, Ph.D.
Picower Professor of Neuroscience
M.I.T. and H.H.M.I.

Keynote Lecture (For abstracts, see page 24) — *Room A*

11:00-12:00 **Assembling Neural Circuits in the Retina**
Joshua Sanes, Ph.D.
Paul J. Finnegan Family Director, Center for Brain Science,
Harvard University

Lunch Break

12:00-2:00 **Poster Viewing and Competitions** ***Atrium***

12:15-2:00 Authors in **Post-doctoral Poster Competition** present.
Post-doctoral Poster Competition chaired by **Irina Calin-Jageman, Ph.D.,** Dominican University

12:15-2:00 Authors in **Graduate Student Poster Competition** present.
Graduate Poster Competition chaired by **Hongkyun Kim, Ph.D.,** Rosalind Franklin University

12:15-2:00 Authors in **Undergraduate Student Poster Competition** present.
Undergraduate Poster Competition chaired by **Naomi Wentworth, Ph.D.,** Lake Forest College

For poster titles and abstracts, go to pages 30 and 41 respectively.

Themed Lunch Tables (open to all Trainees) ***Room A***

12:30-1:30 ***"Diversity in Careers": Know more about your professional options***

Table 1 ***Teaching/Research***

Maureen Rutherford, Ph.D.
Adjunct Faculty, Indiana University Northwest,
Ernesto Bongarzone, Ph.D.
Associate Professor, Dept. of Anatomy and Cell Biology, College of Medicine, University of Illinois Chicago

Table 2 ***Corporate***

Lynne Rueter, Ph.D.
Associate Director, Neuroscience Discovery Research, Abbvie
Jackie Kunzler, MBA, Ph.D.,DABT
Vice-President, Quality Compliance and Integration, Baxter Healthcare Corp.
Silvia Skripkauskas, RN, MPPA, CCRC
Senior Project Manager, Health Economics and Outcomes Research Group, US Medical Affairs, Takeda

Table 3 ***Research Associations and Consulting***

Keith Fargo, Ph.D.
Director of Scientific Programs and Outreach, Alzheimer's Association
Marina Damiano, Ph.D.
Scientific Communications Specialist, HDM/Zoomedia (HDMZ)

Table 4 ***Administration and Law***

Jessica Lewis, Ph.D., J.D.
Attorney-Intellectual Property, Quarles & Brady LLP
Rekha Hanu, Ph.D., J.D.
Counsel-Intellectual Property, Akorn Pharmaceuticals
Jeffrey Masters, Ph.D.
Sr. Director Corporate Partnership and Business Development, Feinberg School of Medicine, Northwestern University

Chicago Public Schools Teachers Workshop — *Weiboldt Hall*

Co-sponsored by NUBAO Graduate Student Association

12:00-1:30 **Lunch-&-Learn Seminar with Kali Woodruff Carr**
"***Rhythm: A Window into Auditory and Language Processing in the Brain"***
Department of Communication Sciences and Disorders, Northwestern University

1:30-4:30 **Pedagogical Workshop**

Plenary Afternoon Symposium (For abstracts, see page 25) — *Room A*

"Neuronal Circuits and Behavior"

2:00-2:05 **Introduction**
Shreaya Chakroborty, Postdoctoral Fellow, Rosalind Franklin University

2:10-2:35 **HELPING ANOTHER IN DISTRESS: WHAT WE CAN LEARN FROM RATS**
PAS1 Peggy Mason, Ph.D.
Department of Neurobiology, University of Chicago, Chicago, IL

2:35-3:00 **FEAR REGULATION WITHIN THE EXTENDED HIPPOCAMPAL CIRCUIT**
PAS2 Jelena Radulovic, M.D., Ph.D.
Dunbar Professor of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University

3:00-3:25 **NEUROPATHOPHYSIOLOGY OF HIV/AIDS WITH SUBSTANCE USE DISORDERS**
PAS3 T. Celeste Napier, Ph.D.
Director, Center for Compulsive Behavior and Addiction, Professor, Departments of Pharmacology and Psychiatry, Rush University Medical Center, Chicago, Illinois

3:25-3:50 **COGNITION AND BRAIN FUNCTION IN HIV-INFECTED WOMEN**
PAS4 Pauline M. Maki, Ph.D.
Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, IL.

Graduate Student Symposium (For abstracts, see page 27) — *Room A*

Chaired by Drs. Monsheel Sodhi and Sara Weisenbach, University of Illinois, Chicago

4:00-4:15 **TEMPERATURE REPRESENTATION IN THE *DROSOPHILA* BRAIN**
GS1 **Dominic D. Frank**
Department of Neurobiology, Northwestern University, Evanston, Illinois
Advisor – Dr. Marco Gallio

4:15-4:30 **ESTRADIOL ENHANCES ETHANOL CONDITIONED PLACE PREFERENCE IN FEMALE C57BL/6J MICE THROUGH ACTIONS AT ERα**

GS2 **Elisa R. Hilderbrand**
Department of Psychiatry, Graduate Program in Neuroscience, University of Illinois at Chicago, Chicago, IL
Advisor – Dr. Amy Lasek

4:30-4:45 **LOSS OF CIRCULATING ESTROGEN RESULTS IN ALTERED KINASE STATUS IN THE BRAIN OF AGED FEMALE RATS**

GS3 **Elena Pinceti**
Loyola University Chicago, Stritch School of Medicine, Department of Cell and Molecular Physiology, Chicago, IL
Advisor – Dr. Toni Pak

4:45-5:00 **THE EFFECT OF PRAMIPEXOLE ON DOPAMINE-ASSOCIATED BEHAVIORS AND SIGNALING MECHANISMS IN A RAT MODEL OF PARKINSON'S DISEASE**

GS4 **Stephanie Tedford**
Dept. of Pharmacology, *Dept. of Psychology, [3]Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL*
Advisors – Dr. T. Celeste Napier

5:00-5:15 **MATURATION OF THE PREFRONTAL CORTICAL GABAERGIC SYSTEM DURING ADOLESCENCE: ROLE OF NMDA RECEPTORS**

GS5 **Daniel R. Thomases**
Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, North Chicago, IL
Advisor – Dr. Kuei-Yuan Tseng

5:15-5:30 **OPIOID MODULATION OF RESPONSES TO SOCIAL REJECTION IN HUMANS**

GS6 **Anya K. Bershad**
Interdisciplinary Scientist Training Program, University of Chicago, Chicago, IL; Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL
Advisors – Harriet de Wit

Business Meeting and Social — *Atrium, Room A*

6:00-7:00 **Wine and Cheese Social ("EtOH Receptor Binding Study")**

Election Results

Recognition of Councilors

Recognition of Chicago area students and student organizations that CSfN annually supports for excellence in neuroscience education and outreach

2015 Chicago Brain Bee winners
2015 Lake Forest College Neuroscience Student Organization SYNAPSE
2015 Northwestern University Brain Awareness Organization (NUBAO)

Announcement of prize winners

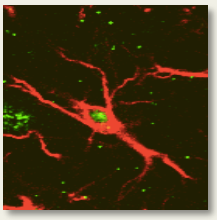
Undergraduate Student Poster Competition
Presented by Dr. Naomi Wentworth, Lake Forest College

Graduate Student Poster Competition
Presented by Dr. Hongkyun Kim, Rosalind Franklin University

Post-doctoral Fellow Poster Competition
Presented by Dr. Irina Calin-Jageman, Dominical University

Graduate Student Symposium
Presented by Drs. Monsheel Sodhi and Sara Weisenbach, University of Illinois at Chicago

Announcing the Call for 2016 CSfN Meeting (April 8)



Loyola University Chicago Stritch School of Medicine Neuroscience Research Institute & Graduate Program

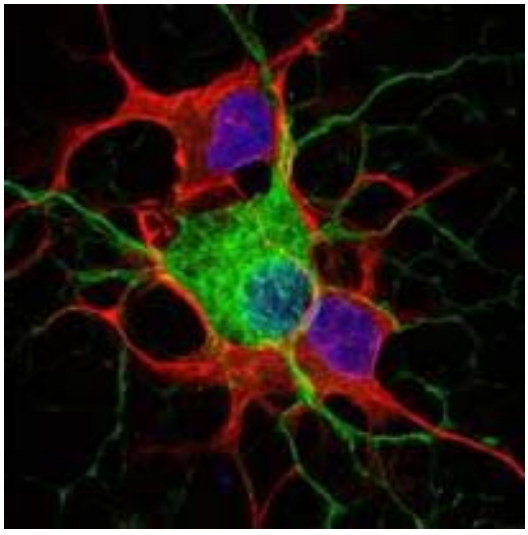
Hands-On Training Opportunities in…

- *Behavioral neuroscience*
- *Biochemistry*
- *Chemistry*
- *Cellular and Molecular Neurobiology*
- *Neuropharmacology*
- *Neuroimmunology*
- *Autoimmune Diseases*
- *Neuroendocrinology*
- *Regeneration and Repair*
- *Stroke*
- *Traumatic Brain Injury*
- *Central and Peripheral Neuropathies*

Neuroscience is one of the most exciting and challenging "frontiers" of the biomedical sciences. The *Neuroscience Program* at Loyola encompasses a vast interdisciplinary track where students are provided with hands-on opportunities to develop and contribute to this rapidly expanding discipline. The student who chooses to join our neuroscience academic community will have options available to them for advanced training in a diverse array of disciplines.

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

Neuroscience Institute Director
Wendy Kartje, M.D., Ph.D.
Wkartje@luc.edu
http://www.stritch.luc.edu/nsi/



RUSH UNIVERSITY

DEPAUL UNIVERSITY

NORTHWESTERN UNIVERSITY


THE UNIVERSITY OF
CHICAGO


FOUNDED
1901
DOMINICAN UNIVERSITY
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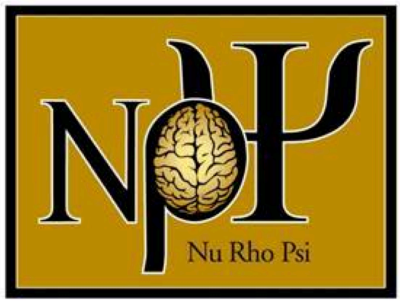
UIC
UNIVERSITY
OF ILLINOIS
AT CHICAGO



***Nu Rho Psi* is the National Honor Society in Neuroscience. Founded in 2006, we now have almost 50 chapters and over 2300 members nationwide. We are an independent non-profit, grass-roots organization comprised of neuroscientists, like you.**

The purpose of *Nu Rho Psi* is to:
(1) encourage professional interest and excellence in scholarship, particularly in Neuroscience;
(2) award recognition to students who have achieved such excellence in scholarship;
(3) advance the discipline of Neuroscience;
(4) encourage intellectual and social interaction between students, faculty, and professionals in Neuroscience and related fields;
(5) promote career development in Neuroscience and related fields;
(6) increase public awareness of Neuroscience and its benefits for individuals and society;
(7) encourage service to the community.

Start a chapter of *Nu Rho Psi* at your College or University:
Colleges or universities with undergraduate neuroscience programs, majors, minors, tracks, or concentrations are encouraged to shelter a chapter of *Nu Rho Psi*. Alternatively, colleges or universities that are geographically close to one another may choose to apply for a charter as a Cooperative Chapter consisting of members from more than one school.

For more information, go to: http://www.nurhopsi.org
Email: nurhopsi@bw.edu

ABSTRACTS

KEYNOTE LECTURE

ASSEMBLING NEURAL CIRCUITS IN THE RETINA

Joshua R. Sanes, PhD

Paul J. Finnegan Family Director, Center for Brain Science, Harvard University

The retina is by no means a camera; instead it processes visual images in complex ways and sends information about salient features to the brain so that decisions can be made and actions taken. In the rodent retina, visual information is passed from retinal photoreceptors to ~70 types of interneurons. The interneurons process the raw image and send it to ~30 types of retinal ganglion cells (RGCs), which in turn send it to the rest of the brain. Each of the RGC types responds selectively to a visual feature—for example motion in a particular direction—based on which interneuronal types synapse on it. As these circuits develop, the processes of these ~100 neuronal types meet in a narrow synaptic layer, the where they form stereotyped and specific patterns of connectivity that underlie visual function. We have therefore sought molecules that mark interneuronal and RGC subtypes and specify the synaptic choices they make. Candidates recognition molecules include, among others, members of the immunoglobulin and cadherin superfamilies. I will describe a combined genetic, morphological and physiological approach for analyzing roles these proteins play in wiring up the retina.

TAKEDA PRESIDENTIAL SYMPOSIUM

SYNAPTIC AND CIRCUIT DYSFUNCTION IN BRAIN DISEASES

PSA
BRAIN WIRING AND BRAIN DISORDERS

Mriganka Sur, PhD, FRS

Newton Professor of Neuroscience; Director, Simons Center for the Social Brain, Massachusetts Institute of Technology, Cambridge, MA

The human brain has 100 billion neurons or brain cells organized into discrete processing systems. Each neuron connects with hundreds of other neurons via thousands of connections or synapses. Yet neurons do not connect indiscriminately: synaptic connections between specific sets of neurons create specific pathways and circuits that enable the brain's remarkable information processing capabilities and give rise to cognition. Such specificity arises during brain development, and is sharpened by plasticity and learning. Brain disorders have their roots in brain wiring. New technologies are transforming our understanding of genes and circuits that mediate brain development and function. Studies from our laboratory of Rett Syndrome, a devastating disorder of brain development, reveals how a single gene mutation alters critical signaling mechanisms that affect synapses, neurons and circuits, and how pharmacological interventions that restore these signals have the potential to correct the disorder.

PSB
ENCODING MEMORIES IN THE BRAIN

Richard L. Huganir, PhD

Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore MD

Neurotransmitter receptors mediate signal transduction at synaptic connections between neurons in the brain. We have been studying the regulation of glutamate receptors, the major excitatory receptors in the central nervous system. Studies in our laboratory have found that glutamate receptors are multiply phosphorylated by a variety of protein kinases. Phosphorylation regulates several properties of these receptors including ion channel properties and membrane targeting. Research in our lab has demonstrated that phosphorylation of glutamate receptors are required for the expression of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), and is critical for several forms of learning and memory. We have also identified a variety of proteins, including the PDZ-domain containing proteins GRIP1/2, PICK1, KIBRA and SynGAP that directly or indirectly interact with glutamate receptors and are necessary for their proper subcellular trafficking. We have shown that this PDZ-domain based complex is critical for several forms of synaptic plasticity and learning and memory. These studies indicate that the modulation of receptor function is a major mechanism for the regulation of synaptic transmission and is a critical determinant of animal behavior. Importantly, recent evidence has implicated the mis-regulation of glutamate receptors in several neuropsychiatric disorders including Alzheimer's disease, intellectual disability, schizophrenia and autism.

PSC

DEVELOPING DISEASE MODIFYING THERAPIES FOR FRAGILE X SYNDROME AND AUTISM

Mark Bear, PhD

Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Howard Hughes Medical Institute and Massachusetts Institute of Technology

Fragile X is caused by transcriptional silencing of the FMR1 gene that encodes FMRP, a repressor of mRNA translation at many synapses. A major regulator of synaptic protein synthesis is metabotropic glutamate receptor 5 (mGluR5), and research in animals has shown that several consequences of mGluR5 activation are exaggerated in the absence of FMRP. These findings led to development of the "mGluR theory", which posits that multiple neurological and psychiatric manifestations of fragile X are a consequence of exaggerated protein synthesis downstream of glutamate signaling. Over the past ten years this theory has been validated in multiple studies using diverse approaches and animal models of fragile X: Many mutant phenotypes can be corrected by inhibition of glutamate signaling at mGluR5. Furthermore, there is growing evidence that synaptic regulation of protein synthesis is disrupted in several other genetically defined diseases that cause autism and intellectual disability. Although human clinical trials to date have failed to hit primary endpoints, there remains considerable optimism amongst scientists and clinicians alike that disease-modifying therapies are feasible in humans with fragile X and related disorders.

PLENARY AFTERNOON SYMPOSIUM

NEURAL CIRCUITS & BEHAVIOR

PAS1
HELPING ANOTHER IN DISTRESS: WHAT WE CAN LEARN FROM RATS

P. Mason, PhD

Department of Neurobiology, University of Chicago, Chicago, IL

Empathy is a fundamental building block of pro-social behavior that promotes social cohesion and has evolved in social mammals. Empathic concern is an other-oriented emotional response to another's distress and is the antecedent to helping. For empathic concern to drive pro-social behavior, separation of the self from the other is needed so that the helper feels *for* rather than *as* the other. We recently established an animal model of empathic helping behavior: a free rat learns to deliberately liberate a cagemate trapped within a restrainer and does so even when immediate social interaction is denied. Rats value liberating a cagemate on a par with accessing highly palatable food (chocolate). As long as they have lived with one individual of a given strain of rat, rats help strangers and familiars of that strain. Remarkably, rats that are raised without ever seeing or interacting with another rat of their own biological strain will not help a rat of their own type. In sum, our findings demonstrate that empathic helping is biologically-driven as well as constrained by experiences.

PAS2
FEAR REGULATION WITHIN THE EXTENDED HIPPOCAMPAL CIRCUIT

Jelena Radulovic, MD, PhD

Dunbar Professor of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University

Environmental contexts associated with stressful experiences often give rise to fear-inducing memories that can be modified by social factors. It is generally agreed that the formation of such memories requires hippocampal and cortical activity, but the role of subcortical areas is not well understood. The lateral septum is one of the main subcortical targets of hippocampal projections implicated in fear and anxiety. We therefore explored the possibility that septal mechanisms contribute to the formation and modulation of fear-inducing context memories. Focusing on the oxytocin system, we found a significant role of oxytocin receptors (Oxtr) that was not direct but that was realized through the formation of social memories. Specifically, Oxtr enhanced and diminished context fear conditioning by strengthening memories of negative and positive social interactions, respectively. The bidirectional effect of Oxtr was thus independent of the valence of social interactions, but it entailed strengthening of the social memory. These findings confirm the role of the lateral septum as a brain area that mediates both the formation of social memories and their effects on context fear.

PSA3

NEUROPATHOPHYSIOLOGY OF HIV/AIDS WITH SUBSTANCE USE DISORDERS

T. Celeste Napier, PhD

Center for Compulsive Behavior and Addiction, Departments of Pharmacology and Psychiatry, Rush University Medical Center, Chicago, IL

Impulsivity and risk-taking are often initial motivators for abusing drugs; these traits are also associated with the tendency to engage in unprotected sexual activity. Accordingly, drug abuse is a risk factor for becoming infected with HIV. The co-morbid condition presents an augmented neuropathological profile, as well as increased morbidity and mortality over that seen in either drug abuse or HIV infection alone. Our laboratory is interested in determining how psychostimulant abuse alters the neuropathological profile of HIV-1 neurotoxic proteins. Our focus is on brain systems that regulate reward-mediated behaviors and are dysregulated in both drug abuse and in neuroAIDS. These include pyramidal neurons in the medial prefrontal cortex (mPFC-PN) and their primary target, medium spiny neurons in the nucleus accumbens core (NAc-MSN). To capture in rats aspects of the enduring maladaptations that occur drug-abusing humans even after withdrawal, we use chronic self-administration protocols followed by forced abstinence. In cocaine self-administering Sprague Dawley rats, the ability of the HIV-1 neurotoxic protein, Tat, to activate mPFC-PN was enhanced to the extent of inducing a pathological, over-activated state. To better reflect the orchestration of chronic exposure to multiple HIV-1 toxic proteins, we also evaluated HIV-1 transgenic Fischer 344 (Tg) rats, which are non-infectious, but express 7 of 9 known HIV-1 neurotoxic proteins throughout their life. In these rats, basal excitability of both mPFC-PN and NAc-MSN was elevated, and cocaine self-administration exacerbated this effect. The co-morbid pathophysiology suggested a common site of maladaptation for cocaine and HIV-1 proteins. L-type Ca^{2+} channels are key players in neuronal excitability, and they are upregulated with chronic cocaine. Accordingly, we determined that (i) expression of a pore forming L-type channel protein was increased in mPFC-PN by Tat, in both mPFC-PN and NAc-MSN in HIV-1 Tg rats, and (ii) pharmacological antagonism of these channels with diltiazam largely normalized neuronal function. Thus, L-channels may contribute to the neuropathophysiology associated with cocaine addiction in HIV/AIDS, and may provide a therapeutic target for treating the co-morbidity. This work was supported by USPHSGs DA033206, DA026746, DA033882 and P30AI082151 (the Chicago D-CFAR), and the Rush University Center for Compulsive Behavior and Addiction.

PAS4

COGNITION AND BRAIN FUNCTION IN HIV-INFECTED WOMEN

Pauline M. Maki, PhD

Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, IL

The introduction of antiretroviral therapy has reduced the most severe form of HIV-associated dementia and has greatly enhanced the health and longevity of individuals living with HIV. However, it is estimated that 40% of individuals living with HIV continue to experience more mild forms of cognitive impairment, even with successful viral suppression. Worldwide, 50% of HIV cases are in women, and in the United States, women make up approximately 24% of cases. Very few studies have adequate numbers of women to sufficiently address questions about determinants, patterns, and mechanisms of cognitive impairment in HIV-infected women. Compared to HIV-infected men who have sex with men, HIV-infected women may be at greater risk for cognitive decline due to poverty, low literacy levels, low educational quality, substance abuse, poor mental health, early life stressors, trauma exposure, barriers to health care services, and environmental exposures prevalent in predominantly minority urban-dwelling individuals. In the Women's Interagency HIV Study (WIHS), we have been conducting the largest cohort study of neuropsychological outcomes among HIV-infected women to date. Recently, we examined the association between HIV status and cognition in relation to other determinants of cognitive function in 1521 (1019 HIV-infected) WIHS participants. Results revealed that the most prominent cognitive deficit in HIV-infected women was in the domain of verbal episodic learning and memory. In contrast, studies in male-dominant HIV cohorts find prominent deficits in executive function, complex attention, and learning. Additional behavioral studies in the WIHS have identified certain factors that were differentially associated with impaired verbal episodic memory in HIV-infected women compared to HIV-uninfected controls, including crack cocaine use, menopausal anxiety, and perceived stress. Neuroimaging studies show that HIV-infected women have alterations in hippocampal function during episodic memory tests, and that illicit substance use, particularly crack cocaine, alters prefrontal circuits in HIV-infected women. Overall, these results indicate that in contrast to men, deficits in verbal episodic memory appear to be a prominent feature of HIV-infection in women, and these deficits are associated with impaired hippocampal function generally and alterations in prefrontal cortex among crack cocaine users.

GRADUATE STUDENT SYMPOSIUM

GS1

TEMPERATURE REPRESENTATION IN THE *DROSOPHILA* BRAIN

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We are interested in the neurobiology of thermosensation, an indispensable sensory modality in all animals. How are hot and cold stimuli detected at the periphery? How are they processed in the brain? How are they integrated to produce behaviors such as temperature preference or avoidance of noxious extremes? We recently showed that temperature stimuli are represented by a spatial map of activity in the Drosophila brain. First, we identified hot- and cold-sensing neurons in the fly antenna and showed that hot and cold receptor cells project onto distinct, but adjacent glomeruli in the Proximal-Antennal-Protocerebrum (PAP), forming a 'thermotopic' map. We used two-photon imaging to reveal the functional segregation of hot and cold responses in the PAP, and showed that silencing the hot- or cold-sensing neurons produces animals with distinct and discrete deficits in their behavioral responses to thermal stimuli. Together, these results demonstrated that dedicated populations of cells orchestrate behavioral responses to different temperature stimuli, and revealed a labeled-line logic for the coding of temperature stimuli. Our current work aims at identifying the central neural mechanisms that shape the behavioral responses to thermal stimuli, and how these become integrated with additional internal and external cues to orchestrate behavior.

GS2

ESTRADIOL ENHANCES ETHANOL CONDITIONED PLACE PREFERENCE IN FEMALE C57BL/6J MICE THROUGH ACTIONS AT ERα

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Recent decades have seen a dramatic increase in the prevalence of alcohol use disorders (AUDs) among women, for whom the health consequences of alcohol abuse are often more severe than those observed in men. Studies of individuals with AUDs have found that women exhibit a so-called "telescoping" pattern of AUD development, characterized by a rapid progression from onset of alcohol use to dependence. In light of this, it is particularly important to identify mechanisms that contribute to the early stages of AUD development in women. Previous studies have demonstrated increased voluntary ethanol consumption in ovariectomized (OVX) female rodents after treatment with supplemental estradiol. A possible explanation for this observation is that estradiol enhances the rewarding (pleasurable) effects of ethanol consumption in females. Using the conditioned place preference (CPP) paradigm, we found that estradiol treatment increases ethanol reward in OVX female mice compared to vehicle-treated controls. To determine whether this effect is mediated by one of the classical estrogen receptors (ERs), we then repeated the experiment using three treatment groups: the ERα-selective agonist propyl pyrazole triol (PPT), the ERβ-selective agonist diarylpropionitrile (DPN), or vehicle (10% ethanol in sesame oil). Like estradiol, PPT treatment increased ethanol CPP, while DPN had no effect. These results suggest that estradiol enhances ethanol CPP through actions at ERα.

GS3

LOSS OF CIRCULATING ESTROGEN RESULTS IN ALTERED KINASE STATUS IN THE BRAIN OF AGED FEMALE RATS

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The loss of circulating estrogen at menopause leads to an increased risk of stroke, neurodegenerative disease, cognitive decline, mood disorders and anxiety. Clinical studies show that hormone therapy (HT) can be beneficial depending on how soon it is initiated following the perimenopausal transition. Importantly, the molecular mechanisms regulating this age-related switch in estrogen action are unknown. One possibility is that increased kinase activity associated with aging and estrogen levels results in increased phosphorylation of estrogen receptor β (ERβ), which is known to mediate both neuroprotective functions of estrogens. Indeed the cellular stress associated with aging activates the Mitogen Activated Protein Kinases (MAPK) p38 and ERK known to target ERβ. Phosphorylation of steroid receptors of the same family as ERβ affects nearly every aspect of their signaling, including its interactions with the coregulatory proteins. Using promoter assays I previously demonstrated that phosphorylation of ERβ indeed alters ERE and AP-1 transcriptional regulation. Our hypothesis is that age and estrogen deprivation following menopause alters the levels of expression and activation of p38 and ERK kinases in the brain.

In order to analyze the effects of age and duration of endogenous estrogen deprivation prior to estrogen treatment, we designed the following *in vivo* paradigm: surgically induced menopause was established in 18 mo. old rats through bilateral ovariectomy (OVX) and an acute dose of 17β-estradiol (E2; 2.5µg/Kg once/day x 3 days) or vehicle then administered at varying time points post-OVX (1 week, 4 weeks, 8 weeks, or 12 weeks). Using qRT-PCR and Western Blot I determined the expression and activation levels of p38 and ERK kinase in the hypothalamus and hippocampus. The results showed an overall age and estrogen dependent increase in expression of these kinases, supporting our hypothesis.

Overall it is well understood that MAPKs signaling plays an integral role in aging, and their aberrant regulation might be involved in age-related disorders. Clinical studies show benefits of HT during early menopause but detrimental effects later, which might be reflective of changes in kinase expression and activation status. Supported by NIH R01AG033605 TRP

GS4

THE EFFECT OF PRAMIPEXOLE ON DOPAMINE-ASSOCIATED BEHAVIORS AND SIGNALING MECHANISMS IN A RAT MODEL OF PARKINSON'S DISEASE

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Parkinson's disease (PD) patients exhibit motor deficits, e.g., postural instability, rigidity and bradykinesia, associated with loss of nigrostriatal dopamine (DA). Pramipexole (PPX), a DA agonist with high affinity for D2/D3 receptors (R), provides excellent relief from PD-related motor deficits; however, some patients develop impulse control disorders during chronic PPX therapy. Mechanisms that underpin the motor improvements vs. impulsivity in these patients remain unclear. To shed light on this issue, we employed a model of PD (i.e., rats with 6-OHDA-induced lesions of the dorsolateral striatum) and studied the effects of PPX on motor function (postural instability), impulsive decision-making (intracranial self-stimulation-mediated probability discounting) and biochemical signaling that may underlie synaptic adaptations to PPX exposure (i.e., GSK-3β linked to AMPA-R trafficking). Acute administration of PPX (0.01, 0.03, 0.1, 0.3 and 1mg/kg) dose-dependently improved postural instability, and this effect was blocked by an antagonist to D2Rs (L741,626) but not to D3Rs (PG01037). PPX increased risk-taking after chronic exposure to 1.2mg/kg PPX. The inactive form of GSK-3β was enhanced in forebrain regions by acute PPX at 0.03-0.6mg/kg, but high doses reduced the inactive form and increased AMPA-R surface expression. These findings parallel the clinical profile, showing that PPX rapidly provides motor benefits, but chronic exposure can increase risk-taking. PPX-induced signaling via GSK-3β-mediated actions may have bimodal effects that are associated with these divergent behavioral outcomes. Such findings may help lead to PD therapies which are motorically efficacious but devoid of ICD side effects.

GS5

MATURATION OF THE PREFRONTAL CORTICAL GABAERGIC SYSTEM DURING ADOLESCENCE: ROLE OF NMDA RECEPTORS

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Functional disruptions of the prefrontal cortex (PFC) and its maturation are thought to contribute to the adolescent onset of cognitive deficits observed in many psychiatric disorders including schizophrenia. However, the neurobiology underlying these deficits remains unclear. Among the contributing factors is the functional maturation of PFC GABAergic activity during adolescence, a developmental process paralleled by an elevation of NMDAR-mediated glutamatergic drive to the PFC. To test if these events are mechanistically linked, we examined how transient blockade of NMDAR transmission (MK-801) during adolescence (postnatal day -P- 35 to 40) impacts PFC maturation and function. *In vivo* and *in vitro* electrophysiological recordings revealed an enduring deficit in PFC GABAergic transmission following adolescent MK-801 exposure. These deficits occurred without affecting PFC glutamatergic function, resulting in an imbalance of excitation and inhibition within the PFC (increased AMPA:GABA ratio). Notably, this state of PFC disinhibition resembles that seen in juvenile animals (P25-35), indicating a retention of a functionally immature PFC state into adulthood. Subsequent analysis of PFC-dependent behaviors revealed deficits in both working memory and extinction of trace fear memory in adult rats that received MK-801 during adolescence. No deficits in PFC function were found when similar treatment was administered during adulthood (P75-80). Taken together, these results demonstrate that NMDA transmission during adolescence is necessary to enable the maturation of GABAergic function within the PFC. Research supported by: NIMH R01-MH086507, Brain Research Foundation, Rosalind Franklin University.

GS6

OPIOID MODULATION OF RESPONSES TO SOCIAL REJECTION IN HUMANS

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In addition to its classical role in mediating responses to pain, the opioid system is strongly implicated in the regulation of social behavior. It has been suggested that the brain networks mediating responses to social distress may have evolved from more primitive pain-processing circuitry, and neuroimaging evidence suggests that social rejection or "social pain" and physical pain activate similar neural networks. In young laboratory animals, low doses of opioid analgesic drugs reduce responses to isolation distress, in addition to enhancing responses to some types of social reward. Despite evidence suggesting a role for the opioid system in mediating responses to social distress in animal models, the effects of opioid analgesic drugs on responses to social stimuli have not been determined in humans. Here we examined the effects of buprenorphine, a μ-opioid partial agonist used to treat opioid dependence and pain, on responses to simulated social rejection in healthy young adults. We hypothesized that buprenorphine would reduce subjective experience of social rejection, and further that the drug would selectively affect responses to social stimuli over other types of affective stimuli. Healthy adult volunteers (N = 36) attended two laboratory sessions during which they received either placebo or 0.2mg sublingual buprenorphine in randomized order, under double-blind conditions. Ninety minutes after drug administration, volunteers participated in a virtual ball-toss game in which they were first included, and then excluded by the other players. They also completed a picture-viewing task, in which they rated standardized positive, negative, and neutral social and non-social images. Throughout the sessions, the participants reported subjective drug effects and mood, and measures of heart rate and blood pressure were collected at regular intervals. Buprenorphine significantly increased participants' estimates of the proportion of time they received the ball during the ball-toss task, as compared to placebo. It also significantly increased positive ratings of images with social content, without affecting ratings of nonsocial images. These results suggest that opioid analgesic drugs reduce perception of social rejection, and that such effects may be specific to social stimuli, rather than influencing responses to affective stimuli more generally. These findings provide further support for the role of the opioid system in mediating responses to social rejection.

UG Undergraduate Student Competition
G Graduate Student Competition
PD Posdoctoral Student Competition

POSTER ABSTRACT TITLES

THEME A. COGNITION AND BEHAVIOR

A1 UG
DEVELOPMENT OF A MOUSE MODEL OF CHEMOBRAIN TO EVALUATE THE EFFICACY OF NUTRITIONAL INTERVENTION
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A2
HELPING ANOTHER IN DISTRESS: WHAT WE CAN LEARN FROM RATS
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A3 UG
HOW MUSIC INFLUENCES ANXIETY IN ZEBRAFISH
B. A. Tengen, S. Saszik
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A4 UG
TRANSCRIPTIONAL ANALYSIS OF A WHOLE-BODY FORM OF LONG-TERM HABITUATION IN APLYSIA CALIFORNICA
Conte C., Schuon J., Herdegen S., Holmes G., Cyriac A., Lass J., Calin-Jageman IE, Calin-Jageman RJ
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A5 PD
NOVEL GENETIC PLATFORMS TO MANIPULATE THE MIDBRAIN DOPAMINERGIC SYSTEM
Jean-Francois Poulin[1], Mei Huang[2], Jian Zou[1], Savio Chan[3], Herbert Y. Meltzer[2], Rajeshwar B. Awatramani[1]
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A6 UG
CHARACTERIZATION OF THE RAPID TRANSCRIPTIONAL RESPONSE TO LONG-TERM SENSITIZATION TRAINING IN APLYSIA CALIFORNICA
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A7 PD
AGE-RELATED COGNITIVE PERFORMANCE CORRELATES WITH L-TYPE CHANNEL PROTEIN EXPRESSION IN CA1 OF DORSAL HIPPOCAMPUS
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A8 PD
MULTI-VARIATE PATTERN ANALYSIS OF PASSIVE SENTENCE PROCESSING
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A9 PD
DEFAULT MODE NETWORK: POTENTIAL BIOMARKER FOR MILD COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE
Sandra L. Kletzel[1], PhD; Brett C. Harton[1], MS; Alicia Kopicki[1,3], MS; Amy A. Herrold[1,2], PhD; Darren Gitelman[5,6], MD; Tanya Simuni[2], MD; Theresa L-B. Pape[1,2,4], DrPH, MA, CCC-SLP/L
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A10 G
NEURAL MECHANISMS OF GRAMMATICAL PRODUCTION: A VOXEL-BASED MORPHOMETRY STUDY OF PRIMARY PROGRESSIVE APHASIA (PPA)
S. Lukic[1], E. Europa[1], M. Mameledzija[1], E. J. Rogalski[2], M. M. Mesulam[2], C. K. Thompson[1, 2]
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A11 PD
RNA EDITING OF THE AMPA RECEPTOR GLUA2 SUBUNIT IS ALTERED BY PRENATAL STRESS AND ANTIPSYCHOTIC DRUGS
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A12 UG
NEUROPSYCHOLOGICAL PREDICTORS OF FACIAL EMOTION PROCESSING IN HEALTHY INDIVIDUALS ACROSS THE LIFESPAN
Chandni Patel[1], Emily Briceno, Ph.D.[2], Jon-Kar Zubieta, M.D., Ph.D.[2], Scott Langenecker, Ph.D.[1,2], Sara Weisenbach, Ph.D.[1,2,3]
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A13 PD
PROBOSCIS EXTENSIONS DURING SLEEP: A NEW SLEEP STAGE IN *DROSOPHILA*?
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THEME B. DEVELOPMENT

B1
EXPRESSION OF CREBL2 AND HDAC7 IN RETINAL DEVELOPMENT IN CHICKEN EMBRYOS
Christina Scribano, Samantha Krysa, Sean Georgi
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B2
LONG NON-CODING RNA/BRG1 INTERACTIONS REVEAL RNA-DEPENDENT EFFECTS ON CHROMATIN REMODELING IN DEVELOPING FOREBRAIN
Ivelisse Cajigas[1], David E. Leib[1], Jesse Cochrane[2], Sean Chen[1], Hao Luo[1], Brian S. Clark[1], James Thompson[3], John R. Yates, III[3], Robert E. Kingston[2], Jhumku D. Kohtz[1]
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B3 G
UNDERSTANDING ROSTRAL FLOOR PLATE PARTITIONING TOWARDS IMPROVED PROTOCOLS FOR DOPAMINE NEURON DERIVATION FROM STEM CELLS
Navid Nouri and Rajeshwar Awatramani
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B4
SEMAPHORIN3A SHIFTS THE MOTILITY RESPONSE OF BREAST EPITHELIAL CELLS THROUGH INCREASED FOCAL ADHESIONS IN RESPONSE TO CHANGES IN FIBRONECTIN CONCENTRATION
Alex M. Miller and Scott Gehler
Biology Department, Augustana College, Rock Island, IL

B5 G

UNDERSTANDING THE INVOLVEMENT OF TPR-1 IN PROTEIN MAINTENANCE AND CELLULAR PROTECTION IN *C. ELEGANS*

DeElegant Robinson[1], Marc Brehme[2], and Cindy Voisine[1]
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B6 G

REACHING NEW DISTANCES: EXTENDING NEURONAL REGENERATION WITH NANOGROOVES *EX VIVO*

Casey D. Sigerson[1], Harsh Sharthiya[1], Karlee Kirkpatrick[2], Joshua Z. Gasiorowski[2], Michele Fornaro[1]
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B7 PD

EVF2 LNCRNA ANTI-SENSE REGULATION CONTROL COMPLEX BEHAVIOR IN MICE

Hao Luo[1], Sean Chen[1], Shari Birnbaum[3], Maximiliano Nigro[2], Marco Martina[2], Jhumku, D. Kohtz[1]
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B8 UG

THE IMPORTANCE OF A BALANCED DIET: THE EFFECT OF PROTEIN-TO-CARBOHYDRATE RATIO IN BODY AND ORGAN SIZE IN *DROSOPHILA*

Josephine Masandika[1], Yuqing Zhu[1], Lily Thorsen[1], Diego R Rojas-Toledo[1], Christen K. Mirth[2], Alexander W. Shingleton[1,3]
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THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 G

MODELING A CLOSED-HEAD CONCUSSION IN THE ADULT RAT

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C2 G

FAST AXONAL TRANSPORT DEFICITS INDUCED BY MUTANT HUNTINGTIN INVOLVE ACTIVATION OF A SPECIFIC MAPK PATHWAY

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C3 PD

CENTRAL AND SYSTEMIC EFFECTS OF DRONABINOL, A CANNABINOID AGONIST, ON APNEA.

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C4

MOTOR CORTEX EXPRESSION OF MECHANO GROWTH FACTOR mRNA AND RELATED GENES IN RATS FOLLOWING HYPOXIA

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C5 PD

OPTOGENETIC DISSECTION OF STN-GPe IN VIVO NETWORK ACTIVITY IN EXPERIMENTAL PARKINSON'S DISEASE

Joshua W. Callahan, Ryan F. Kovaleski, and Mark D. Bevan
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C6 PD

PRESENILIN-DEPENDENT MODULATION OF AXODENDRITIC OUTGROWTH REQUIRES APP FUNCTION

Deyts, C., Clutter, M., Herrera, S., Jovanovic, N., Goddi, A. and Parent, A.T.
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C7 UG

USING ANTISENSE OLIGONUCLEOTIDES (ASO) AS A THERAPY FOR BATTEN DISEASE

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C8 UG

INSIGHT INTO PARKINSON'S DISEASE: EVALUATION OF FAMILIAL MUTANTS AND SUMOYLATION OF α-SYNUCLEIN IN YEAST

Alexandra Roman, Maiwase Tembo, Galina Lipkin, Charles Alvarado, Maribel Muñoz, and Shubhik DebBurman.
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C9 PD

A NOVEL THERAPY FOR EPILEPSY USING BIODEGRADABLE IMMUNE-MODIFYING NANOPARTICLES

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C10 G

WITHDRAWN

C11 UG

INSIGHT INTO PARKINSON'S DISEASE: EVALUATION OF SPLICE VARIANTS AND C-TERMINAL TRUNCATIONS OF α-SYNUCLEIN IN YEAST

Saul Bello Rojas, Khadijah Hamid, Charles Alvarado, Katrina Campbell, Natalie Kukulka, and Shubhik DebBurman.
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C12 G

SEX DIFFERENCES IN DENDRITIC COMPLEXITY CORRELATE WITH POST-STROKE RECOVERY IN AGED RATS

Vincent J. Borkowski[1, 2], Shih-Yen Tsai[2], Ian C. Vaagenes[2] , Kevin S. Hsu[2], Catherine M. Papadopoulos[2], Gwendolyn L. Kartje[1, 2, 3]
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C13

AMINO-NOGO-A NEUTRALIZATION FAILS TO POTENTIATE THE EARLY SUBVENTRICULAR ZONE RESPONSE TO FOCAL ISCHEMIA IN ADULT RATS

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C14 G

THE EFFECT OF PRAMIPEXOLE ON DOPAMINE-ASSOCIATED BEHAVIORS AND SIGNALING MECHANISMS IN A RAT MODEL OF PARKINSON'S DISEASE

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C15 G

ACTIVATION OF NLRP3 INFLAMMASOME IN MICE WITH THE OPTIC NERVE CRUSH INJURY

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C16 PD

HYPER-ACTIVATION OF L-TYPE CA^{2+} CHANNELS, INDEPENDENT OF NMDA RECEPTOR, MEDIATES INCREASED CA^{2+} INFLUX IN PYRAMIDAL NEURONS FROM THE RAT MEDIAL PREFRONTAL CORTEX IN THE CONTEXT OF HIV INFECTION

Christina E. Khodr*[1]; Sonya Dave*[1]; Chunxiang Zhang[1]; Lena Al-Harthi[2]; Xiu-Ti Hu[1]
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C17 PD

SEX DIFFERENCES IN GABAERGIC GENE EXPRESSION OCCUR IN THE ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA

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C18 G

USING YEAST AS A MODEL TO UNDERSTAND THE MECHANISMS THAT UNDERLIE PROTEIN AGGREGATION, AMYLOID FORMATION, AND PRIONIZATION

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C19

ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF JUVENILE NEURONAL CEROID LIPOFUSCINOSIS

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C20 UG

DEGREE OF DOPAMINE LESION IN THE SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA REFLECTS SEVERITY OF AKINETC BEHAVIOR IN A RODENT MODEL OF PARKINSON'S DISEAES

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C21

ISOLATION AND ANALYSIS OF THE AMYLOID PRECURSOR PROTEIN INTRACELLULAR DOMAIN (AICD) INTERACTOME

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C22

PARKINSONIAN SUBTHALAMIC NUCLEUS-EXTERNAL GLOBUS PALLIDUS NETWORK ACTIVITY DURING STEREOTYPED CORTICAL ACTIVITY STATES

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C23 G

IMPAIRMENTS IN CREB SIGNALING IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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C24 G

DEFECTS IN LYSOSOME-AUTOPHAGOSOME REGULATION EMERGE PRIOR TO PROTEIN AGGREGATION IN ALZHEIMER'S DISEASE PATHOGENESIS

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C25

CRYOPRESERVED IPSC-DERIVED MIDBRAIN DOPAMINE NEURONS SURVIVE AND PROJECT FIBERS INTO HOST TISSUE

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C26

ANTISENSE OLIGONUCLEOTIDE-MEDIATED SPLICING MODULATION FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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C27

TARGETING INTRACELLULAR CALCIUM CHANNELS AS A THERAPEUTIC APPROACH FOR TRAUMATIC BRAIN INJURY AND PREVENTING CONVERSION TO AD

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C28 G

TRANSPLANTATION AND INNERVATION OF MIDBRAIN DOPAMINE NEURONS DERIVED FROM HUMAN EMBRYONIC STEM CELLS IN ANIMAL MODELS OF PARKINSON'S DISEASE

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C29 PD

IMPACT OF PHOSPHODIESTERASE 10A INHIBITION ON SPONTANEOUS AND CORTICALLY-EVOKED SPIKE ACTIVITY IN THE STRIATUM OF Q175 MICE THAT MODEL HUNTINGTON'S DISEASE

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C30 UG

MICROPROCESSOR COMPLEX SUBUNIT DIGEORGE SYNDROME CRITICAL REGION GENE 8 (DGCR8) IS REQUIRED FOR SCHWANN CELL MYELINATION AND MYELIN MAINTENANCE

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C31 G

STABILIZING ER CA2+ CHANNELS WITH NOVEL COMPOUNDS NORMALIZES CA2+ RELEASE AND PRESERVES SYNAPSES IN ALZHEIMER'S DISEASE

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C32 G

DEVELOPMENT OF mGluR-LTD IN THE NUCLEUS ACCUMBENS DURING WITHDRAWAL FROM EXTENDED-ACCESS COCAINE SELF-ADMINISTRATION

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C33 PD

EXAMINING PROTEIN SYNTHESIS IN THE NUCLEUS ACCUMBENS AFTER WITHDRAWAL FROM EXTENDED-ACCESS COCAINE SELF-ADMINISTRATION

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C34

GUANYLATE CYCLASE STIMULATION IS A TRIGGER OF MIGRAINE PAIN

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C35 PD

THE DELTA OPIOID RECEPTOR AGONIST SNC80 PREFERENTIALLY RECRUITS β-ARRESTIN 1 TO PROMOTE BEHAVIORAL TOLERANCE

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C36 G

UNDERLYING MECHANISMS AND FUNCTIONAL CONSEQUENCES OF AUTONOMOUS FIRING LOSS IN THE PARKINSONIAN SUBTHALAMIC NUCLEUS

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C37 G

EFFECTS OF FITC FLUOROPHORE LABELING ON ALPHA-SYNUCLEIN HIGHER ORDER AGGREGATION STATE AND CELLULAR TOXICITY

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THEME D. HISTORY AND TEACHING OF NEUROSCIENCE

D1 UG

EFFECTIVENESS OF THE SLICE CONCUSSION EDUCATION PROGRAM FOR CHICAGO YOUTH

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THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1 G

AGING AND LOSS OF CIRULATING 17β–ESTRADIOL RESULTS IN BRAIN-REGION SPECIFIC CHANGES IN THE ALTERNATIVE SPLICING OF ESTROGEN RECEPTOR β IN FEMALE RATS

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E2 G

BASOLATERAL AMYGDALA CIRCUITRY UNDERLYING MODULATION OF STRESS-RELATED BEHAVIOR

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E3 UG

A COMPARISON OF THE NEURAL CONNECTIONS FROM THE SUBDIVISIONS OF THE ORBITOFRONTAL CORTEX TO THE AMYGDALA AND THE EXTENDED AMYGDALA IN THE RAT

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THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG

HETEROGENEOUS ABLATION OF PERISYNAPTIC SCHWANN CELLS RECOGNIZED BY THE MONOCLONAL ANTIBODIES ANTI-HNK-1 AND 2A12.

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F2

AMBIENT EXTRACELLULAR GLUTAMATE MODULATES SYNAPTIC STRENGTH AT HIPPOCAMPAL CA3-CA1

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F3 PD

GENETIC ABLATION OF KLHL1 ALTERS $Ca_V3.2$ EXPRESSION IN DRG NEURONS AND MECHANICAL PAIN TRANSMISSION

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F4 UG

THE ROLE OF RAB27B IN SYNAPTIC TRANSMISSION: A COMPENSATORY PARTNERSHIP BETWEEN RAB3 AND RAB27B

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F5 G

EVIDENCE FOR PKA DEPENDENT REGULATION OF TOMOSYN

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F6 G

DIFFERENTIAL REGULATION OF DROSOPHILA GLUTAMATE RECEPTOR SUBUNIT PRODUCTION BY OPTIMUS-PRIME, A NOVEL MRNA ASSOCIATED GENE

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F7 PD

HETEROSYNAPTIC REGULATION OF EXTERNAL GLOBUS PALLIDUS INPUTS TO THE SUBTHALAMIC NUCLEUS BY MOTOR CORTEX

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F8 PD

METHAMPHETAMINE ALTERS RESTING MEMBRANE POTENTIAL AND REDUCES VOLTAGE-SENSITIVE K+ CURRENT IN PRIMARY HUMAN FETAL ASTROCYTES

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F9 G

GROUP I MGLUR-β-ARRESTIN SIGNALING MEDIATES EXCITATORY SYNAPTIC PLASTICITY

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F10 UG

THE EFFECTS OF STRESS ON DOPAMINE AND SOCIAL BEHAVIOR IN ADULT ZEBRAFISH

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F11 UG

INHIBITING EXTRACELLULAR CARBONIC ANHYDRASE INCREASES THE DOSE-DEPENDENT, K^+-INDUCED INCREASE IN PROTON FLUX OF MULLER CELLS

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F12 UG

ROLE OF Slp4 IN NEUROENDOCRINE VESICLE DOCKING AND FUSION

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THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1 PD

AXONAL OUTGROWTH RATES OF PRIMARY NEURONS USING CUSTOM MUTICOMPARTMENTALIZED MICROFLUIDIC CHAMBER SYSTEM

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G2 PD

CHARACTERIZING DEMYELINATION AND REMYELINATION IN ANIMAL MODELS OF DEMYELINATION

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G3 G

EVALUATION OF LIPOSOMAL NANOCARRIERS LOADED WITH ET_B RECEPTOR AGONIST, IRL-1620, USING CELL BASED ASSAYS

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G4

DIRECT CONVERSION OF RESIDENT OLIGODENDROCYTE PROGENITOR CELLS INTO MATURE NEURONS WITH MULTIPLE NEURONAL SUBTYPE SPECIFICATION

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G5 PD

FLUORINATED 4-AMINOPYRDINES AS PET TRACERS FOR MULTIPLE SCLEROSIS

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G6 PD

ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF USHER SYNDROME

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G7

HUMAN IPSC-DERIVED NEURONS: A SUITABLE MODEL FOR TOXICOLOGICAL ASSAYS

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THEME H. SENSORY AND MOTOR SYSTEMS

H1 PD

A NOVEL RETINAL AMACRINE CELL MICROCIRCUIT

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H2

RHO GTPASES ARE REQUIRED FOR SMAD3-MEDIATED INDUCTION OF ET-1 IN HUMAN TRABECULAR MESHWORK CELLS

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H3 G

TRANSFORMING GROWTH FACTOR-β2 ATTENUATES BRADYKININ B2 RECEPTOR EXPRESSION IN HUMAN TRABECULAR MESHWORK CELLS

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H4 G

DOPAMINE DEPLETION RESULTS IN FREQUENCY-DEPENDENT DISINHIBITION OF CORTICOSTRIATAL TRANSMISSION *IN VIVO*: ROLE OF LOCAL STRIATAL CGMP AND GABAERGIC SIGNALING

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H5 UG

CONCENTRATION AND PATTERN-DEPENDENT DOPAMINE NEUROMODULATION OF MOTOR PATTERNS

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H6 G

DOPAMINERGIC NEUROMODULATION OF THE SUBTHALAMIC NUCLEUS

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H7 PD

FUNCTIONAL CHARACTERIZATION OF TWENTY TYPES OF RETINAL GANGLION CELLS AND THEIR SPIKING SIGNALS IN THE MOUSE RETINA

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H8

MODELING AMYOTROPHIC LATERAL SCLEROSIS IN C. ELEGANS: EVALUATING HOW TDP-43 EXPRESSION IMPACTS MOTOR AND SENSORY NEURON FUNCTION

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H9 G

TEMPERATURE REPRESENTATION IN THE *DROSOPHILA* BRAIN

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H10 G

MECHANISMS UNDERLYING ORIENTATION SELECTIVITY IN THE MOUSE RETINA

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H11 G

HIGH-INTENSITY EXERCISE AUGMENTS SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR IN HUMANS WITH INCOMPLETE SPINAL CORD INJURY

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H12 G

ENHANCED ACTIVITY FOR SEARCH TARGETS IN FRONTAL EYE FIELD DEPENDS ON TARGET AWARENESS

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H13 G

INVOLVEMENT OF CAMKII ALPHA IN MULTIPLE SCLEROSIS-ASSOCIATED PAIN

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H14

CENTRAL PROJECTIONS OF NERVES INNERVATING THE NASAL PASSAGES OF THE RAT

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H15

DIFFERENTIAL MODES OF SYNAPTIC TRANSMISSION WITHIN FAST SPINAL LOCOMOTOR CIRCUITRY

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H16 PD

STRUCTURES OF SYNAPTIC DRIVE UNDERLYING SELF-SUSTAINED MOTOR UNIT DISCHARGE IN THE DECEREBRATE CAT

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H17

DEVELOPMENTAL MODIFICATIONS OF PREMOTOR EXCITATORY DRIVE MATCH CHANGES IN MOTONEURON PROPERTIES

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H18 UG

COMPLEX AND NON-REDUNDANT SIGNALS FROM INDIVIDUAL ODOR RECEPTORS THAT UNDERLIE CHEMOTAXIS BEHAVIOR IN DROSOPHILA MELANOGASTER LARVAE

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POSTER ABSTRACTS

THEME A. COGNITION AND BEHAVIOR

A1 UG

DEVELOPMENT OF A MOUSE MODEL OF CHEMOBRAIN TO EVALUATE THE EFFICACY OF NUTRITIONAL INTERVENTION

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Chemobrain refers to long-lasting deficits in cognitive performance resulting from chemotherapy. Objective evidence for chemobrain is mixed and mechanisms unknown. One leading hypothesis is that the chemotherapeutic agents cross the blood-brain barrier and reduce the progenitor cell population in the hippocampus, a critical region for learning and memory that continues to generate new neurons throughout life. The purpose of this study was to first determine whether a reliable behavioral deficit can be found in mice in response to administration of the chemotherapeutic agents standardly used to treat breast cancer in humans, and second whether a nutritional intervention could ameliorate those deficits in association with increased adult hippocampal neurogenesis. Mice received doxorubicin (IV, 4mg/kg), cyclophosphamide (IP, 80mg/kg) and 5-fluorauracil (IP, 40mg/kg) and were injected with bromodeoxyuridine (BrdU, 50mg/kg) to label dividing cells. Following recovery from the chemotherapy, mice received intervention diets containing fish oil rich in omega-3 & 6 fatty acids or a standard control diet. Docosahexanoic acid (DHA), an omega-3 fatty acid found in fish oil, is suggested to enhance survival of neurons. Locomotor activity in the home cage was recorded using continuous video tracking. Behavioral performance on a battery of learning and memory tasks including the Morris water maze, Y-maze, and novel odor recognition was conducted. Chemotherapy was correlated with impaired performance on the Morris water maze and a reduction in hippocampal neurogenesis. These deficits were not ameliorated from the dietary interventions. Results suggest reliable behavioral and neurological deficits can be found from chemotherapy using our mouse model but that an alternative dietary intervention will be needed to reverse these deficits. This study is funded by Abbott Nutrition, Columbus OH.

A2

HELPING ANOTHER IN DISTRESS: WHAT WE CAN LEARN FROM RATS

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Empathy is a fundamental building block of pro-social behavior that promotes social cohesion and has evolved in social mammals. Empathic concern is an other-oriented emotional response to another's distress and is the antecedent to helping. For empathic concern to drive pro-social behavior, separation of the self from the other is needed so that the helper feels *for* rather than *as* the other. We recently established an animal model of empathic helping behavior: a free rat learns to deliberately liberate a cagemate trapped within a restrainer and does so even when immediate social interaction is denied. Rats value liberating a cagemate on a par with accessing highly palatable food (chocolate). As long as they have lived with one individual of a given strain of rat, rats help strangers and familiars of that strain. Remarkably, rats that are raised without ever seeing or interacting with another rat of their own biological strain will not help a rat of their own type. In sum, our findings demonstrate that empathic helping is biologically-driven as well as constrained by experiences.

A3 UG

HOW MUSIC INFLUENCES ANXIETY IN ZEBRAFISH

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The purpose of this study was to examine the effect of music on the level of anxiety in zebrafish. Anxiety levels in zebrafish were determined by their swim behavior where anxiogenic related behavior included reduced exploration, increased erratic movements and freezing behavior (Egan et al., 2009). Twenty zebrafish were randomly selected from a population and their swim behavior was observed and recorded after treatment. Ten of the zebrafish were randomly placed into a control group and the other ten into an experimental group. While the control group was reared in a music free environment, the experimental group was reared in an environment where classical music was played by use of

water immersion speakers. Both the control and experimental groups experienced their respective treatment conditions for seven days prior to testing. During testing, both conditions were video recorded and assessed for their levels of anxiety. Anxiety levels were determined by electronically analyzing how much swimming the zebrafish did, which was measured by the distance the zebrafish travelled; and, how much time the zebrafish spent in one location which was measured by the time spent in the central versus peripheral locations of the test tank. The more mobile the zebrafish was, or the greater the swim distance, was suggestive of a less anxious zebrafish, and the less travel the zebrafish did, or the greater the freezing behavior, suggested a more anxious zebrafish.

A4 UG

TRANSCRIPTIONAL ANALYSIS OF A WHOLE-BODY FORM OF LONG-TERM HABITUATION IN APLYSIA CALIFORNICA

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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 protocol for producing whole-body 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 d of training (10 rounds of stimulation/day; each round = 15 min brushing at a 10-sec ISI; 15-min rest between rounds) produces habituation with several characteristics favorable for mechanistic investigation. First, habituation is widespread, with SWR durations reduced whether the reflex is evoked by tactile stimulation to the head, tail, or the siphon. Second, long-term habituation is sensitive to the pattern of training, occurring only when brushing sessions are spaced out over 3 d rather than massed into a single session. Using a custom-designed microarray and quantitative PCR, we show that long-term habituation produces long-term up-regulation of an apparent Aplysia homolog of cornichon, a protein important for glutamate receptor trafficking. Our training paradigm provides a promising starting point for characterizing the transcriptional mechanisms of long-term habituation memory.

A5 PD

NOVEL GENETIC PLATFORMS TO MANIPULATE THE MIDBRAIN DOPAMINERGIC SYSTEM

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Dopamine, produced mainly by midbrain dopaminergic (DA) neurons, influences a spectrum of behaviors including motor, learning, reward, motivation, and cognition. In accordance with its diverse functions, DA dysfunction is implicated in a range of disorders affecting millions of people, including Parkinson's disease (PD), schizophrenia, addiction, and depression. How a small group of neurons underpins a gamut of key behaviors and diseases remains enigmatic. To investigate DA function, it is imperative to develop tools that facilitate manipulation of the DA system *in vivo*. Here we developed two distinct genetic platforms to manipulate the DA system. First we generated a mouse with a tyrosine hydroxylase (*Th*) conditional allele and used a *Dat::iCre* driver to embryonically delete *Th* and deprive midbrain neurons of their ability to synthesize dopamine. In opposition to previous studies, these mice had a severe hypokinesia, weight loss, and did not survive through weaning. Second, we developed a acute DA depletion paradigm in adult mice using a chemogenetic approach. Silencing of the DA system resulted in a pronounced reduction of dopamine efflux in the striatum and prefrontal cortex, and a reduction in locomotion, feeding and other energy expenditure parameters. These results suggest that in both embryonic and adult settings, DA depletion does not inevitably lead to compensatory mechanisms preserving motor function. Together, these novel genetic platforms will facilitate the investigation of the midbrain DA system, as well as that of newly identified DA subtypes using specific genetic entry points.

A6 UG

CHARACTERIZATION OF THE RAPID TRANSCRIPTIONAL RESPONSE TO LONG-TERM SENSITIZATION TRAINING IN APLYSIA CALIFORNICA

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We used a custom-designed microarray and qPCR to characterize the rapid transcriptional response to long-term sensitization training in the marine mollusk Aplysia californica. Aplysia were exposed to repeated noxious shocks to one side of the body (4 ten- second shocks at

90mA, 30 min ISI), a procedure known to induce a transcription-dependent and long-lasting increase in reflex responsiveness that is restricted to the side of training. One hour after training, pleural ganglia from the trained and untrained sides of the body were harvested; these ganglia contain the sensory nociceptors which help mediate the expression of long-term sensitization memory. Microarray analysis on 8 animals suggests that long-term sensitization training strongly and rapidly regulates at least 102 transcripts. We used qPCR to test a subset of these transcripts and found that 86% were confirmed in the same samples, and 83% of these were again confirmed in an independent sample (n = 9 animals). Thus, our new microarray design shows very strong predictive and convergent validity for analyzing the transcriptional correlates of memory in Aplysia. Fully validated transcripts include some previously identified as regulated in this paradigm (apC/EBP and apEgr) but also include novel findings. Specifically, we show that long-term sensitization training rapidly up-regulates the expression of transcripts which seem to encode a C/EBP gamma, a glycine transporter, and a vacuolar protein-sorting- associated protein.

A7 PD

AGE-RELATED COGNITIVE PERFORMANCE CORRELATES WITH L-TYPE CHANNEL PROTEIN EXPRESSION IN CA1 OF DORSAL HIPPOCAMPUS

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The calcium (Ca^{2+}) hypothesis of aging predicts that age-related cognitive impairments result from disruption of Ca^{2+} homeostasis. In aged animals Ca^{2+} influx is increased in CA1 pyramidal neurons, resulting in a decrease in the intrinsic excitability of these cells. One common measure of intrinsic excitability, the post-burst afterhyperpolarization (AHP), is increased in CA1 pyramidal neurons from aged animals. This age-related increase in the AHP results in reduced neuronal excitability and impaired synaptic plasticity. Increased intracellular Ca^{2+} is believed to underlie these age-related biophysical and behavioral deficits, as administration of L-type Ca^{2+} channel antagonists reduces Ca^{2+} influx and the amplitude of AHP in vitro, and ameliorates age-related learning impairments in vivo. Therefore, an age-related increase in the number, and/or function, of L-type voltage-gated Ca^{2+} channels in CA1 pyramidal neurons is believed to mediate age-related cognitive impairments. There are two subtypes of L-type Ca^{2+} channel in CA1, the $Ca_v1.2$ and $Ca_v1.3$ subtypes. To date, no experiments have determined whether activity of either $Ca_v1.2$ and/or $Ca_v1.3$ mediates these impairments. To determine whether activity of $Ca_v1.2$ mediates age-related cognitive impairments we designed short hairpin RNA (shRNA) to reduce expression of $Ca_v1.2$, which was packaged into an adeno-associative viral (AAV) vector. Infusion of AAV-shRNA resulted in widespread infection of dorsal CA1 in both young and aged rats. In young rats AAV-shRNA reduced $Ca_v1.2$ protein expression by 25%. Surprisingly, no reduction in L-type expression was observed in aged virally-injected animals. Aged rats were impaired during water maze training and fear conditioning. However, administration of $Ca_v1.2$ AAV-shRNA did not ameliorate these impairments. Regardless, significant correlations were observed between levels of $Ca_v1.2$ protein in dorsal CA1 and cognitive measures in aged animals. Together, these results suggest that an age-related increase in the number and/or function of $Ca_v1.2$ channels in CA1 may mediate age-related cognitive impairments. Therefore, compounds and/or manipulations that reduce activity of the $Ca_v1.2$ channel subtype in CA1 pyramidal neurons may ameliorate these age-related deficits. Future research will explore this possibility using pharmacological manipulations to extend results of previous in vivo systemic injection studies, by determining whether intra-hippocampal blockade of L-type channel activity ameliorates age-related biophysical and cognitive deficits. This work was supported by NIH R37 AG008796 & R01 AG017139 to John F. Disterhoft; T32 AG20506 & P30 AG13854 to Daniel M. Curlik

A8 PD

MULTI-VARIATE PATTERN ANALYSIS OF PASSIVE SENTENCE PROCESSING

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Processing of passive sentences has been investigated by a few neuroimaging studies, which indicate a primary role of the left inferior frontal gyrus (IFG), with some evidence for involvement of the right IFG and posterior perisylvian areas (Mack et al., 2013; Hirotani et al., 2011). Volumetric and metabolic studies with aphasic patients also point to the same regions and to the insula as neural networks supporting syntactic processing (Caplan et al., 2007, Wilson et al., 2010). The present study aims to shed light on the role of left language areas and their right homologues in processing passive sentences using a) a standard univariate

(GLM) analysis and b) a multivariate pattern analysis (MVPA) performed in PRoNTo (Schrouff et al., 2013).

Thirteen healthy participants underwent fMRI (3T scanner) using an acceptability judgment task (experimental task) on passive (N=40) and active (N=40) sentences. Subjects were asked to press a button to indicate if a sentence was plausible or implausible (e.g. *The piano was played in the sky*). Blocks of the experimental task (8 passives, 8 actives) were interspersed within blocks (N=8) of a control task (pitch discrimination task).

For the univariate GLM analysis, blocks of passive sentences were averaged across runs and contrasted with active sentences, showing no significant areas associated with processing of passive sentences. In the MVPA analysis, data were entered in a GLM analysis to contrast each experimental block with the control blocks in the same run. Contrast files were then used to train a support vector machine (SVM) algorithm, whose classification accuracy was tested on the whole brain as well as on 5 regions-of-interest (ROIs). Results indicated above-chance classification accuracy at the whole brain level (.048), within the language network in the left hemisphere (.046) as well as within a subset of language areas (left IFG, STG and insula, p=.037), where accuracy was driven by correct classification of passive sentences (p=.013 and p=.019, respectively). Classification accuracy was at chance in right hemisphere homologous regions as well as in a region including the occipital lobes and fusiform gyri bilaterally.

Data indicate that machine-learning algorithms can be a useful tool for the investigation of syntactic processing, while univariate analyses may not be sensitive to fine-grained linguistic differences. Additionally, above-chance classification of passive sentences can be successfully carried out only in the left hemisphere, and accuracy increased when targeting a subset of areas associated with syntactic processing.

A9 PD

DEFAULT MODE NETWORK: POTENTIAL BIOMARKER FOR MILD COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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In Parkinson's disease (PD), mild cognitive impairment (PD-MCI) is a common non-motor symptom and a risk factor for developing dementia. Currently there are no effective treatment options for PD-MCI. Resting state functional connectivity (rsFC), as measured with Functional Magnetic Resonance Imaging, is a method to investigate neurobiological mechanisms underlying cognitive impairment. The Default Mode Network (DMN) is believed to support cognition, and dysfunction of the DMN is associated with cognitive impairment in PD (Baggio, 2015). To date, all reported rsFC PD studies that have investigated cognition have included participants on dopaminergic medication. These medications can influence cortico-striatal network rsFC (Kwak 2010) and it is possible they may influence DMN rsFC. In this study we (i) describe DMN rsFC in newly diagnosed, never medicated PD-MCI patients compared to newly diagnosed, never medicated PD patients with normal cognitive function (PD-NC) and healthy controls (HC) and (ii) correlate cognitive test scores with DMN rsFC between groups. Imaging and neuropsychological data were obtained from the Parkinson's Progression Marker Initiative (PPMI; www.ppmi-info.org). Participants were evaluated for memory, visuospatial function, executive function, and attention. In our data analysis, participants were grouped based on Montreal Cognitive Assessment (MoCA) total scores: PD-NC (MoCA >25; n=25), PD-MCI (MoCA 21-25; n=7) and HC (MoCA >25; n=6). DMN rsFC was assessed using independent component analysis and region of interest analyses. Imaging data revealed that PD-MCI participants had mostly hypoconnectivity in parietal regions, the precuneus and anterior cingulate cortex compared to HC. Verbal fluency scores correlated negatively with connectivity in the right temporal parietal region. Compared to PD-NC, PD-MCI had hyperconnectivity in the ventral prefrontal cortex (PFC) and hypoconnectivity in parietal and frontal cortical regions and the posterior cingulate cortex (PCC). Visuospatial scores correlated negatively with medial PFC and precuneus connectivity. Memory scores correlated positively with left PCC connectivity. These data suggest that there are changes of DMN rsFC in PD-MCI and some of these changes may underlie cognitive impairment. Moreover, such changes cannot be attributed to PD medications. Future analyses will focus on rsFC of other cognitive networks and how these measures correlate with cognitive test performance. Collectively, these imaging and neuropsychological assessments may be useful in identifying PD-MCI biomarkers that can be targeted for cognitive rehabilitation therapies. Data used in the preparation of this presentation were obtained from the PPMI database (data last accessed on 9/14/14; http://www.ppmi-info.org/data). PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, such funding partners can be found at www.ppmi-info.org/fundingpartners. This work was

supported with resources and the use of facilities at the Edward Hines Jr., Veterans Affairs Hospital, Hines IL.

A10 G

NEURAL MECHANISMS OF GRAMMATICAL PRODUCTION: A VOXEL-BASED MORPHOMETRY STUDY OF PRIMARY PROGRESSIVE APHASIA (PPA)

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Primary progressive aphasia (PPA) is a neurodegenerative disease that typically affects left hemisphere tissue and can impair grammatical production in some patients (e.g., Mesulam et al., 2014, Rogalski et al., 2011, Thompson & Mack, 2014), however, associated atrophy patterns have been little studied. Studies using voxel-based morphometry (VBM) in PPA have generated atrophy maps associated with noun naming and found a link between temporal lobe atrophy and poor noun performance (Migliaccio et al., 2013, Wilson et al., 2010). Notably, no VBM studies have examined atrophy patterns associated with verb naming across PPA variants. Also, a few studies investigated sentence comprehension deficits, reporting associated atrophy in both the left frontal and temporoparietal cortices (Amici et al., 2007, Peellee et al., 2008), but no studies of sentence production have been reported. The present study examined the relation between regional brain volume and measures of verb and sentence production in PPA using VBM. Of particular interest was identification of the neural mechanisms associated with processing syntactically complex verbs and sentences.

We obtained T1-weighted scans from 64 PPA patients and 44 age-matched controls (AM). The *Verb Naming Test* (VNT) and *Sentence Production Priming Test (SPPT)*(*NAVS*, Thompson, 2011) were administered and used to measure verb and sentence production ability, respectively. First, the T1 scans were analyzed using the VBM procedure to quantify gray matter (GM) volume in PPA and compared it to AM using a two-sample t-test. Next, a Spearman correlation analysis was performed between GM volume in select regions-of-interest (ROI) and grammatical test scores in PPA. ROIs included inferior frontal gyrus (IFG), superior temporal gyrus (STG), middle temporal gyrus (MTG), supramarginal gyrus (SMG), angular gyrus (AG), and insula. The signal density within each ROI was extracted using MarsBar toolbox.

Results showed that the PPA group (compared to 44 AM) had significantly reduced GM in the left MTG, IFG and middle frontal gyrus (MFG). An ROI analysis revealed that reduced GM volume in IFG, STG, and MTG significantly correlated with poor verb production, whereas, that in IFG correlated with sentence production deficits. Additionally, the significant IFG and STG correlations were found for complex verbs, while significant IFG correlation was linked to production of syntactically complex sentences. After controlling for multiple comparisons, significance was determined at the 0.05 level. These findings are important in order to elucidate the relationship between patterns of language decline and tissue degeneration in PPA.

A11 PD

RNA EDITING OF THE AMPA RECEPTOR GLUA2 SUBUNIT IS ALTERED BY PRENATAL STRESS AND ANTIPSYCHOTIC DRUGS

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Glutamatergic transmission through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPARs) is impaired in stress-related psychiatric disorders, including schizophrenia. AMPAR trafficking and function are regulated by the RNA editing and splicing of the AMPAR subunit, GluA2. In the current study, we have investigated the role of GluA2 alternative splicing and RNA editing in mice subjected to prenatal stress (PRS). Reduced social interaction was observed in the PRS mice, which was reversed by administration of the antipsychotic drug clozapine, but not haloperidol. PRS mice had lower levels of GluA2 RNA editing in the hippocampus relative to non-stressed (NS) mice. Clozapine administration in PRS mice increased hippocampal GluA2 RNA editing to levels similar to the NS mice. These differences were specific to the alternatively spliced GluA2 flop isoform. RNA editing of GluA2 flop had a linear relationship with social interaction behavior in the vehicle-control mice. In NS mice, clozapine administration specifically lowered levels of GluA2 flop editing in the hippocampus, while haloperidol administration lowered levels of GluA2 flip RNA editing in the prefrontal cortex and GluA2 flop editing in the hippocampus. Expression analyses of the RNA editing enzymes, ADAR1, 2 and 3, revealed significantly lower ADAR3 mRNA levels in NS mice administered with clozapine, while higher ADAR3 mRNA levels were detected in the PRS

mice administered with clozapine in the hippocampus. These data indicate that prenatal stress and clozapine may influence behavior through altered GluA2 RNA editing in the hippocampus. Therefore, prenatal stress may result in long-term changes in AMPAR function, which may contribute to the pathophysiology of psychiatric disorders. Furthermore, the downstream effects of antipsychotic drugs may include altered GluA2 RNA processing, which could contribute to the efficacy of these drugs in the treatment of schizophrenia. This work was funded by the Vahlteich Scholars Award to MS and the National Institutes of Health Grant to AG.

A12 UG

NEUROPSYCHOLOGICAL PREDICTORS OF FACIAL EMOTION PROCESSING IN HEALTHY INDIVIDUALS ACROSS THE LIFESPAN

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Nonverbal cues represent an integral part of interpersonal interactions; with non-verbal cues such as facial emotions, people can glean information not explicitly said by the people with whom they communicate. Face emotion processing has been studied extensively, but it is not clear how other cognitive processes inform facial emotion processing skills. This study investigates the relationship between performance on the Face Emotion Perception Test (FEPT; Langenecker et al., 2005) and neuropsychological factors among healthy individuals across the lifespan. This study included 215 healthy individuals across four age groups: 18-34 (n = 79), 35-54 (n = 44), 55-74 (n = 52); and 75-88 (n = 40). Participants completed a standard neuropsychological battery. Cognitive tests were categorized into seven different domains, including Verbal Memory, Processing Speed, Verbal Fluency, Visuoperceptual, Complex Attention, Cognitive Control, and Cognitive Flexibility. First, pearson correlation analyses were conducted between FEPT accuracy and performance in cognitive domains within each age group. Domains that were significantly associated with FEPT performance were then included in multiple regression analysis. Sex and education were entered in the first step, while cognitive performance was entered in the second step, with FEPT accuracy as the outcome variable. Results: In the youngest age group, Processing Speed predicted FEPT accuracy. Among individuals 35-54, Cognitive Flexibility predicted FEPT performance. For participants aged 55-74, both Cognitive Flexibility and Cognitive Control predicted FEPT accuracy. In the oldest age group, Complex Attention predicted FEPT performance. Cognitive abilities predict face emotion processing skill, though relationships between specific cognitive functions and face emotion processing change across the adult lifespan, with processing speed being more relevant during earlier adulthood, and executive functioning becoming more germane as the brain ages. During normal aging, emotion processing skills may undergo changes as executive functioning declines, a skill that is especially disposed to age-related changes. In clinical practice, assessment of emotion processing, in addition to other cognitive skills, may be imperative to informing functional outcomes. This study was funded by NIMH (SAL), VA Rehabilitation Research & Development (SLW), The Brain and Behavior Research Foundation (SAL), the Michigan Institute for Clinical and Health Research (SLW), the Michigan Alzheimer's Disease Research Center (SAL/SLW) and the University of Michigan Depression Center (SAL/SLW).

A13 PD

PROBOSCIS EXTENSIONS DURING SLEEP: A NEW SLEEP STAGE IN *DROSOPHILA*?

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Despite its relaxed appearance, sleep is an active process where the brain cycles through different stages of activity. Although the exact function of sleep remains the topic of a lively debate, its proposed functions include memory consolidation and metabolite clearance. Sleep in *Drosophila* has all the hallmarks of mammalian sleep, including homeostasis, altered brain activity, stages of lighter and deeper sleep, increased arousal thresholds and a characteristic posture.

We discovered a novel sleep stage in *Drosophila*, where the fly repeatedly extends its proboscis in a stereotypical manner during inactivity. Experiments in tethered flies showed that, during these proboscis extensions, arousal thresholds are higher than during regular sleep, suggesting deeper sleep. Local field potential recordings showed brain activity that corresponds to deeper sleep stages.

Proboscis extensions are normally an appetitive response, where a hungry fly extends its mouthparts when its gustatory receptors come in contact with sugars. Also, proboscis extensions have also been shown to correlate with CO_2 release during flight, suggesting that proboscis extensions facilitate respiration. So why do flies extend their proboscis during sleep?

We found that proboscis extensions increase with starvation duration, suggesting a link to appetitive mechanisms, where either gustatory receptors become more sensitized or (more

tantalizing) hungry flies replay wake experience. However, we also found substantial evidence that proboscis extensions facilitate a clearing mechanism. Increasing a fly's metabolic rate and CO_2 production, by increasing ambient temperature, increased the rate at which proboscis extensions occur. Also, increasing waste products in the brain by inducing traumatic brain injury resulted in an immediate six fold increase in proboscis extension rate. These data suggest that, besides feeding, a fly uses its proboscis as a pump to increase the rate at which hemolymph flows through its body, increasing gas exchange and metabolite clearance rate. We are currently investigating what sensory mechanisms drive these extensions. This study is funded by an RO1 from NIMH to RA (R01 MH092273-01A).

THEME B. DEVELOPMENT

B1

EXPRESSION OF CREBL2 AND HDAC7 IN RETINAL DEVELOPMENT IN CHICKEN EMBRYOS

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The retina is regarded as a model system for studying neuronal development due to the fact that it is comprised of only seven different cell types, and its neural circuitry is well understood. Progenitor cell differentiation, a vital process in neuronal development, is regulated by the activation and repression of certain genes; however, the exact molecular mechanisms underlying this process remain unclear. Previous studies have shown that the conditional knockout of Dicer prevents the change in competence of progenitors to generate later retinal cells types, therefore suggesting that microRNAs (miRNAs) are required for this developmental progression. Two genes, CREBL2 and HDAC7, whose expression levels increased upon Dicer knockout and thus show potential for miRNA regulation, are further investigated in this study. This inquiry includes an analysis of the gene expression patterns for these two genes across embryonic chicken retinal development. The results of these studies are used to draw preliminary conclusions regarding the roles of these genes in retina development in chicken embryos.

B2

LONG NON-CODING RNA/BRG1 INTERACTIONS REVEAL RNA-DEPENDENT EFFECTS ON CHROMATIN REMODELING IN DEVELOPING FOREBRAIN

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Transcription-regulating long non-coding RNAs (lncRNAs) have the potential to control site-specific gene expression of thousands of targets. Previously, we showed that *Evf2*, the first described ultraconserved lncRNA, stabilizes the transcriptional activator, DLX1 to key DNA enhancers, but represses gene expression. Using mass spectrometry, this report shows that *Evf2*-dependent-DLX1 complexes contain SWI/SNF related chromatin-remodelers, Brahma related gene 1 (BRG1, SMARCA4) and Brahma-associated factor (BAF170, SMARCC2) in developing forebrain. *Evf2* co-localizes with BRG1 in nuclear clouds and increases BRG1 association with key DNA regulatory enhancers in developing forebrain. While BRG1 directly interacts with DLX1 and *Evf2* through distinct binding sites, *Evf2* directly inhibits BRG1 ATPase and chromatin remodeling activities. We propose a mechanism of negative feedback inhibition where *Evf2* attenuates DLX1 activation by binding to chromatin remodelers, inhibiting remodeling activity, and converting an active enhancer to an RNA-dependent repressed enhancer. In vitro studies show that RNA binding to BRG1 and RNA-dependent inhibition of BRG1 remodeling activity occur independently of RNA sequence, suggesting that context is a critical factor in RNA-dependent chromatin remodeling inhibition. Together, these experiments address the apparent paradox of RNA-mediated stabilization of transcriptional activators at enhancers, with a repressive outcome.

B3 G

UNDERSTANDING ROSTRAL FLOOR PLATE PARTITIONING TOWARDS IMPROVED PROTOCOLS FOR DOPAMINE NEURON DERIVATION FROM STEM CELLS

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Cell replacement studies using surgically transplanted fetal grafts have yield mixed results in patients with Parkinson's Disease, owing to graft quality, implantation technique, and patient variation. A tractable and ethically justifiable alternative is the use of easily grown and genetically

modifiable embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSC). Based on developmental studies showing that mDA neurons arise from the Lmx1a+/Foxa2+ rostral floor plate (FP), recent protocols have generated DA neurons from human ESC (hESC). However, the final cellular pool obtained was heterogeneous with significant upregulation of the diencephalic non-mDA markers *DBX1* (developing brain homeobox 1) and *PITX2* (paired-like homeodomain transcription factor 2), indicative of imperfect programming. Our lineage tracing confirm that two non-overlapping microdomains exist within the rostral FP, defined by En (Engrailed) and Dbx1. Our initial data reveal that En1+ progenitors appear to define the extent of the DA progenitor domain. In contrast Dbx1+ progenitors appear to define the origin of Pitx2+ subthalamic neurons. In order to test this microdomain model, conditional mouse genetics will be utilized to spatio-temporally manipulate *En* and *Dbx* gene expression in order to investigate their effects on mDA neuronal identity which will be important to ensure efficient DA production *in vitro*.

B4

SEMAPHORIN3A SHIFTS THE MOTILITY RESPONSE OF BREAST EPITHELIAL CELLS THROUGH INCREASED FOCAL ADHESIONS IN RESPONSE TO CHANGES IN FIBRONECTIN CONCENTRATION

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During the development of the nervous system, axonal pathfinding is directed by guidance molecules. Semaphorin 3A (Sema3A) plays an important role in axonal pathfinding and growth cone guidance. Interestingly, Sema3A has also been shown to inhibit cancer cell migration and metastasis (Herman and Meadows, 2007; Pan et al., 2009). Various studies have suggested that cells encounter an optimal level of adhesiveness to the extracellular matrix (ECM) to enable maximal cell motility (DiMilla et, al. 1993). Since Sema3A has been found to increase integrin receptor expression in breast cancer cells (Pan et al., 2009), we propose Sema3A alters breast epithelial cell motility on different concentrations of fibronectin through enhanced integrin adhesion dynamics. Using a range of concentrations for fibronectin, MDA-MB-231 breast epithelial cells exhibited maximal migration and spreading at intermediate concentrations, while Sema3A treated cells demonstrated maximal migration and spreading at lower concentrations of fibronectin, but inhibited migration at intermediate and high concentrations. Also, Sema3A increased focal adhesion formation in cells at all fibronectin concentrations compared to control. Taken together, these results indicate that Sema3A shifts the balance between ECM concentration and integrin-based adhesion to produce maximal cell migration speeds at lower concentrations of fibronectin, while reducing speeds higher concentrations.

B5 G

UNDERSTANDING THE INVOLVEMENT OF TPR-1 IN PROTEIN MAINTENANCE AND CELLULAR PROTECTION IN C. ELEGANS

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The stability of the proteome depends on the activities of molecular chaperones, which prevent the accumulation of misfolded and damaged proteins. Since protein aggregation is a hallmark of many age-related neurodegenerative diseases, identifying chaperones that fail to remedy folding problems during the disease process is important. Using the well-established *C. elegans* Alzheimer's disease ($A\beta_{42}$) and Huntington's disease (Q35) models, a chaperone-wide RNAi screen revealed that knockdown of an uncharacterized conserved gene, *tpr-1*, enhances age-related proteotoxicity. TPR-1 contains a conserved TPR domain, which is found in co-chaperones such as HOP/STI-1. The TPR domain of HOP/STI-1 binds EEVD sequences located in the C-terminus of HSP70 or HSP90, facilitating the folding of client proteins. Possibly TPR-1 cooperates with HSP70 or HSP90 to protect cells from age-related proteotoxicity. Therefore, we are comparing the spatial and temporal expression patterns of *tpr-1* with the *C. elegans hsp70* and *hsp90* genes. To understand the role of *tpr-1* during aging, we performed RNA interference (RNAi) against *tpr-1*. Our data show that knockdown of *tpr-1* leads to a decrease in lifespan, providing evidence that TPR-1, along with HSP70 and HSP90, could serve as a protector against age-related proteotoxicity.

B6 G

REACHING NEW DISTANCES: EXTENDING NEURONAL REGENERATION WITH NANOGROOVES *EX VIVO*

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Introduction: Peripheral nerve damage is a common result of many injuries and disease states. While the peripheral nervous system regenerates spontaneously, the extent to which it does is often insufficient to fully restore function. Such a loss can have a severe impact on quality of life for many patients. There is a great deal of research in increasing

axonal growth using biochemical growth factors. While these growth factors may increase axonal development, it is often uncontrolled and random in direction. Such growth is inefficient in delivery of neurites to more distant structures. Therefore, the aim of this study is to control the direction of axonal growth using nano- to micron scale grooves as topographical cues. We believe organized and direct axonal growth will increase the effective reach of these neurites and could lead to a more functional recovery.

Hypothesis: Our hypothesis is that axons will use the biophysical signals as a guide and propagate parallel to them which will lead to a longer effective axonal length.

Methods: For the purposes of this study, we used *ex vivo* explants of mouse dorsal root ganglia (DRGs) as our experimental model. Cervical and thoracic DRGs were harvested and cultured on varying sizes of anisotropic grooves. Three groove widths were tested: 200nm, 700nm, and 2,000nm. A chemically identical flat surface was used as a control. All groups were maintained in Serum Free Medium (SFM) with 5ng/mL Nerve Growth Factor (NGF) for 6 days. They were then fixed, immunolabeled, and visualized using fluorescent confocal microscopy.

Results: Imaging and analysis demonstrated that axons align and grow in a linear fashion along the 700 and 2,000 nm grooves significantly more than the control. No significant difference was seen for the 200nm grooves. This manner of direct propagation also significantly extended the average radius of growth of the axons in the 700 and 2,000 nm groups. There was over a 50% increase in the average effective axonal length seen in the 700 nm group over the control.

Conclusion: These results may translationally be applied toward novel treatments to directionally enhance spontaneous nerve regeneration across distances greater than those which occur naturally.

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B7 PD

EVF2 LNCRNA ANTI-SENSE REGULATION CONTROL COMPLEX BEHAVIOR IN MICE

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The ultra-conserved long non-coding RNA *Evf2* represses expression of homeodomain transcription factors Dlx5 and Dlx6, key regulators of GABAergic interneuron development in mouse brain. Previous work showed that the numbers of early postnatal hippocampal GABAergic interneurons are reduced in mice lacking ($Evf2^{TS/TS}$), followed by decreased synaptic inhibition in adult hippocampus. Here, we show that $Evf2^{TS/TS}$ mice are more sensitive to the seizure-inducing drug pentenetetrazol (PTZ), a result that is consistent with loss of hippocampal interneurons and reduced inhibition. However, $Evf2^{TS/TS}$ mice have reduced immobility times in the forced swim test (FST), a test for depressive-like behavior in mice. In order to further investigate possible causes of FST reduced immobility, we examined synaptic activity in CG1 frontal cortex, a region known to mediate depressive-like behavior. Despite decreased numbers of CG1 interneurons, GABAergic synaptic inhibition increases in $Evf2^{TS/TS}$ frontal cortex. In addition, the calcium binding proteins, calbindin (CLB) and calretinin (CLR), increase in $Evf2^{TS/TS}$ frontal cortex but not in the hippocampus. These data support the idea that *Evf2* modulates depressive-like behavior by regulating calcium binding protein expression and decreasing the number of interneurons involved in disinhibition in frontal cortex. Increased seizure susceptibility and decreased forced swim immobility in mice lacking *Evf2* suggest that a single long non-coding RNA controls complex behavior through regional effects on interneurons.

B8 UG

THE IMPORTANCE OF A BALANCED DIET: THE EFFECT OF PROTEIN-TO-CARBOHYDRATE RATIO IN BODY AND ORGAN SIZE IN *DROSOPHILA*

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Proteins and carbohydrates are essential for organismal growth and development. While the individual effects of protein- and carbohydrate-deprivation on final body size have been well studied, what is less well understood is how the relative amount of proteins to carbohydrates in a diet affects growth. Here, we explore how the absolute amount and relative ratio of dietary proteins and carbohydrates affect final body size and body proportion, using *Drosophila* as a model organism. We reared flies on 24 different combinations of proteins and carbohydrates (four different food levels, each with six different protein-to-carbohydrate ratios), and measured the body parts of the

resulting adults. As expected, a decrease in total amount of nutrients in a diet results in a decrease in final body and organ size. However, our data indicate an interaction between the quantity of proteins and carbohydrates on size, such that the effect of increasing carbohydrates depends on the quantity of proteins in a diet, and vice versa. Intriguingly, at low protein levels an increase in carbohydrates actually decreases body and organ size, whilst the opposite is true at high protein levels. Further, this interaction between proteins and carbohydrates is only detected in females, suggesting that it is a sex-specific effect. These data indicate that body size is not only influenced by the absolute amount of nutrients in a diet, but also how balanced the diet is.

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 G

MODELING A CLOSED-HEAD CONCUSSION IN THE ADULT RAT

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Recently, cases of multiple concussions in athletes and soldiers have received increased attention. Most cases of a single concussion recover well with adequate time, but repeat concussions (rTBI) can produce significant long-term behavioral and physiological consequences and result in an increased incidence of neurodegenerative disorders. The mechanisms underlying why rTBI is more detrimental than a single concussion are poorly understood, and can best be elucidated in an animal model. However, while models of rTBI are established in the adult mouse and juvenile rat, a closed head impact model of concussion or rTBI in the adult rat is lacking. Therefore, we developed a clinically-relevant closed-head injury model of concussion in the adult rat using a Benchmark Impactor commonly used to model moderate/severe TBI. The impactor delivers a blunt force injury of a specific velocity and depth, typically through a craniotomy. We delivered the impact directly onto the surface of the head centered over the forelimb sensorimotor cortex. Our final injury parameters included a 5 mm tip to deliver an impact at 6.5 m/s at a depth of 10.0mm from the surface of the skin. Animals were placed in a stereotaxic frame with a foam bed base without ear bars. The head was stabilized against a Plexiglas frame to control the area of impact while allowing the head to move in response to the injury. Several parameters in both velocity and depth were tested until injuries resulted in several clinical markers of concussion: the absence of mortality, skull cracks, surface damage to the cortex, and gross pathology under cresyl violet; and the presence of some mild behavioral deficits. Behavioral parameters included tests of memory (Novel Object Recognition), forelimb coordination (foot fault) and general locomotion (open field). Our results indicate that three days after the injury, rats displayed memory deficits in the NOR task. Five and seven days after injury, injured animals also show deficits in forelimb coordination, hypolocomotion, and spend less time in the center of an open field, an anxiety response. To date, this is the only model of closed head injury in the adult rat to show deficits in memory and motor coordination, hypoactivity, and a mild anxiety response without cortical pathology. This model is now being used to examine differences in behavior and pathology in rats with both single and multiple concussions.

C2 G

FAST AXONAL TRANSPORT DEFICITS INDUCED BY MUTANT HUNTINGTIN INVOLVE ACTIVATION OF A SPECIFIC MAPK PATHWAY

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Huntington's disease (HD) results from expansion of a polyglutamine (polyQ) tract located at the amino terminus of the Huntingtin (Htt) protein. Despite this knowledge, underlying mechanisms of HD pathogenesis remain elusive. Several independent studies reported inhibition of fast axonal transport (FAT) in cellular and animal models of HD. Recent work from our lab further demonstrated that mutant Htt (mHtt) inhibits FAT through activation of c-Jun N-terminal Kinase 3 (JNK3), which in turn phosphorylates and inhibits conventional kinesin, a major motor protein. However, mechanisms mediating JNK3 activation by mHtt were not revealed by these studies. JNK3 is activated by upstream kinases mitogen-activated protein kinases (MAP2Ks), which are activated by mitogen-activated protein kinase kinase kinases (MAP3Ks). Among several MAP3K members, mixed-lineage kinases (MLKs) feature an intramolecular interaction between a Src homology (SH3) domain and an internal SH3-binding motif (PXXP), which renders the kinase inactive. Interestingly, Htt features SH3-binding motifs within proline-rich domains (PRDs) immediately adjacent to its polyQ tract. This observation led us to hypothesize that mHtt might activate MLKs through allosteric mechanisms. Here, we present data from biochemical and microscopy-based experiments in isolated squid axoplasm demonstrating that the inhibition of FAT

induced by mHtt involves activation of axonal MLKs. Furthermore, our data mapped specific PXXP motifs within the PRDs of Htt that suffice to inhibit FAT. Collectively, our data suggest that the inhibitory effect of mHtt on FAT involves activation of MLKs through an allosteric mechanism. This study is funded by CHDI Foundation.

C3 PD

CENTRAL AND SYSTEMIC EFFECTS OF DRONABINOL, A CANNABINOID AGONIST, ON APNEA

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Untreated obstructive sleep apnea (OSA) is associated with cardiovascular and metabolic diseases. Treatments for OSA are limited, and there are no pharmacological treatments. In anesthetized rats, dronabinol attenuates reflex apnea via activation of cannabinoid (CB) receptors located on vagal afferents, and reflex apnea attenuation is blocked by systemic pre-treatment with cannabinoid type 1 (CB_1) and/or type 2 (CB_2) receptor antagonists. Here, we examine the effects on apnea on centrally- or systemically-administered dronabinol in an acute anesthetized or chronic conscious animal model, respectively. In acute anesthetized animal model, Sprague-Dawley rats were anesthetized and instrumented with a piezoelectric strain gauge to monitor respiratory pattern. Serotonin (12.5 µg/kg) was intravenously infused into a femoral vein to induce apnea. After baseline recordings and intracerebroventricular (ICV) injections of dronabinol (100 or 10 µg/3 µl DMSO), 5-HT was infused again to induce apnea. **In chronic conscious animal model,** Sprague-Dawley rats were anesthetized and implanted with bilateral stainless steel screws into the frontal/parietal bones of the skull for EEG recording and bilateral wire electrodes into the nuchal muscles for EMG recording. The EEG/EMG leads were soldered to a miniature connector and fixed to the skull. Rats were allowed to recover from surgery for one week. Each animal was recorded by polysomnography on multiple occasions (10:00-16:00) separated by at least 3 days. The study was a fully nested, repeated measures crossover design, such that each rat received each of 8 intraperitoneal injections one time: vehicle alone (DMSO/sesame oil in PBS); vehicle and CB_1 antagonist (AM 251, 5 mg/kg); vehicle and CB_2 antagonist (AM 630, 5 mg/kg); vehicle and CB_1/CB_2 antagonist (5 mg/kg); dronabinol alone (10 mg/kg); dronabinol and CB_1 antagonist; dronabinol and CB_2 antagonist; dronabinol and CB_1/CB_2 antagonist. Data were analyzed using repeated measures ANOVA with Tukey's Multiple Comparison Test. In the acute anesthetized animal model, ICV injections did not attenuate 5-HT-induced apnea. In the chronic conscious animal model, dronabinol decreased the percent time spent in REM sleep compared to vehicle controls. Cannabinoid receptor antagonists did not reverse this effect. Moreover, dronabinol did not suppress apneas. In conclusion, central and systemic administration of dronabinol did not suppress apneas. This supports published literature that apnea attenuation occurs specifically via peripheral CB receptors on the nodose ganglia of the vagus nerve. Future work will concentrate on CBs that do not cross the blood-brain barrier. This work is funded by a research grant from the National Institutes of Health (1UM1HL112856).

C4

MOTOR CORTEX EXPRESSION OF MECHANO GROWTH FACTOR mRNA AND RELATED GENES IN RATS FOLLOWING HYPOXIA

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It has been proposed that mechano growth factor (MGF) – a splice variant of insulin-like growth factor-1 (IGF-1) – has neuroprotective properties. In our study we hypothesize that MGF is endogenously expressed in the brain and that it is regulated by a brain injury – such as ischemia. In addition, based on previous research on the possible neuroprotective role of MGF in an animal model of stroke, we hypothesize that MGF plays its neuroprotective role via activation of heme oxygenase – 1 (HO-1) associated pathway. In our study, we exposed adult male Wistar rats to various degrees of hypoxia for 4h (6-12% oxygen levels) using isobaric hypoxia chamber. The rats were then sacrificed at either 2 or 24h post hypoxia treatment. Brains were rapidly frozen in isopentane and stored in -80˚C until they were sectioned into 200 µl sections on a cryostat and the motor cortex was micro-dissected using 2mm Palkovit's brain micro-dissection tool. RNA was isolated using TriReagent according to the manufacturer's instructions. RNA expression was analyzed using real time reverse transcription- polymerase chain reaction (RT-PCR).

We confirmed the hypoxia treatment effect by observing hypoxia-inducible factor – 1α (HIF-1α) mRNA expression. Additionally, hypoxia induced cell damage was measured by observing caspase 3 and caspase 8 mRNA expression. Our study showed that MGF mRNA was endogenously expressed in the rat motor cortex at very low levels and that hypoxia treatment altered MGF mRNA expression in a time and dose specific manner. In addition, our study showed a possible

correlation between changes in MGF mRNA levels and HO-1 associated pathway. There was a time and dose specific regulation of HO-1 and biliverdin reductase A mRNA - a downstream enzyme in HO-1 associated pathway - due to hypoxia conditions.

This is the first demonstration that MGF is expressed endogenously in the rat brain and that its expression pattern changes upon brain injury. Moreover, our study showed that MGF may exert its neuroprotective effects via activation of HO-1 associated pathway in the motor cortex. These results warrant further investigation to further elucidate the role that MGF has in the brain. This study is supported by LUHS internal funding.

C5 PD

OPTOGENETIC DISSECTION OF STN-GPe IN VIVO NETWORK ACTIVITY IN EXPERIMENTAL PARKINSON'S DISEASE

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Abnormal, synchronous neuronal activity in the cortico-basal ganglia thalamo-cortical network is believed to underlie motor dysfunction in Parkinson's disease (PD). Neurons in the subthalamic nucleus (STN) and reciprocally connected external globus pallidus (GPe) are thought to be fundamental to the emergence of parkinsonian activity. Using the unilateral 6-hydroxydopamine-lesion mouse model, the goal of my research is to determine the origins of parkinsonian cortico-basal ganglia thalamo-cortical network activity *in vivo*. I am using silicon tetrodes/optrodes to simultaneously record cortical, STN and GPe activity in anesthetized mice in order to compare the impact of stereotyped cortical activity patterns on the normal and dopamine–depleted basal ganglia. Our studies confirm that following the loss of dopamine, STN-GPe network activity becomes excessively synchronized to cortical inputs and neurons in the GPe discharge in anti-phase or in-phase to cortical and STN activity. We are applying light-sensitive inhibitory opsins in cell type-specific transgenic mouse lines to manipulate STN-GPe activity in order to study its impact on rhythmic cortico-basal ganglia thalamo-cortical loop activity. Initial studies suggest that hyperexcitability of D2 striatal projection neurons (D2-SPNs) following dopamine depletion promotes widespread anti-phasic GPe-STN synchronization.

C6 PD

PRESENILIN-DEPENDENT MODULATION OF AXODENDRITIC OUTGROWTH REQUIRES APP FUNCTION

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Presenilin 1 (PS1) is an essential component of the γ-secretase complex, the enzyme responsible for intramembraneous cleavage of amyloid precursor protein (APP) that generates β-amyloid peptides (Aβ) and APP intracellular domain (AICD). Mutations in PS1 lead to dominant inheritance of early onset familial Alzheimer's disease (FAD). Although there is a consensus that FAD-linked PS1 mutations affect toxic Aβ production, the importance of APP per se and other PS1-dependent substrates in the etiology of the disease has not been confirmed. Recently, we have observed that primary cortical neurons generated from PS1 knock-out ($PS1^{KO}$) and PS1 knock-in ($PS1^{KI}$) mice harboring FAD-linked PS1-M146V variant exhibit an increase of axodendritic outgrowth. These outcomes parallel a large and moderate increases of APP-CTF and DCC-CTF in brain lysates prepared from either $PS1^{KO}$ or $PS1^{KI}$ mice, respectively. Accordingly, these results are in support of a partial lost of function of γ-secretase activity in PS1 mutant. Strikingly, lack of APP expression in cortical neurons expressing PS1-M146V variant led to a decrease in both axonal and dendritic outgrowth; an effect that was not seen in neurons lacking DCC expression. These results indicate that APP is required for PS1-dependent change in neurite outgrowth associated with PS1 mutation. Treatment with γ-secretase inhibitor does not induce additional morphological change in $APP^{KO}PS1^{KI}$ supporting again the importance of APP in PS1-induced neurite outgrowth. Moreover, we observed that accumulation of APP-CTF through concomitant overexpression of APP full-length and γ-secretase inhibition or overexpression of membrane-tethered APP intracellular domain (mAICD) rescue axodendritic outgrowth in $PS1^{KI}$ neurons lacking APP expression. Taken together, our findings provide the first demonstration that a pathological loss of PS1 function lead to a gain of APP function. Our results also identify APP-CTF accumulation as a key player in axodendritic outgrowth. Because accumulation of APP-CTF at the membrane is an invariable outcome of therapeutic inhibition of γ-secretase aimed at reducing cerebral amyloid burden, our findings could have important implications in Alzheimer's disease treatment. Supported by NINDS and Alzheimer's Association.

C7 UG

USING ANTISENSE OLIGONUCLEOTIDES (ASO) AS A THERAPY FOR BATTEN DISEASE

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Juvenile neuronal ceroid lipofuscinoses (JNCL) or more commonly known as Batten disease, is an autosomal recessive lysosomal disorder that is caused by a mutation in the *cln3* gene. Patients with Batten disease experience progressive vision loss, seizures, ataxia or clumsiness. It is difficult to determine a successful therapy for Batten disease because the function of the *cln3* protein remains unknown. 85% of batten disease cases result from a frame shift mutation caused by a 1.02 kb deletion of exons seven and eight. Our approach is to use antisense oligonucleotides (ASO) to skip axons 6 or 9 to put the *cln3* mRNA transcript back into frame using a $cln3^{\Delta ex7/8}$ mouse model. In this study, we test the effects of ASO A and B to skip exon 6 and exon 9 of the *cln3* gene, respectively. Motor coordination and learning abilities were assessed in the mice by rotarod test and Morris Water Maze (MWM) at 2 and 4 months of age. Our results show that heterozygous mice perform significantly better when compared to mutant mice in the Rotarod and MWM, which suggests ASO is a potential therapeutic approach for batten disease.

C8 UG

INSIGHT INTO PARKINSON'S DISEASE: EVALUATION OF FAMILIAL MUTANTS AND SUMOYLATION OF α-SYNUCLEIN IN YEAST

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Parkinson's disease (PD) is a hypokinetic neurodegenerative disorder linked to the death of midbrain dopaminergic neurons. Within affected cells are Lewy bodies composed primarily of insoluble aggregates of the protein α-synuclein. PD can be genetic or sporadic; genetic forms account for 10% of cases and thus far, seven mutant genes have been identified, including α-synuclein. Six mutations on α-synuclein cause PD (A30P, E46K, H50Q, G51D, A53E, A53T). Of these, A30P, E46K, and A53T are well studied in diverse model systems and each appears to confer toxicity in a distinct way. The three newer mutants (H50Q, G51D, A53E) identified since 2013, have only recently begun to be characterized. α-Synuclein is also a highly post-translationally modified protein. While phosphorylation and nitration effects on α-synuclein are very well documented, less is known about sumoylation, which is proposed to be neuroprotective based on limited studies. Sumoylation influence on familial mutants of α-synuclein is also not well understood. The majority of sumoylation takes place on lysine-96 and lysine-102 in α-synuclein. Our goal was to test two related PD-related hypotheses: 1) the three newer familial mutants will exhibit several known toxicity-related properties in their own distinct ways; 2) sumoylation will protect against α-synuclein toxicity by modifying these PD related properties characteristic of wild-type α-synuclein and each familial mutant. First, we have created and expressed all new familial mutants and sumoylation-blocking variants (K96R, K102R, K96R/K102R) in our well-established budding and fission yeast models and are actively testing multiple pathology-related properties in these models. Second, we have preliminary evidence that the three new familial α-synuclein mutants each exhibit a distinctive profile of membrane association and intracellular aggregation in both yeast models; one appears to be more toxic than the others. Third, we find that reducing α-synuclein sumoylation not only increases its aggregation, but also reduces its association with the plasma membrane. We believe this is the first description of the sumoylation effects on α-synuclein membrane association. In the future, we plan to expand our assessment of other PD-related properties with the familial mutants and examine sumoylation effects not only on familial mutants, but also on other known variants of α-synuclein, namely, C-terminal truncations and splice variants. This study is funded by a research award from the National Institutes of Health (R15) to SD.

C9 PD

A NOVEL THERAPY FOR EPILEPSY USING BIODEGRADABLE IMMUNE-MODIFYING NANOPARTICLES

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Rationale: Recurrent or prolonged seizures lead to activation of immune responses, which can further precipitate seizures and create a deleterious positive feedback loop. Ample evidence has shown effectiveness of immune-modulatory agents in treating certain epileptic encephalopathies. We have previously reported detection of brain-infiltrating innate and adaptive immune cells in the resected brain of patients with intractable epilepsy and mice subjected to two-hit induced status epilepticus. In murine models of experimental autoimmune encephalomyelitis and West Nile virus encephalitis, we have documented the efficacy of immune modulating nanoparticles to significantly reduce

inflammatory tissue damages. The goal of this project is to adopt a similar approach to treat childhood epilepsy using biodegradable nanoparticles capable of dampening the inflammation in the brain parenchyma through inhibition of peripheral immune cell infiltration.

Methods: C57Bl/6 mice were injected intraperitoneally with proconvulsant kainic acid (KA) to induced status epilepticus (SE). High negatively charged nanoparticles derived from poly (lactic-co-glycolic acid) (PLGA) were intravenously delivered to these mice immediately after KA injection. Mice were perfused with cold PBS and brain tissues were processed to generate single cell suspension suitable for flow cytometric analyses.

Results: We detected brain-infiltrating antigen presenting cells and lymphocytes in control mice that had KA-SE. Significant reduction of antigen presenting cells, including inflammatory monocytes, macrophage, and dendritic cells, and lymphocytes were observed in the brain of mice treated with nanoparticles after KA-SE. Selective retention of some antigen presenting cell and lymphocytes in the spleen was detected, closely corresponding to a decrease in brain-infiltrating populations of immune cells. Additionally, the blood-derived immune cells detected in the brain parenchyma were poorly activated compared to the untreated control animals with KA-SE.

Conclusions: Our preliminary data demonstrated for the first time that the control of peripheral leukocytes infiltration into the brain of mice with status epilepticus can be achieved using biodegradable immune-modulatory nanoparticles. This treatment altered the migratory behavior of major innate and adaptive immune cells and can potentially be used therapeutically to reduce immune-mediated seizure pathology and perhaps promote repair cascade.

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C10 G

WITHDRAWN

C11 UG

INSIGHT INTO PARKINSON'S DISEASE: EVALUATION OF SPLICE VARIANTS AND C-TERMINAL TRUNCATIONS OF α-SYNUCLEIN IN YEAST

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Parkinson's disease (PD) is a neurodegenerative disease caused by the death of midbrain dopaminergic neurons linked to misfolding and aggregation of the protein α-synuclein. Familial PD accounts for 10% cases and is linked to at least seven genes. Six different mutations on α-synuclein itself cause PD. While the full-length α-synuclein (which is 140 amino acids long) is the major misfolded form in all PD forms, smaller versions of α-synuclein were recently discovered, including three splice variants (α-syn126, α-syn112, and α-syn98) and several carboxyl-terminal truncation variants (α-syn103, α-syn110, α-syn120, and α-syn123). Truncation variants are better studied, but in the wild-type α-synuclein background only, and in cell culture and *in vitro* systems; current splice variants studies are limited to just one report. Evaluation of both variant types needs to be extended to additional model systems. Furthermore, properties of neither type of variants are known for the six familial mutant α-synuclein backgrounds. We tested the hypotheses that both types of variants would possess a higher pathogenic potential compared to the full-length form, and that this increased pathogenicity would be further potentiated on the six familial mutant backgrounds. We used our well-developed budding yeast model to test our hypotheses. Here, we firstly describe the creation, subcloning, and yeast transformation of all 32 splice variant forms of α-synuclein and 18 familial splice variants needed for this study. Thus far, we have examined both types of variants in the wild-type α-synuclein background. With them, we describe evidence that the truncation variants have altered solubility, membrane association and aggregation potential; the degree of change depends on how much of the C-terminus is removed. Finally, we show that splice variants possess reduced membrane association and increased aggregation, depending on the variant. In the future, we will compare variant properties in familial mutant backgrounds and add several more pathology-linked characteristics for fuller evaluation. Our longer-term expectation is that our completed studies will provide a fuller picture of the contributions of the diversity of naturally occurring α-synuclein variants in PD pathogenesis. (Support: NIH R15 grant to SD and Parkinson Disease Foundation grant to NK).

C12 G

SEX DIFFERENCES IN DENDRITIC COMPLEXITY CORRELATE WITH POST-STROKE RECOVERY IN AGED RATS

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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 clinical population, post-menopausal females have been shown to recover from stroke less successfully than age-matched males, and therefore studying sex differences in rat models of stroke is clinically relevant. . Our previous work has shown that aged female rats learn the sensorimotor tasks faster than age-matched males, but following a stroke age-matched males recovered better. We then sought to correlate these behavioral results with dendritic plasticity.18 month-old Fischer 344 male and female aged rats were divided into four groups: ovariectomized (OVX) females, intact females, sham OVX males, and intact males. Pre-stroke, animals were trained in the skilled forelimb reaching task. 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, and then sacrificed for Golgi-Cox staining and dendritic characterization of pyramidal layer V motor neurons for complexity, length, number and the density of dendritic spines. Analysis of dendritic arborization showed that pre-stroke, intact females had the greatest number of dendrites in the higher complexity levels whereas the OVX females had the lowest in the earlier complexity levels. Intact females also had the greatest length and number of dendrites whereas the OVX females had the lowest. OVX females had the lowest density of spines compared to all other groups. Post-stroke, all groups showed a decrease in complexity with the largest decrease seen in the intact female group. In conclusion, our results show that removing ovarian produced estradiol results in less dendritic complexity, number, length and spine density in the pyramidal layer V motor cortex neurons in aged female rats. We also found a correlation between final reaching score on the sensorimotor task and dendritic number, with a higher final score correlated with higher dendritic counts. This study was funded by the Loyola Neuroscience Research Institute and the Department of Veterans Affairs.

C13

AMINO-NOGO-A NEUTRALIZATION FAILS TO POTENTIATE THE EARLY SUBVENTRICULAR ZONE RESPONSE TO FOCAL ISCHEMIA IN ADULT RATS

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Stroke is a leading cause of adult disability with no approved pharmacological treatments beyond the acute phase. Experimental approaches to improving functional recovery include treatments that enhance plasticity of existing neural circuits or the inherent regenerative capacity of the brain. One such treatment, neutralizing antibodies to the myelin-associated neurite outgrowth inhibitor Nogo-A ("anti-Nogo-A immunotherapy"), has been shown by our laboratory to enhance structural plasticity and functional recovery after stroke in adult and aged rats. However, the exact cellular targets of this novel treatment are not fully understood. A recent study proposed a role for Nogo-A in the maintenance of the subventricular zone (SVZ), one of the adult brain's main neurogenic niches (Rolando et al., J Neurosci, 2012). Endogenous neural precursor cells may contribute to injury mitigation and behavioral recovery after stroke, raising the intriguing question of whether neural precursor cells are a therapeutic target of anti-Nogo-A immunotherapy. To investigate this possibility, we induced cortical ischemia in rats via middle cerebral artery occlusion, followed by two weeks of anti-Nogo-A immunotherapy delivered by osmotic minipump into the ipsilesional lateral ventricle. Cellular proliferation in the SVZ was measured by bromodeoxyuridine injection and stereological cell counting, and the neuroblast response was assessed using quantitative immunohistochemistry. We confirmed Nogo-A expression by neuroblasts in the SVZ by double label immunofluorescence. However, despite adequate penetration of the antibody into the brain parenchyma and proximity of the infused antibody to the SVZ, we found no evidence of changes in proliferation or neuroblast density after this two week anti-Nogo-A treatment. We are currently analyzing additional time points and plan to investigate whether Nogo-A neutralization influences longer-term parameters of neurogenesis, including the differentiation, integration, and survival of newborn neurons. This work is supported by the Department of Veterans Affairs and the Loyola Neuroscience Research Institute.

C14 G

THE EFFECT OF PRAMIPEXOLE ON DOPAMINE-ASSOCIATED BEHAVIORS AND SIGNALING MECHANISMS IN A RAT MODEL OF PARKINSON'S DISEASE

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Parkinson's disease (PD) patients exhibit motor deficits, e.g., postural instability, rigidity and bradykinesia, associated with loss of nigrostriatal dopamine (DA). Pramipexole (PPX), a DA agonist with high affinity for D2/D3 receptors (R), provides excellent relief from PD-related motor deficits; however, some patients develop impulse control disorders during chronic PPX therapy. Mechanisms that underpin the motor improvements vs. impulsivity in these patients remain unclear. To shed light on this issue, we employed a model of PD (i.e., rats with 6-OHDA-induced lesions of the dorsolateral striatum) and studied the effects of PPX on motor function (postural instability), impulsive decision-making (intracranial self-stimulation-mediated probability discounting) and biochemical signaling that may underlie synaptic adaptations to PPX exposure (i.e., GSK-3β linked to AMPA-R trafficking). Acute administration of PPX (0.01, 0.03, 0.1, 0.3 and 1mg/kg) dose-dependently improved postural instability, and this effect was blocked by an antagonist to D2Rs (L741,626) but not to D3Rs (PG01037). PPX increased risk-taking after chronic exposure to 1.2mg/kg PPX. The inactive form of GSK-3β was enhanced in forebrain regions by acute PPX at 0.03-0.6mg/kg, but high doses reduced the inactive form and increased AMPA-R surface expression. These findings parallel the clinical profile, showing that PPX rapidly provides motor benefits, but chronic exposure can increase risk-taking. PPX-induced signaling via GSK-3β-mediated actions may have bimodal effects that are associated with these divergent behavioral outcomes. Such findings may help lead to PD therapies which are motorically efficacious but devoid of ICD side effects. Acknowledgments: USPHSGs #DA033121, #NF087559 and the Michael J Fox Fdn.

C15 G

ACTIVATION OF NLRP3 INFLAMMASOME IN MICE WITH THE OPTIC NERVE CRUSH INJURY

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Background: Microglia-mediated neuroinflammation is associated with many neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's disease. A major player of microglia function is NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome, which is the sensor for a variety of pathogen-associated stimuli as well as self-danger signals. Much remains to be investigated about its role in optic neuropathy. In this study, we examined whether NLRP3 inflammasome is involved in the retinal ganglion cell (RGC) degeneration in a mouse model of partial optic nerve crush (pONC).

Methods: pONC model was used to examine RGC death in optic neuropathy. The pONC was performed using the self-closing forceps at the site about 1mm behind the eye ball from the superior and temporal side. NLRP3 knockout mice were used to examine the role in optic neuropathy. In vivo imaging of the Thy-1-YFP transgenic mouse retina was performed to track the cell loss after the pONC injury.

Results: Significant RGC loss was observed following the pONC injury. The number of Iba-1-immunostained microglia cells significantly increased in the inner retina at 1-day after the pONC with enlarged nuclei and thick, short and less ramified processes, indicating the activated phenotype. The assembly of a large NLRP3 inflammasome complex was found in retinal microglial cells in response to the pONC injury, resulting in the maturation of caspase-1 and IL-1β. In vivo imaging showed the RGC death was significantly delayed in the NLRP3 knockout mice post the pONC injury.

Conclusions: Our data suggested that NLRP3 inflammasome was activated in microglia following the optic nerve crush injury, and that knocking out of *nlrp3* gene delayed RGC death.

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C16 PD

HYPER-ACTIVATION OF L-TYPE CA^{2+} CHANNELS, INDEPENDENT OF NMDA RECEPTOR, MEDIATES INCREASED CA^{2+} INFLUX IN PYRAMIDAL NEURONS FROM THE RAT MEDIAL PREFRONTAL CORTEX IN THE CONTEXT OF HIV INFECTION

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Human immunodeficiency virus-1 (HIV) infection induces neurological and neuropsychological deficits. The medial prefrontal cortex (mPFC) regulates cognition, emotion and motivation-driven behavior which are functions that are disrupted by HIV. In the current study, we evaluated the consequences of HIV infection on the mPFC, as modeled in HIV-1 transgenic (Tg) rats. Whole-cell patch-clamp recordings were performed to assess cell membrane properties and Ca^{2+} influx (reflected by Ca^{2+} plateau potentials). We found that neurons from HIV-1 Tg rats displayed depolarized resting membrane potentials, reduced rheobase, decreased action potential amplitude, increased numbers of action potentials elicited by depolarizing currents, as well as aberrant firing properties when compared to those from non-Tg rats. Inward rectification was also reduced at hyperpolarized membrane potentials in neurons from HIV-1 Tg rats, suggesting dysregulated subthreshold excitability. Additionally, such neuronal hyper-excitation was associated with abnormally-enhanced Ca^{2+} influx through L-channels, which was abolished by L-channel blockade, independent of NMDAR. Our findings show that HIV infection alters mPFC neuronal function by dysregulating membrane excitability and voltage-sensitive Ca^{2+} influx, specifically at the L-channel and most importantly independent of NMDA receptor. Overall, these findings demonstrate that HIV renders mPFC pyramidal neurons more susceptible and vulnerable to excitatory stimuli, which could contribute to HIV-associated neuropathogenesis.

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C17 PD

SEX DIFFERENCES IN GABAERGIC GENE EXPRESSION OCCUR IN THE ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA

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GABAergic dysfunction has been strongly implicated in the pathophysiology of schizophrenia. In this study, we analyzed the expression levels of several GABAergic genes in the anterior cingulate cortex (ACC) of postmortem subjects with schizophrenia (n=21) and a comparison group of individuals without a history of psychiatric illness (n=18). Our analyses revealed a significant sex by diagnosis effect, along with significant differences in GABAergic gene expression based on medication status. Analyses revealed that in male groups, the expression of GABAergic genes was generally lower in schizophrenia cases compared to the controls, with significantly lower expression levels of GABA-Aα5, GABA-Aβ1, and GABA-Aε. In females, the expression of GABAergic genes was higher in the schizophrenia cases, with significantly higher expression of the GABA-Aβ1 and GAD67 genes. Analysis of the effect of medication in the schizophrenia subjects revealed significantly higher expression of GABA-Aα1-3, GABA-Aβ2, GABA-Aγ2, and GAD67 in the medicated group compared to the unmedicated group. These data show that sex differences in the expression of GABAergic genes occur in the ACC in schizophrenia. Therefore our data support previous findings of GABAergic dysfunction in schizophrenia and emphasize the importance of considering sex in analyses of the pathophysiology of schizophrenia. Sex differences in the GABAergic regulation of ACC function may contribute to the differences observed in the symptoms of male and female patients with schizophrenia. In addition, our findings indicate that antipsychotic medications may alter GABAergic signaling in the ACC, supporting the potential of GABAergic targets for the development of novel antipsychotic medication. This work was funded by the UIC Collaborative Engagement in Novel Therapeutic Research and Enterprise award to MS, and NIH R01 awards MH066392 and MH064673 to VH.

C18 G

USING YEAST AS A MODEL TO UNDERSTAND THE MECHANISMS THAT UNDERLIE PROTEIN AGGREGATION, AMYLOID FORMATION, AND PRIONIZATION

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Current knowledge of prion biology has been greatly enhanced by studies in *Saccharomyces cerevisiae,* which contains several epigenetic elements known as yeast prions. The yeast prion [SWI^+], whose protein determinant is Swi1, a subunit of an evolutionarily conserved ATP-dependent

chromatin-remodeling complex SWI/SNF, was discovered in our laboratory. We showed that the first 38 amino acids of Swi1 were able to aggregate, and maintain and propagate [*SWI*$^+$]. However, further deletion to the first 32 amino acids resulted in a dramatic reduction in aggregation, indicating that the minimal prion domain (PrD) of Swi1 lies between residues 32 to 38. Further analysis showed that the first 33 amino acids of Swi1 are able to aggregate, and maintain a prion conformation in the absence of full-length Swi1, suggesting that this region is likely the minimal PrD of Swi1. Using a newly designed reporter system that can faithfully report the prion status of Swi1, we conducted high-throughput screens to identify compounds that can eliminate or inhibit [*SWI*$^+$] and have obtained a number of promising anti-[*SWI*$^+$] compounds. We are currently elucidating the hit compounds' mechanism of action and investigating their ability to antagonize PrP^{Sc} and inhibit Aβ-induced toxicity in a mammalian cell culture system. These studies will shed light on the mechanisms of protein misfolding, aggregation, and amyloid fiber formation – all of which are relevant to prion diseases and other amyloid-based neurological disorders.

C19

ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF JUVENILE NEURONAL CEROID LIPOFUSCINOSIS

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Juvenile neuronal ceroid lipofuscinosis (JNCL), or Batten disease, is an autosomal recessive neurodegenerative lysosomal storage disease caused by mutations in the *CLN3* gene. Disease onset occurs at five-eight years of age with symptoms including vision loss, progressive motor function decline, seizures, loss of cognitive function and ultimately death. There is no treatment for the disease. The function of the CLN3 protein is not well understood, but it is implicated in membrane trafficking, phospholipid distribution, and response to oxidative stress. Most cases of Batten disease are caused by a deletion of exons 7 and 8 (*CLN3Δ78*), which causes a frameshift and a premature stop codon in exon 9. We rationalize that correction of the reading frame in transcripts with nonsense mutations will result in a protein with partial function that may be therapeutic in Batten disease. To this end, we have developed an antisense oligonucleotide (ASO) that targets CLN3 splicing to restore the reading frame of the *CLN3Δ78* mRNA. This ASO efficiently restores CLN3 reading frame in patient cells in culture. Mice with the *CLN3Δ78* mutation have motor deficits by two months of age. Treatment of *CLN3Δ78* mice with a single neonatal ICV injection of the ASO restores the *CLN3Δ78* reading frame and improves motor coordination in the mice. Our results suggest that ASO-mediated reading-frame correction may be a promising therapeutic approach for Batten disease.

C20 UG

DEGREE OF DOPAMINE LESION IN THE SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA REFLECTS SEVERITY OF AKINETC BEHAVIOR IN A RODENT MODEL OF PARKINSON'S DISEAES

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Parkinson's Disease is a neurodegenerative disease associated with akinesias. These akinesias are driven by the loss of dopamine-producing neurons in the substantia nigra. Parkinson's Disease patients do not show symptoms until 80% of these dopamine cells are lost. Similarly, previous studies in animal models show that dopamine depletion of at least 70% is necessary for motor deficits to begin and is accompanied by a 55% loss of dopamine neurons in the neighboring ventral tegmental area. How this loss of dopamine neurons in the ventral tegmental area plays into akinetic behavior remains unknown. The goal of this study is to determine if the loss of dopamine cells in the VTA is correlated with akinetic behaviors in a similar manner to that seen when substantia nigra dopamine cells are lost. Towards this goal we used a unilateral 6-hydroxydopamine rodent model. Akinetic behavior was measured via stepping performance tests and compared to cell loss as measured by a stereological technique. Additionally, motivational deficits were measured via a five minute isolated cylinder exploration assay and also compared to cell loss as measured by a stereological technique. Results showed an unexpected stronger correlation between the stepping task and ventral tegmental area dopamine neuron counts (R^2=0.85) over substantia nigra counts (R^2=0.64). Additionally, cylinder performance tasks showed a similarly unexpected stronger correlation with substantia nigra dopamine neuron counts (R^2=0.51) over ventral tegmental area counts (R^2=0.43).

C21

ISOLATION AND ANALYSIS OF THE AMYLOID PRECURSOR PROTEIN INTRACELLULAR DOMAIN (AICD) INTERACTOME

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Alzheimer's disease is pathologically characterized by the accumulation of Beta-Amyloid (Aβ) plaques in brain, the result of metabolic processing of the Amyloid Precursor Protein (APP). While the function of APP in healthy brains has remained elusive, the series of metabolic events leading to Aβ pathology has been well characterized. APP is a type I integral membrane protein, which can be cleaved either by β-secretase to release Aβ peptides into the extracellular space (the "amyloidogenic pathway") or by α-secretase (the "non-amyloidogenic pathway") which releases the non-pathogenic p3 peptide. Both pathways ultimately result in the release of a C-terminal fragment into the cytosol – the APP Intracellular Domain (AICD). AICD has been implicated in nuclear signaling, particularly in the regulation of gene expression related to APP processing. This theorized pattern of self-regulation by an intracellular fragment is seen in other metabolic pathways, and AICD protein interactions could be a determining factor of the metabolic fate (amyloidogenic or non-) that APP follows. In this way, AICD and its network of interacting proteins have become an inroad to study, and hopefully influence, APP processing from a new angle. Conversely, the biological role of AICD, if any, remains controversial due to its short half-life and modest effects in *in vitro* gene expression studies. Thus, there is a need to discover potential AICD interacting proteins and to clarify any potential function for this metabolic fragment. The current project involves the identification of the AICD interactome by affinity purification of a tagged AICD followed by Mass Spectrometry (MS) and bioinformatic analysis. Among the interactors identified are proteins implicated in nuclear signaling, APP regulation, and modulation of AICD levels. This work was supported by the DePaul University/Rosalind Franklin University Collaborative Research Grant 400021.

C22

PARKINSONIAN SUBTHALAMIC NUCLEUS-EXTERNAL GLOBUS PALLIDUS NETWORK ACTIVITY DURING STEREOTYPED CORTICAL ACTIVITY STATES

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The reciprocally connected subthalamic nucleus (STN)-external globus pallidus (GPe) network is a key component of the movement suppressing hyperdirect and indirect pathways of the basal ganglia. To determine the mechanisms underlying parkinsonian STN-GPe activity during stereotyped cortical activity states, we recorded STN-GPe unit activity concurrently with the motor cortex electrocorticogram in control and 6- hydroxydopamine (6-OHDA)-injected mice under urethane anesthesia. Although STN firing was consistently entrained to the active phase of cortical slow wave activity (SWA), discharge intensified after dopamine depletion (control = 6.4 Hz; 6-OHDA = 11.2 Hz). Dopamine loss had no effect on firing during activated cortical states (ACS) evoked by tail pinch. GPe neurons exhibiting SWA-correlated firing increased after dopamine depletion (control = 61%; 6-OHDA = 85%). GPe neurons fired out-of-phase (control = 14%; 6-OHDA = 75%) or in-phase with SWA (control = 47%; 6-OHDA = 10%) or were uncorrelated (control = 39%; 6-OHDA = 15%). Published data together with optogenetic manipulations (see Callahan poster) indicate that following dopamine loss, out-of-phase neurons correspond to prototypical GPe-STN neurons, whereas in-phase neurons are arkypallidal GPe neurons that project to striatum only. During ACS, out-of-phase GPe discharge rate increased in control mice (SWA = 14 Hz; ACS = 17 Hz) but decreased in 6-OHDA mice (SWA = 31 Hz; ACS = 22 Hz), whereas in-phase GPe discharge increased in control and 6-OHDA mice (control: SWA = 12 Hz, ACS = 19 Hz; 6-OHDA: SWA = 10 Hz, ACS = 18 Hz). Finally, elevated beta band (13-30 Hz) activity, a motor suppressing activity pattern in Parkinson's disease, was only observed in the STN LFP during ACS (control = 2281 uV2; 6-OHDA = 4678 uV2). Because anesthesia may inhibit beta band activity across the circuit, we have recently initiated recordings in head-fixed, awake mice. Support: NIH-NINDS (NS041280, NS047085).

C23 G

IMPAIRMENTS IN CREB SIGNALING IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Alzheimer's disease is a neurodegenerative disorder characterized by cognitive impairment and memory deficits. Phosphorylation of CREB on Serine 133 (pCREB-SER^{133}) and the recruitment of the transcriptional cofactor, CREB Binding Protein (CBP), are necessary for Cyclic-AMP Response Element (CRE)-driven transcription of genes important for learning and memory. Here, we show that, steady state levels of pCREB and CBP are reduced in the hippocampus of the APPSwe/PS1ΔE9 mouse model of Alzheimer's disease

compared to their wild type littermates. Notably, the APPSwe/PS1ΔE9 mice show impairments in memory in a fear conditioning task, and these impairments are correlated with reduced levels of pCREB and CBP in the hippocampus. In addition, reporter CRE-β-galactosidase/ APPSwe/PS1ΔE9 mice exhibit reduced CRE-gene transcription in the hippocampus compared to CRE-β-galactosidase/wild type littermates. These impairments in CREB signaling are observed prior to the onset of amyloid pathology and inflammation in these mice. Taken together, these experiments suggest that a critical pathway in learning and memory is impaired in FAD-linked APPSwe/PS1ΔE9 mice and may underlie learning and memory impairments exhibited by these mice.

C24 G

DEFECTS IN LYSOSOME-AUTOPHAGOSOME REGULATION EMERGE PRIOR TO PROTEIN AGGREGATION IN ALZHEIMER'S DISEASE PATHOGENESIS

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Cellular pathophysiology of Alzheimer's disease (AD) includes the maladaptive accumulation of protein aggregates such as amyloid and hyperphosphorylated tau, among others. Normally, dysfunctional proteins or peptide fragments are digested and recycled through autophagosome-lysosome complexes. A fundamental component of lysosomal function is the vacuolar ATPase proton pump (V-ATPase) which maintains the acidic pH necessary to break down cargo transported from autophagosomes. Without proper subunit composition or expression of the vATPase, lysosomal pH becomes alkaline, resulting in an accumulation of mature autophagosomes as well as damaged organelles and mis-aggregated proteins within the cell. This would develop and lead to more global neurodegenerative cascades, such as the increased b-amyloid and phosphorylated tau species seen in AD.

In this study we examine differences in V-ATPase subunit expression in presymptomatic 3-month old AD mice models compared to non-transgenic (NTg) controls. Our hypothesis is that defects in lysosomal composition precede the pathogenic protein aggregation known to occur in AD, and this is manifested as increased autophagosome accumulation in vulnerable brain regions in AD mice. To test this, we used immunohistochemistry and confocal microscopy to examine density of the V1B2 subunit of V-ATPase in the hippocampus and cortex of 3xTg-AD and non-transgenic mice. Notably, in the AD mice, the density of cortical and hippocampal V1B2 staining was significantly decreased relative to age-matched controls. This suggests the lysosome pH may be altered and its function impaired, resulting in accumulated autophagosomes. We next measured this directly by immunohistochemically labeling mature autophagosomes with LC3B, and found that the density of mature autophagosomes is significantly increased in AD models. Since these defects are occurring prior to AD-linked protein aggregation, this suggests an alternative upstream mechanism may be involved. Ca^{2+} homeostasis is also necessary for proper lysosome function, and intracellular Ca^{2+} signaling is profoundly altered in early stages of AD. We are examining this relationship by treating mice with Ryanodex, a ryanodine receptor modulator which normalizes Ca^{2+} levels and reduces amyloid and tau accumulation in AD models. We wish to show that by stabilizing Ca^{2+}, V1B2 and LC3B expression can be restored and lysosome-autophagosome function preserved, thus preventing accumulation of aberrant proteins in AD. This research was supported by NIH AG030205.

C25

CRYOPRESERVED IPSC-DERIVED MIDBRAIN DOPAMINE NEURONS SURVIVE AND PROJECT FIBERS INTO HOST TISSUE

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Induced pluripotent stem cells (iPSCs) have recently been shown to provide structural and functional benefit in animal models of Parkinson's disease (PD) when differentiated into midbrain dopamine (iPSC-mDA) neurons (Kriks *et al.*, 2011, Morizane *et al*., 2013). Cellular Dynamics International Inc. developed a method to cryopreserve post-mitotic, floor-plate derived iPSC-mDA neurons that consistently thaw with high viability (>80%) and retain gene and protein expression profiles consistent with the midbrain dopaminergic phenotype. In addition, *in vitro* analyses revealed that cultured iPSC-mDA neurons secrete dopamine and exhibit typical electrophysiological characteristics with appropriate responses to pharmaceutical inhibition. In the present study, we examined the engraftment potential of iPSC-mDA neurons cryopreserved at different developmental time-points. Sprague-Dawley rats were immunosuppressed by cyclosporine to prevent immunorejection and injected bilaterally into the striatum with iPSC-mDA neurons.

Immunohistochemistry for human specific markers (huNCAM, huNuclei) demonstrated robust graft survival and maintenance of the dopaminergic phenotype (TH+) with extensive fiber innervation into host tissue at two and six weeks post-transplantation. No cell proliferation or abnormal growth was observed by Ki-67 staining, indicating initial safety *in vivo*. Long-term studies are underway to evaluate the functional benefit provided by cryopreserved iPSC-mDA neurons in the 6-OHDA-lesioned rat and MPTP-lesioned nonhuman primate models of PD.

C26

ANTISENSE OLIGONUCLEOTIDE-MEDIATED SPLICING MODULATION FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Apolipoprotein E receptor 2 (ApoER2 or LRP8) is a post-synaptic apolipoprotein E (apoE) and Reelin receptor involved in long-term potentiation, learning and memory. Signaling through *ApoER2* requires amino acids encoded by the alternatively spliced *ApoER2* exon 19. The exon 19-encoded domain is important for synaptic neurotransmission and memory, and to protect against neuronal cell death in normal aging. Here, we demonstrate that ApoER2 mRNA lacking this critical exon is enriched in post-mortem brain tissue from Alzheimer's disease (AD) patients compared to non-diseased samples. A similar decrease in exon 19 splicing was observed in transgenic mouse models of AD when compared to non-transgenic controls. We identified negative regulators of exon 19 splicing in human cells and used antisense oligonucleotides (ASO) to block the predicted negative regulatory sequences recognized by these splicing proteins. Treatment of neonatal transgenic AD mice with a single dose of ASO improved their performance on learning and memory tasks months after treatment, validating *ApoER2* exon 19 splicing as a candidate target for the treatment of AD. These results reveal an association between *ApoER2* exon 19 skipping and AD in humans and provide preclinical evidence for the utility of ASOs as a therapeutic approach to mitigate cognitive decline in Alzheimer's disease by improving *ApoER2* exon 19 splicing.

C27

TARGETING INTRACELLULAR CALCIUM CHANNELS AS A THERAPEUTIC APPROACH FOR TRAUMATIC BRAIN INJURY AND PREVENTING CONVERSION TO AD

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Traumatic brain injuries (TBIs) can trigger the formation of amyloid aggregates and hyperphosphorylated tau within days, while associated cognitive impairments and dementia can emerge months to years later. The tauopathies and histopathology following a TBI are reminiscent of the obligate features of Alzheimer's Disease (AD); indeed, TBI is a leading risk factor for sporadic AD. Currently, it is unknown if the similar pathological features seen in both TBI and AD share common upstream pathogenic mechanisms or if they are mechanistically distinct and converge to a similar phenotype. However, we do know there is at least one common element between TBI and AD which is intracellular-mediated Ca^{2+} dysregulation. Our focus is on the ER-localized ryanodine receptor (RyR); increased Ca^{2+} release through this large conductance channel accelerates amyloid and tau pathology and leads to structural, synaptic, and plasticity deficits in AD models. In AD mice, stabilizing the RyR has profound therapeutic effects which include a reduction in b-amyloid and phospho-tau staining, as well as preservation of synaptic structure and function.

Here, we are testing if stabilizing RyR-mediated Ca^{2+} release, with either dantrolene or one of our novel RyR negative allosteric modulators, can prevent the progression of amyloid and tau aggregation in a single controlled cortical impact (CCI) TBI model in control and AD mice. Following a CCI, animals were treated with either a RyR-targeted compound or vehicle (0.9% saline) for varying time periods post-injury. We subsequently stained for and measured amyloid and tau markers using *in vivo* 2-photon microscopy or immunohistochemical techniques combined with confocal microscopy in fixed brain tissue. Our data indicate that stabilizing RyR-Ca^{2+} signaling after TBI reduces tau-histopathology as soon as 2-days post-injury. *In vivo* imaging and immunoassays demonstrate reduced plaque load in dantrolene-treated TBI and AD models. Dantrolene-treated AD mice also showed neurons with preserved spine density similar to control models. These data support the hypothesis that the histopathology that emerges in TBI shares a common upstream Ca^{2+}-mediated mechanism with AD. By

stabilizing aberrant Ca^{2+} signaling post-TBI, these drugs can produce immediate and long term protective benefits and may reduce the conversion to AD.

C28 G

TRANSPLANTATION AND INNERVATION OF MIDBRAIN DOPAMINE NEURONS DERIVED FROM HUMAN EMBRYONIC STEM CELLS IN ANIMAL MODELS OF PARKINSON'S DISEASE

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Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by degeneration of neurons in the substantia nigra and consequent loss of striatal dopaminergic function. In order to supply the diseased brain with a renewable source of dopamine, efforts are underway, testing transplantation of dopamine neurons derived from pluripotent stem cells. In the present study, midbrain dopamine neurons (mDA) were differentiated from human embryonic stem cells (hESC-mDA), simulating normal floor-plate development (Kriks et al., 2011). In an effort to purify the population of A9-subtype dopamine neurons, magnetic activated cell sorting (MACS) was applied for cell surface marker CD142 at day-25 post-differentiation. MACS and unsorted hESC-mDA neurons were transplanted bilaterally into the striatum of athymic NUDE rats, cyclosporine immunosuppressed Sprague-Dawley rats, and MPTP-lesioned monkeys. Across different time points, grafted cells were assessed for survival using human specific antigens. Maturation and maintenance of midbrain lineage identity was analyzed up to 6-months post transplantation. Grafted neurons developed from immature, bi-polar neurons at 2-weeks, to characteristic FoxA2+/TH+ midbrain dopamine neurons by 6-months. As early as two weeks post-transplantation, fibers from engrafted cells innervated the host striatum and extended through white matter tracts. In addition, graft derived human NCAM+ fibers projected from the striatum into the substantia nigra by six months. As proof-of-concept for clinical scale-up, MPTP-lesioned monkeys received striatal hESC-mDA neuron injections. Over the course of 3-months, grafted FoxA2+/TH+ neurons matured with extensive fiber outgrowth, innervating the host striatum. Analysis for proliferation (Ki-67+) in grafted cells indicated no evidence for aberrant growth or tumor formation. Long-term functional studies in MPTP-lesioned monkeys are underway to determine the safety and efficacy of cell therapy for PD. This study is funded by New York Stem Cell Science (NYSTEM), Rush University Medical Center-Rush Translational Sciences Consortium, and funding from the National Institutes of Health (NIH 1-R21NS080380, NIH 1-R21NS074187).

C29 PD

IMPACT OF PHOSPHODIESTERASE 10A INHIBITION ON SPONTANEOUS AND CORTICALLY-EVOKED SPIKE ACTIVITY IN THE STRIATUM OF Q175 MICE THAT MODEL HUNTINGTON'S DISEASE

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Huntington's disease (HD) is a genetic neurodegenerative disorder associated with abnormal expansion in CAG trinucleotide repeats within the Huntingtin gene. This genetic mutation induces the degeneration of striatal medium-sized spiny projection neurons (MSNs) via the synthesis of mutant huntingtin protein. It is now clear that one consequence of this mutation may be abnormalities in the metabolism of cyclic nucleotides by phosphodiesterases (PDEs). Specific findings point to decreased striatal cAMP/cGMP production, which may be linked to aberrant spontaneous discharge of MSNs and deficits in corticostriatal transmission. Thus, drugs designed to inhibit striatal PDE activity may be useful therapeutic agents for slowing disease progression and alleviating motor and cognitive symptoms of HD. The current study monitored spontaneous and cortically-evoked firing in aged (5-7 months old) wild-type (WT) and Q175 heterozygous knock-in mice treated with vehicle or the potent and selective PDE10A inhibitor CHDI-00396437. WT and Q175 mice were anesthetized with urethane and single-unit spike activity was isolated during low frequency electrical stimulation of the ipsilateral motor cortex. MSNs recorded in Q175 mice exhibited higher spontaneous firing rates than MSNs recorded in WT controls. The incidence of spontaneously firing MSNs was also significantly increased in Q175 mice, indicating that overall population activity is elevated in the HD striatum. Furthermore, MSNs recorded in Q175 mice exhibited significant decreases in cortically-evoked firing. Given this, it is likely that corticostriatal transmission is compromised in the HD striatum in a manner that leads to increased background noise (spontaneous firing) and a decrease in the cortically-driven signal (i.e., decrease in the signal to noise ratio). Observations from within-subjects MSNs recorded in WT mice revealed robust increases in cortically-evoked spike activity following PDE10A inhibitor

administration. This facilitatory effect was also present in the Q175 mice, although it was less robust in these animals. These findings support the use of PDE10A inhibitors for augmenting corticostriatal transmission and striatal output, processes which are compromised in the HD striatum.

C30 UG

MICROPROCESSOR COMPLEX SUBUNIT DIGEORGE SYNDROME CRITICAL REGION GENE 8 (DGCR8) IS REQUIRED FOR SCHWANN CELL MYELINATION AND MYELIN MAINTENANCE

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MicroRNAs, generated by the microprocessor complex, modulate a myriad of gene expression programs involved in developmental and physiological scenarios. Here, we investigated the role of a key component of the microprocessor complex, DGCR8, in the regulation of Schwann cell (SC) differentiation as well as SC myelin maintenance. Conditionally ablating *Dgcr8* during development results in an arrest of SC differentiation. SCs fail to form 1:1 relationship with axons or associate with axons but fail to wrap them with myelin sheaths. The expression of genes normally found in undifferentiated SCs such as Sex determining region Y-box 2 (*Sox2*) are increased in these SCs, while the expression of myelin-related genes, including the master regulatory transcription factor Early growth response 2 (*Egr2*), are decreased. Additionally, we demonstrate that a novel gene expression program involving Sonic Hedgehog (*Shh*), activated *de novo* in injured nerves, is elevated in *Dgcr8* mutants. This increased expression of *Shh* is not observed in *Egr2* null mice, a model of SC differentiation arrest, suggesting that the elevation of the injury program in *Dgcr8* mutants is not attributed to differentiation arrest. Interestingly, when *Dgcr8* is inducibly ablated in adult SCs, similar gene expression changes, such as increases in the expression of *Sox2* and *Shh*, are observed. Analyses of these nerves mainly reveal normal myelin thickness and axon size distribution, but the presence of dedifferentiated SCs and increased macrophage infiltration. Together our data suggests that *Dgcr8* is responsible for modulation of gene expression programs underlying myelin formation and maintenance, and the suppression of an injury-related gene expression program.

C31 G

STABILIZING ER CA2+ CHANNELS WITH NOVEL COMPOUNDS NORMALIZES CA2+ RELEASE AND PRESERVES SYNAPSES IN ALZHEIMER'S DISEASE

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease with no known cure. One of the earliest pathophysiological AD features is increased Ca^{2+} release from ER-localized ryanodine receptors (RyR). The Ca^{2+} dyshomeostasis is associated with synaptic dysfunction in AD mice, and comparable dysfunction is likely in human patients based on similar RyR upregulation. Altered Ca^{2+} signaling accelerates many AD features, including synaptic deficits. This is particularly relevant to the cognitive impairment that defines AD, as synaptic loss correlates with memory loss in AD.

The purpose of this study is to examine synaptic changes that occur in early-stage AD and validate the RyR as a drug target to restore Ca^{2+}homeostasis and synaptic structure. Our hypothesis is that increased RyR-Ca^{2+} release in axonal terminals depletes synaptic vesicle stores and contributes to eventual synaptic depression. Thus, we examined the CA3-CA1 hippocampal glutamatergic synapse using electron microscopy, and quantified the number of synapses and synaptic vesicles in 3-month old 3xTg-AD and control mice. Vesicles were classified into three pools (ready releasable, reserve, and resting). Our results show that presymptomatic 3xTg mice had significantly fewer total synapses, and reduced vesicle content in the readily releasable and reserve pools, while the resting pool was significantly increased *vs*. controls. This suggests there are marked structural deficits at critical memory-encoding synaptic junctures prior to the onset of cognitive deficits. In parallel, we also investigated the RyR as a potential drug target to prevent synaptic pathology. Prior studies using dantrolene, a RyR negative allosteric modulator, demonstrate that RyR stabilization restores Ca^{2+} homeostasis and synaptic integrity in AD mice. However, the utility of dantrolene for CNS targets is limited. Thus, we formulated a series of improved structural analogs which we screened using a RyR2-expressing N2a cell-based assay. We show here that several of our analogs demonstrate RyR-regulating activity and preserve homeostatic Ca^{2+} signaling, and may thus serve a therapeutic role for AD treatment. In summary, we show

that early-stage AD mouse models have significantly reduced presynaptic vesicle stores that likely contributes to synaptic depression, and a novel therapeutic strategy exists to preserve synaptic structure and function through improved and CNS-targeted RyR stabilizing compounds.

C32 G

DEVELOPMENT OF mGluR-LTD IN THE NUCLEUS ACCUMBENS DURING WITHDRAWAL FROM EXTENDED-ACCESS COCAINE SELF-ADMINISTRATION

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Prolonged withdrawal from extended-access cocaine self-administration (6 h/d, 10d) is associated with incubation of cocaine craving as well as several changes in medium spiny neurons (MSN) of the nucleus accumbens (NAc). These include accumulation of Ca2+- permeable AMPA receptors (CP-AMPAR) and a switch from group I metabotropic glutamate receptor (mGluR) 5- to mGluR1-mediated synaptic depression, typically after withdrawal day (WD) 40. More importantly, these adaptations are disrupted by protein-synthesis interference, indicating ongoing active processes required for their maintenance and therefore the maintenance of drug-seeking behavior. In order to better understand the mechanisms underlying the emergence of this novel form of plasticity, we conducted whole-cell patch-clamp recordings of NAc MSN at multiple time-points during withdrawal and examined the nature of mGluR-mediated synaptic depression through bath-application of the group I mGluR agonist, DHPG (50μM). In contrast to results obtained in saline controls or earlier in withdrawal from cocaine, DHPG application in slices obtained after WD15 induced a form of synaptic depression which persisted for >30min after washout of the drug (mGluR-LTD). This mGluR-LTD was maintained through WD45 and beyond. To determine if this mGluR-LTD was mediated by the removal of CP-AMPARs as indicated by previous work characterizing mGluR-mediated synaptic depression after prolonged withdrawal (>WD45), we used the rectification index in addition to the CP-AMPAR antagonist naspm (100μM) to quantify the contribution of CPAMPAR transmission at numerous points during withdrawal. Surprisingly, we found that CPAMPAR-mediated synaptic transmission in the NAc was significantly elevated only after WD25. Together, these results indicate that additional mechanisms underlie the development of mGluRLTD at earlier withdrawal points. Ongoing studies will identify the mechanisms underlying the emergence of mGluR-LTD, thereby illuminating the processes that underpin the development of aberrant behaviors following prolonged withdrawal from extended-access cocaine self administration.

C33 PD

EXAMINING PROTEIN SYNTHESIS IN THE NUCLEUS ACCUMBENS AFTER WITHDRAWAL FROM EXTENDED-ACCESS COCAINE SELF-ADMINISTRATION

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During withdrawal from extended-access cocaine self-administration, there is a progressive intensification (incubation) of cue-induced cocaine craving that is associated with numerous synaptic adaptations in the nucleus accumbens (NAc). Recent work from our lab suggests these adaptations are maintained by dysregulated local protein translation. Aberrant translation has a profound impact on cellular function and is a key feature in Fragile X syndrome and some other disorders of the nervous system. Treatments to normalize protein synthesis have proven successful in reversing some behavioral and cellular abnormalities in a mouse model of Fragile X. Currently, little is known about mechanisms regulating translation in the NAc. Furthermore, the possibility of long-term alterations in translation following cocaine exposure has been largely uninvestigated and provides an intriguing novel target for therapeutic intervention.

We examined the hypothesis that incubation of cocaine craving is associated with dysregulation of protein translation in the NAc. Male Sprague Dawley rats underwent extended-access cocaine or saline self-administration (6hr/10days, 0.5mg/kg/infusion), followed by >40 days of withdrawal. We used ^{35}S-Met/Cys incorporation to measure protein translation in NAc tissue. Preliminary data indicate that overall translation is not different between cocaine and saline groups, suggesting that translation of only a small subset of proteins may be differentially regulated. Work is underway to compare patterns of translation using non-canonical amino acid tagging of newly synthesized proteins to specifically examine translation rates of key synaptic targets. We are also comparing the regulation of translation in cocaine versus saline rats by mGluR and NMDA receptors. These studies are the first to characterize how synaptic transmission regulates protein translation in the NAc under basal conditions and whether drugs of abuse cause persistent alterations in the synthesis of proteins linked to addiction. This work is supported by NIDA grant DA015835 (MEW).

C34

GUANYLATE CYCLASE STIMULATION IS A TRIGGER OF MIGRAINE PAIN

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Migraine is a complex brain disorder that affects hundreds of millions of individuals worldwide. Although there have been great advances in migraine medication, the available treatments are only effective in a limited number of patients, therefore it is necessary to identify novel therapeutic targets. Nitroglycerin (NTG) is a known migraine trigger, and produces migraine-related hyperalgesia in mice. How NTG induces migraine is unclear, as it activates the nitric oxide-guanylate cyclase pathway but also produces radical oxygen species which lead to oxidative stress. The aim of this study was to determine the specific contribution of the guanylate cyclase pathway to migraine-associated pain. C57Bl6/J mice were treated acutely and chronically with either vehicle or the guanylate cyclase stimulator VL-102. Basal and post-treatment mechanical responses were determined using von Frey hair stimulation. VL-102 produced acute hyperalgesia in a dose-dependent manner. Chronic administration of VL-102 produces both acute and basal hypersensitivity. VL-102-induced hyperalgesia was blocked by the anti-migraine medications sumatriptan and topiramate. These results are similar to the migraine-related pain induced by NTG. Stimulation of guanylate cyclase mimics the effects of NTG-induced pain, and appears to be migraine-associated. These results suggest that the effects of NTG on migraine are due to direct activation of the nitric oxide pathway and not to other non-specific effects. Furthermore, this work indicates that guanylate cyclase may be a novel therapeutic target for the treatment of migraine. This work was supported by NIH DA031243, the Department of Psychiatry UIC, and the UICentre.

C35 **PD**

THE DELTA OPIOID RECEPTOR AGONIST SNC80 PREFERENTIALLY RECRUITS β-ARRESTIN 1 TO PROMOTE BEHAVIORAL TOLERANCE

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Ligand directed signaling via the delta opioid receptor (DOR) has important implications given the potential therapeutic uses of delta agonists in the treatment of chronic pain and emotional disorders. We had previously shown that repeated injection of the high-internalizing delta agonist (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide or SNC80, produced acute behavioral desensitization while the low-internalizing delta agonist N,N-diethyl-4-(phenyl-piperidin-4-ylidenemethyl)-benzamide or ARM390 did not. Since β-arrestins are well known to regulate G protein-coupled receptors signaling and trafficking, we therefore investigated the behavioral significance of ligand-specific interactions between β-arrestin 1 and the DOR. Mice lacking β-arrestin 1 showed enhanced and longer lasting pain-relieving effects of SNC80, and decreased behavioral tolerance following repeat exposure to the agonist. In contrast, ARM390 produced similar analgesic effects and no tolerance in both WT and KO animals. Following chronic treatment, the absence of β-arrestin 1 attenuated the extent of tolerance to SNC80, but not to ARM390. Furthermore, chronic treatment with SNC80 abolished delta-agonist induced GTPγS binding in WT brain membranes, whereas DOR-G protein coupling remained intact in KO mice. Overall, these results indicate that delta agonists interact with β-arrestins in a ligand-biased manner, and that the high-internalizing agonist SNC80 preferentially recruits β-arrestin 1. This work was supported by the NIH Grant DA031243, the Shirley and Stefan Hatos Research Foundation, and the Dept. of Psychiatry at UIC.

C36 **G**

UNDERLYING MECHANISMS AND FUNCTIONAL CONSEQUENCES OF AUTONOMOUS FIRING LOSS IN THE PARKINSONIAN SUBTHALAMIC NUCLEUS

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The motor symptoms of Parkinson's disease (PD) are associated with abnormally synchronous cortico-basal ganglia-thalamo-cortical activity. In animal models, parkinsonian activity emerges slowly, several days to weeks following loss of dopamine, implying a critical contribution of neuronal plasticity. The subthalamic nucleus (STN) is a key component of the movement-suppressing indirect and hyperdirect pathways of the basal ganglia. Following dopamine depletion in the 6-hydroxydopamine (6-OHDA) mouse model, the autonomous activity of STN neurons *ex vivo* was profoundly disrupted (control: 9.3 Hz; 6-OHDA: 3.0 Hz), and the proportion of inactive cells increased from 18 to 40%. Disrupted autonomous activity was caused by an increase in ATP-sensitive potassium (K_{ATP}) channel current

because antagonism of K_{ATP} channels with 100 nM glibenclamide *ex vivo* fully rescued firing.

In the absence of dopamine, the STN is disinhibited due to hyperactivity of the indirect pathway and consequently more powerfully patterned by hyperdirect cortical excitation. We hypothesized that following dopamine depletion, excessive activation of STN NMDA receptors (Rs) at cortico-STN synapses triggers K_{ATP} channel-dependent disruption of STN activity. Indeed, pre-incubation of control slices in 25 µM NMDA mimicked K_{ATP} channel-mediated firing disruption in the 6-OHDA model. Conversely, knockdown of STN NMDARs through viral expression of cre recombinase in 6-OHDA-treated *GRIN1*$^{lox/lox}$ mice prevented activity disruption *ex vivo* and ameliorated motor dysfunction *in vivo.* Because autonomous STN activity renders excitatory synaptic integration phase-dependent, we further hypothesized that its disruption following loss of dopamine promotes abnormal, synchronous activity and motor dysfunction. In order to test this hypothesis we are developing a pharmacogenetic approach to restore intrinsic STN activity and assess its impact on motor dysfunction.

C37 G

EFFECTS OF FITC FLUOROPHORE LABELING ON ALPHA-SYNUCLEIN HIGHER ORDER AGGREGATION STATE AND CELLULAR TOXICITY

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Parkinson's disease (PD) is a proteinopathy characterized by pathological aggregation and accumulation of the protein α-synuclein (α-syn) within dopaminergic neurons of the substantia nigra. Despite the fact that early-onset familial forms of PD have been linked to missense mutations (E46K, A53T, A30P, G51D) in the α-syn protein that alter aggregation propensity, the vast majority of PD cases are idiopathic, exhibiting aggregation of wild type (WT) α-syn. Although biochemical and biophysical characterization of α-syn aggregation *in vitro* has had a profound impact on understanding the detrimental consequences of this process for cells in the brain, carefully defining aggregate species produced *in vitro* and their effect on target cells is necessary to obtain meaningful and consistent results. In this regard, we performed electron microscopic (EM) inspection of WT, E46K, A53T, A30P, and G51D α-syn aggregates before and after labeling with amine-reactive FITC fluorophore. We used ImageJ image analysis software to measure α-syn fibril lengths and assign each measured fibril to a category corresponding to its level of association with other fibrils, either grouped or single. Our results indicated that there was no appreciable difference in fibril length between labeled and unlabeled α-syn preparations, but that FITC labeling significantly increased the proportion of single fibrils in each population. In addition, our measurements of single fibrils demonstrated a significantly shorter length when compared to grouped fibrils, regardless of mutant type. Taken together, an increase in single fibril proportion combined with a shorter overall length of single fibrils increases the homogeneity of the sample, and upon aggregate addition to neuronal cells in culture, increases the frequency by which affected cells encounter smaller α-syn aggregates. Critically, given the recent demonstration by our lab that α-syn aggregates can induce vesicle rupture following endocytosis, a process which requires smaller α-syn aggregates, we also observed that labeled α-syn preparations have an increased potency of vesicle rupture compared to unlabeled preparations. A deeper understanding of the characteristics of α-syn aggregation can allow for the future development of drug therapies to prevent this process in the treatment of PD. This study is funded by the Michael J. Fox Foundation.

THEME D. HISTORY AND TEACHING OF NEUROSCIENCE

D1 UG

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

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The Centers 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. The original SLICE program in Boston was shown to have a significant impact on students' concussion knowledge (Bagley et al., 2012). DePaul University's SLICE program was the first chapter established outside of Boston, and therefore its effectiveness was assessed during its first year. In the present Chicago study, students in participating schools, ranging in age from 9-19 years, were given an interactive presentation complete with demonstrations, discussions, and case studies. To assess the SLICE program, participants

completed surveys before (*n* = 360), immediately after (*n* = 377), and approximately 1-month post presentation (*n* = 274). The survey was meant to assess knowledge of concussion symptoms and appropriate responses to a concussion. Each survey was scored by two independent researchers; and a total score was calculated for each survey. Compared to the pre-presentation surveys, passing rate (defined as 50% of the total score), significantly increased immediately post- presentation (z=29.9, p<. 017), demonstrating an increase in concussion knowledge. This knowledge was retained approximately 1- month later with the passing rate still significantly higher than pre-presentation surveys (z=20.5, p<.017). Furthermore, compared to pre- presentation, participants scored 16.03% higher immediately post- presentation, and 13.89% higher 1-month post- presentation. Gender differences were found across all three time points such that females scored significantly higher than males on surveys before the presentation (t=-3.350, p<.05), immediately post-presentation (t=5.216, p<.001), and 1- month post-presentation (t=4.177, p<.001). There was no effect of age, race, or athletic involvement on survey performance. Results suggest that the SLICE program in Chicago is effective in promoting concussion knowledge. SLICE is now offering presentations across multiple cities in the United States.

THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1 UG

AGING AND LOSS OF CIRULATING 17β–ESTRADIOL RESULTS IN BRAIN-REGION SPECIFIC CHANGES IN THE ALTERNATIVE SPLICING OF ESTROGEN RECEPTOR β IN FEMALE RATS

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Aging increases global alternative gene splicing (AS) in the brains of both healthy and neurodegenerative individuals. The loss of circulating estrogens associated with menopause further compounds the effects of aging in women, yet increases in age-related AS events have not been studied in females. The loss of the major circulating estrogen, 17β-estradiol (E2), contributes to the decline of cognitive function including mood disorders and memory impairment observed in postmenopausal women, and longer periods of E2 deprivation correlate with poor outcomes from E2 replacement therapy. The nuclear steroid receptors through which E2 mediates its actions, ERα and ERβ, are both subject to AS. Recent studies have linked increased expression of the dominant negative ERβ2 splice variant to decreased hippocampal neurogenesis and depressive-like behaviors in female rats. This form of the receptor has decreased affinity for E2, which might result in altered E2 signaling pathways. We hypothesized that ERβ2 splice variant expression increases with age, and longer periods of E2 deprivation in the brain. In our model of surgically-induced menopause, 18 month old animals were ovariectomized (OVX), and then, after varying deprivation periods (1 wk, 4 wks, 8 wks, 12 wks), were treated with either vehicle or 2.5ug/kg E2 for 3 consecutive days. All animals were sacrificed 24 hours after the last treatment for tissue collection and data analysis. We also compared young animals (3 mo) with aged animals following 1 week of E2 deprivation to directly assess the effects of age. Contrary to our hypothesis, ERβ2 splice variant expression decreased with age in the hypothalamus, but not the dorsal or ventral hippocampus. However, treatment with E2 increased alternative splicing of ERβ in the older animals. Also in our deprivation paradigm, E2 treatment increased ERβ alternative splicing in the hypothalamus at 1 and 12 weeks following OVX compared to vehicle-treated animals. Further, ERβ2 expression significantly decreased following 4 weeks deprivation in vehicle-treated animals in the dorsal and ventral hippocampus, and also decreased following E2 treatment in the dorsal hippocampus. These data suggest that both age and E2 contribute to brain region-specific changes in alternative splicing of ERβ that may be dependent upon other brain region-specific factors whose expression may change due to these factors.

E2 G

BASOLATERAL AMYGDALA CIRCUITRY UNDERLYING MODULATION OF STRESS-RELATED BEHAVIOR

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The amygdala is traditionally regarded as the emotional center of the brain, and as such it functions as a central hub interconnecting a variety of brain regions. The basolateral nucleus of the amygdala (BLA) plays an important role in the balance between anxiolysis or stress resilience (seen with intra-BLA effects of neuropeptide Y-NPY) and anxiogenesis or stress vulnerability (seen with intra-BLA effects of corticotropin releasing factor-CRF). The effects of these endogenous neuropeptides are mediated by inhibition or potentiation, respectively, of the hyperpolarization activated

current (I_h). These actions result in inhibition or potentiation of BLA output, which is then consistent with the behavioral outcomes observed. However, the neuroanatomical circuit responsible for the manifestation of these behaviors in response to NPY and CRF is currently not well understood.

The goal of these studies was to examine the neurochemical phenotype of the BLA projections to the central nucleus of the amygdala (ceA) and to the bed nucleus of the stria terminalis (BST). We used a combination of retrograde and anterograde tracers combined with immunohistochemistry to characterize BLA projections and their downstream targets. The anterograde tracer Phaseolus vulgaris-leucoagglutinin (PHAL) was injected into the BLA. Examination of the tissue 7 days later demonstrated strong projections to the ceA, the lateral division of BST and the oval BST. Furthermore, the retrograde tracer Fluorogold (FG) was injected into either the ceA or BSTL resulting in retrograde identification of BLA neurons. Multiple-label immunohistochemistry was used to characterize whether these cells expressed hyperpolarization-activated, cyclic nucleotide-gated channel subunit 1 (HCN1) immunoreactivity. A number of FG-filled cells expressing HCN1 immunoreactivity were identified within localized regions of the BLA. These data indicate that alterations in BLA output mediated by the I_h current are poised to manipulate the activity of ceA and BSTL.

This knowledge will aid our understanding of the functional neuroanatomy of NPY- and CRF-related circuits in the BLA and how their projections coordinate stress or anxiety related behaviors. This study is funded by R01 MH090297 (JHU, WFC).

E3 UG

A COMPARISON OF THE NEURAL CONNECTIONS FROM THE SUBDIVISIONS OF THE ORBITOFRONTAL CORTEX TO THE AMYGDALA AND THE EXTENDED AMYGDALA IN THE RAT

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Generation of an appropriate behavioral response to changing situations and potential threats relies on a complex network of brain regions. In order to better understand this network, the present study investigated the connections from the orbitofrontal cortex (OFC), a region that receives and evaluates sensory input, to the amygdala and extended amygdala. There is increasing evidence that in the rat, as in primates, the subdivisions of the OFC are functionally heterogeneous. These functional differences suggest that the regions may differ in their connectivity within the emotional processing network. This study employed injections of the anterograde tracer, biotinylated dextran amine, into the OFC to investigate patterns of axonal projections from distinct OFC subdivisions to key components of the amygdala and extended amygdala. OFC subdivisions differ in their axonal projections to the basolateral nucleus of the amygdala (BLA), a region involved in conditioned fear and stimulus evaluation. Lateral subdivisions of the OFC (the dorsal anterior agranular insula and dorsolateral orbital area) project more densely to the BLA than do more medial subdivisions (the ventral anterior agranular insula, ventrolateral orbital area, and lateral orbital area). In contrast, results indicated that there are comparable patterns of sparse direct neuronal connections from the subdivisions in the OFC to the anterolateral and anteromedial subdivision of the bed nucleus of the stria terminalis (BNST). Results also indicated that neurons within the studied OFC subdivisions project sparsely to the central nucleus (CeA), with slightly denser axonal projections than those found to the BNST. The comparison of axonal projections across OFC subdivisions indicates that they communicate similarly to extended amygdala regions involved in the expression of responses to threats. Additionally, the different patterns of axonal projections from the lateral and more medial OFC subdivisions to the BLA suggest that lateral subdivisions may be more involved than adjacent, more medial subdivisions in the ongoing evaluation of stimuli. This research is supported by Grinnell College.

THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG

HETEROGENEOUS ABLATION OF PERISYNAPTIC SCHWANN CELLS RECOGNIZED BY THE MONOCLONAL ANTIBODIES ANTI-HNK-1 AND 2A12

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Understanding the contributions of glial cells to communication at the chemical synapse has blossomed in the past few decades as evidence increasingly mounts for their more active role in neuronal signaling. Within the model of the tripartite synapse, astrocytes of the central nervous system and perisynaptic Schwann cells (PSCs) of the peripheral nervous system have been shown to play important roles in modulating information transfer at the synapse. Much is still unknown and uncertain, however, concerning the mechanisms by which glial cells influence synaptic plasticity and the extent of their importance to normal synaptic function. Utilizing complement-mediated

ablation specific to these glial cells, we are developing techniques to address these important questions. After performing these ablation procedures using the monoclonal antibodies anti-HNK-1 and 2a12, which both recognize epitopes on the extracellular surface of PSCs at the lizard neuromuscular junction (NMJ), we report that complement-mediated ablation with either antibody leads to partial ablation of PSCs at the NMJ, but 2a12 appears to ablate significantly more cells than HNK-1. Additionally, ablated nuclei tend to be in closer association with areas of higher HNK-1 or 2a12 staining – often marked by a ring surrounding the ablated nucleus – and tend to be rounder than the oval or crescent shape of unablated nuclei. Current research is ongoing to further describe the distinct morphological features of ablated PSCs – specifically, to address whether their observed characteristics are truly unique or a result of the process of ablation – and to ascertain their contribution to glial calcium currents at the lizard NMJ. Funding for this research is supported by NIH grant R15 NS072735-02.

F2

AMBIENT EXTRACELLULAR GLUTAMATE MODULATES SYNAPTIC STRENGTH AT HIPPOCAMPAL CA3-CA1

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Synapses in the mammalian brain are exposed to two biologically active pools of glutamate: 1) transient synaptic glutamate resulting from neuronal vesicular release and 2) ambient nonsynaptic glutamate released from both neurons and glia through a variety of molecular mechanisms. While the role of synaptic glutamate has been extensively studied, much of the function of nonsynaptic glutamate remains unknown. Several lines of evidence have shown that changes in nonsynaptic glutamate are linked to developmental, physiological, and behavioral defects in mammals. Approximately 60% of extracellular glutamate in the mouse hippocampus is released by the xCT transporter, a cystine-glutamate antiporter which is highly expressed and active on astrocytes surrounding CA1 pyramidal neurons. Mice lacking a functional xCT transporter ($xCT^{-/-}$) show both enhanced synaptic strength and increased AMPA receptor abundance at hippocampal CA3-CA1 synapses. Additionally, mutant $xCT^{-/-}$ miniature excitatory post-synaptic potentials (mEPSCs) are phenocopied by incubating control slices in glutamate-free solution. Here we show the effect of external glutamate application on both control and $xCT^{-/-}$ slices over time and propose a possible mechanism by which extracellular glutamate acts to modulate synaptic strength at hippocampal CA3-CA1 synapses.

F3 PD

GENETIC ABLATION OF KLHL1 ALTERS $Ca_V3.2$ EXPRESSION IN DRG NEURONS AND MECHANICAL PAIN TRANSMISSION

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Pain signaling is initiated by the detection of noxious stimuli through specialized primary nociceptors located in peripheral endings in dorsal root ganglion (DRG) neurons. Low voltage activated $Ca_V3.2$ T-type calcium channels play a major role in sensory perception in these neurons; silencing their activity with antisense RNA or genetic ablation results in anti-nociceptive, anti-hyperalgesic and anti-allodynic effects[1-3]. These channels are regulated by a plethora of proteins, including KLHL1, a neuronal actin binding protein that stabilizes channel activity by increasing its recycling back to the plasma membrane *via* recycling endosome activity. We explored the role of KLHL1 and its effects on $Ca_V3.2$ and mechanical peripheral pain transmission using the KLHL1 KO mouse model. Total T-type calcium current amplitude was smaller in KO DRG neurons (8.24 ± 2.03 pA/pF, n=9) compared to controls (12 ± 1.89 pA/pF, n=7; $p<0.05$), without significant changes in voltage dependence as expected in the absence of its modulator. Western blot analysis confirmed $Ca_V3.2$ but not $Ca_V3.1$ or $Ca_V3.3$ protein was significantly decreased; and von Frey hair tests show paw withdrawal threshold in KO mice was increased. Our data establishes KLHL1 is a calcium channel regulator in DRG neurons, providing a novel target to control peripheral pain sensation. Interestingly, downregulation of $Ca_V3.2$ activity by ~30% was sufficient to alter pain perception in the KO model.

F4 UG

THE ROLE OF RAB27B IN SYNAPTIC TRANSMISSION: A COMPENSATORY PARTNERSHIP BETWEEN RAB3 AND RAB27B

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Neuronal communication involves orchestrated protein interactions that guide synaptic vesicles (SVs) through a cycle of filling, docking, priming, fusion, and endocytosis. We focus on those proteins engaged in the docking and priming of SVs in the active zone. Specifically, on the influence of

monomeric Ras-like G proteins (Rab) on exocytosis within the brain, known to be Rab3 and Rab27. Rab3 is shown to play a role in stabilizing docking/priming events and stimulating exocytosis. Rab3 has four paralogs, Rab3A-D. Reported results demonstrated that when Rab3 isoforms are individually knocked down a decrease in fusion is observed; however, when all isoforms were absent, fusion retained ~80% functionality. The role of Rab27B in neurotransmission has yet to be determined. Previous studies indicate that Rab27B is ~50% homologous to Rab3A, and that the two Rabs co-localize to synaptic boutons. Moreover, we find that Rab27B is highly expressed in the mouse hippocampus. Because of this we propose that, besides distinct functions, Rab27B may play a compensatory role for Rab3A-D. This could account for the high-level retention of transmission in the Rab3 quadruple knockdown studies. To initially test this, we determined the effect of Rab27B on presynaptic protein expression by comparing hippocampal lysate samples from wild type (WT) and Rab27B knockout (KO) mice. Immunoblot results revealed a significant difference only for Synapsin1, which showed a two-fold increase in expression in Rab27B KO tissue. We next assessed differences in SV pools and release kinetics between Rab27B WT and KO conditions in cultured hippocampal neurons transfected with vGlut-pHluorin. vGlut-pHluorin, a pH-sensitive GFP fused to the vesicle associated protein vGLUT1, becomes fluorescent upon exocytosis or when the vesicles are deacidified using ammonium chloride. Co-transfection of vGlut-pHluorin with Rab3GAP, which effectively shifts all isoforms of Rab3 into their inactive GDP-bound form, into Rab27B KO neurons was used to reveal the effects of functionally knocking out the Rab proteins in discussion. Preliminary data shows a slight decrease in the releasable pool of SVs in Rab27B KO neurons compared to WT. Further, Rab27B KO neurons overexpressing Rab3GAP demonstrate a greater decrease in releasable SVs than WT or Rab27B KO neurons. These data reflect compensatory actions of Rab3 and Rab27B in that sufficient transmission can continue in the absence of one, but that both are necessary for most efficient neurotransmission. Support for this study comes from NIH NIDDK DK077050 (ELS); Endowment for Basic Sciences Bridging Support (ELS) through the University of Michigan Medical School.

F5 G

EVIDENCE FOR PKA DEPENDENT REGULATION OF TOMOSYN

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Tomosyn, a syntaxin binding protein, has been postulated to negatively regulate synaptic vesicle fusion by forming nonfusogenic complexes with the plasma membrane SNAREs, syntaxin and SNAP-25, thereby inhibiting SNARE complex assembly. Using RNAi knockdown we recently demonstrated that *Drosophila* tomosyn not only inhibits synaptic transmission but also disrupts PKA-dependent aversive olfactory learning in flies[1]. Biochemical evidence indicates that vertebrate tomosyn is a direct PKA-target. Phosphorylation reduces the ability of tomosyn to inhibit fusogenic SNARE complex assembly by lowering its syntaxin binding affinity[2]. The possibility that tomosyn is a potentially important PKA-target *in vivo* is supported by the following observations: 1) Acute activation of cAMP phenocopies the tomosyn loss-of-function phenotype and manifests as increased synaptic vesicle docking and enhanced release. 2) cAMP activation results in the translocation of tomosyn away from the plasma membrane and 3) cAMP activation combined with tomosyn RNAi shows no additivity, suggesting they act in the same pathway. To definitively establish that the phosphorylation of tomosyn accounts for these cAMP synaptic effects we have generated a tagged tomosyn construct using CRISPR/Cas9 for pull down and subsequent kinase activity assays to determine the most probable PKA binding site. Based on both bioinformatics and molecular evidence potential phosphomimetic and non-phosphorylatable tomosyn fly strains will be generated using CRISPR/Cas9 and will be the subject of electrophysiological and immunohistochemical analyses.

F6 G

DIFFERENTIAL REGULATION OF DROSOPHILA GLUTAMATE RECEPTOR SUBUNIT PRODUCTION BY OPTIMUS-PRIME, A NOVEL MRNA ASSOCIATED GENE.

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Postsynaptic receptor abundance is a critical determinant of synapse strength. We are identifying and studying mechanisms that control glutamate receptor (GluR) abundance in *Drosophila* embryonic and larval neuromuscular junctions (NMJ). Regulation of the production, trafficking, stability, and translation of GluR mRNA appears to be of particular importance in controlling GluR abundance. We have shown GluR subunit mRNA in

embryonic and larval NMJs is associated with messenger ribonucleoprotein (mRNP) complexes, which are distributed throughout the cytoplasm of postsynaptic muscle cells. A novel protein was identified in a biochemical screen that appears to associate specifically with *GluRIIA* mRNA and regulate GluRIIA protein abundance. We named this novel gene, CG12149, '*optimus-prime* (*opr*)'. Mutants and muscle-specific RNAi of *OPr* leads to loss of GluRIIA protein but no change in *GluRIIA* mRNA quantity or loss of other GluR subunits. A polyclonal antibody raised against OPr shows immunoreactivity distributed throughout the central nervous system and muscle cells. Optimus prime is shown to be highly conserved and is the founding member of a novel protein family. SNPs in the human opr homolog are associated with autism spectrum disorders.

F7 PD

HETEROSYNAPTIC REGULATION OF EXTERNAL GLOBUS PALLIDUS INPUTS TO THE SUBTHALAMIC NUCLEUS BY MOTOR CORTEX

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The two principal movement-suppressing pathways of the basal ganglia, the so-called hyperdirect and indirect pathways interact within the subthalamic nucleus (STN). An appropriate level and pattern of hyperdirect pathway cortical excitation and indirect pathway external globus pallidus (GPe) inhibition of the STN are critical for normal movement and greatly perturbed in Parkinson's disease (PD). Here, we demonstrate that motor cortical inputs to the STN heterosynaptically regulate, through activation of postsynaptic NMDA receptors, the number of functional $GABA_AR$-mediated GPe-STN inputs. Thus, a homeostatic mechanism, intrinsic to the STN, balances cortical excitation by adjusting the strength of GPe inhibition. However, following loss of dopamine, excessive cortical activation of STN NMDA receptors triggers GPe-STN inputs to strengthen abnormally, potentially contributing to the emergence of pathological, correlated activity. This study was funded by NIH NINDS grants 2R37 NS041280 (M.D.B), P50 NS047085 (D.J.S. and M.D.B) and P30 NS054850 (D.J.S. and D.W.).

F8 PD

METHAMPHETAMINE ALTERS RESTING MEMBRANE POTENTIAL AND REDUCES VOLTAGE-SENSITIVE K+ CURRENT IN PRIMARY HUMAN FETAL ASTROCYTES

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Methamphetamine (Meth) is a potent and commonly-abused psychostimulant. Chronic exposure to Meth induces decreased neuronal activity in the medial prefrontal cortex and nucleus accumbens (two key regulators of cognition and addiction in the reward pathway), which may contribute to mechanisms underlying Meth addiction. It is not fully understood whether such decrease results from alterations in synaptic/intrinsic excitability of neurons, and/or dysregulation of the extracellular environment (e.g., glutamate and K^+ levels) mediated by surrounding astrocytes. To fill this knowledge gap, we assessed the effects of Meth on functional activity of certain voltage-gated ion channels in the cell membrane of primary human fetal astrocytes (HFA) using whole-cell voltage-clamp recording. We found that HFA displayed a large out-flowing voltage-gated K^+ current (VGKC, a characteristic of immature or reactive astrocytes), while voltage-gated Ca^{2+} currents were not seen. Further, exposure of HFA to Meth (20 μM, 100 μM, or 300 μM for 3-6 hrs) induced significant depolarization of the resting membrane potential (RMP), and decreased VGKC (100 or 300 μM Meth) at 60-100 mV membrane potential levels, as compared to vehicle-treated HFAs (all $p<0.05$). These novel findings reveal that Meth disturbs HFA activity by altering RMP and VGKC. Given that Meth-induced decrease of VGKC from astrocytes can consequentially reduce local extracellular K^+ levels, such a reduction could ultimately contribute to decreased excitability in neurons surrounded by these astrocytes. Supported by NIH grants NS084817-01 (X-TH) and DA033966-01A1 (LAL).

F9 G

GROUP I MGLUR-β-ARRESTIN SIGNALING MEDIATES EXCITATORY SYNAPTIC PLASTICITY

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The discovery of non-canonical, G protein-independent signaling mediated by β-arrestins (βarrs) has generated intense interest in harnessing these pathways for therapeutic targeting of seven transmembrane receptors (7TMRs). Yet, for some 7TMR classes such as the group I metabotropic glutamate receptors (mGluR1 and mGluR5), the function of βarr signaling remains unclear. In this project we test the hypothesis that group I mGluR-βarr signaling is involved in synaptic plasticity and identify

downstream effectors of mGluR1-βarr 2 signaling the hippocampal mossy fiber pathway.
We assessed synaptic plasticity in patch clamp recordings from CA3 pyramidal neurons in hippocampal slices prepared from wildtype, βarr 1 and βarr 2 knockout mice. mGluR1-dependent potentiation of EPSCs induced by low frequency, paired stimulation of mossy fiber inputs to CA3 pyramidal neurons was absent in mice lacking βarr 2 (91 ± 9% n=14 for βarr $2^{-/-}$, 131 ± 7% n=11 for wildtype, p=0.002) but intact in mice lacking βarr 1 (130 ± 15% n=14 for βarr $1^{-/-}$, 134 ± 8% n=11 for wildtype, p=0.85). In contrast, mossy fiber long-term potentiation induced by high frequency stimulation was unaffected by gene targeting of either βarr isoform (190 ± 23% n=9 for βarr $1^{-/-}$, 159 ± 14% n=8 for wildtype, p=0.26; 165 ± 16% n=8 for βarr $2^{-/-}$, 167 ± 14% n=6 for wildtype, p=0.94). Pharmacological dissection implicated ERK1/2 of the MAPK pathway (102 ± 7% n=7 for u0126-treated slices, 137 ± 9% n=17 for vehicle slices, p=0.004), and Src family tyrosine kinases (111 ± 8% n=10 for PP2-treated slices, p=0.03 compared against same vehicle cohort), and indicated that cRaf-1 was not critical (137 ± 20% n=9 for GW5074-treated slices, p=.98 compared to vehicle). These data reveal a novel role for βarrs when coupled to mGluR1 and support the involvement of βarr signaling in learning and memory processes. Our findings also suggest that future therapeutic strategies targeting group I mGluRs could benefit by focusing on ligand-directed pathway selection.

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F10 UG

THE EFFECTS OF STRESS ON DOPAMINE AND SOCIAL BEHAVIOR IN ADULT ZEBRAFISH

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There is a complex relationship between stress induced anxiety and social behavior that is mediated by hormonal modulation of dopaminergic circuitry in the midbrain structures. The purpose of this research was to gain a greater understanding of the effect of stress related hormones on social behaviors that are regulated by dopamine, by examining the effects of chronic psychosocial and chemically induced stress on the prosocial behavior of adult zebrafish. Psychosocial (ostracism and overcrowding) and pharmaceutical (ethanol and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP) manipulations are hypothesized to decrease the prosocial behavior of shoal participation. Zebrafish were ostracized (OST; 3-5 days), housed in overcrowded tanks (OC; 5 days), exposed to a low dosage of ethanol (ETH; 0.5% for 5 days), treated with MPTP (2 mM for 2 minutes), or treated with MPTP and OST (MPTP/OST). To examine social behavior, one treated zebrafish from each condition was introduced to a control group of four fish and swim behavior recorded for a period of two minutes. Videos were analyzed using ImageJ (NIH) Manual Tracking plugin, measuring distance (cm), velocity (cm/sec), and nearest neighbor distance (NND; distance to nearest fish, cm). Analysis of distance and velocity showed that treatment conditions had no aversive effect on motor function. There was no difference in the total swim distance and average velocity between the control and treatment conditions (p>0.16). However, analysis of NND showed that all treatment conditions, except ETH, significantly decreased social behavior (p<.02). The NND increased after OST, OC, MPTP, and MPTP/OST, compared to control (83.9±22.6 cm, 118.1±66.4 cm, 89.5±26.4 cm, 89.8±23.5 cm, and 66.6±18.5 cm respectively). There was no difference in the NND between OST, OC, MPTP, or MPTP/OST (p>0.05). Unlike other treatment conditions, ETH only showed s light increase in NND (66.6±18.5 cm and 68.4±18.3 cm, control and ETH respectively). These results show that chronic exposure to ethanol is not a comparable stressor to ostracism or overcrowding. Additionally, the results support previous research that suggests prosocial behavior relies on dopamine signals that can be modulated by hormones released in response to psychosocial stressors.

F11 UG

INHIBITING EXTRACELLULAR CARBONIC ANHYDRASE INCREASES THE DOSE-DEPENDENT, K^+-INDUCED INCREASE IN PROTON FLUX OF MULLER CELLS

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Within the retina and the broader CNS, synaptic transmission is extremely sensitive to changes in pH. A growing number of studies suggest that regulation of extracellular pH plays an important role in shaping neuronal communication. Tightly regulated levels of HCO_3^- are an understated contributor to extracellular pH. HCO_3^- levels are impacted by blood flow, CO_2 levels, as well as the activity of HCO_3^- transporters and the enzyme carbonic anhydrase (CA). Previous work (Newman 1996) detected the presence of HCO_3^- transporters and CA on radial glia (Müller cells) that span much of the overall thickness of the retina, playing

important roles in regulating many aspects of the retinal environment. Taking extracellular pH measurements, using an electrophysiology technique known as self-referencing, our lab previously examined a K^+-induced acidification, dependent upon HCO_3^- transport across the membrane of the Muller cell. This mechanism may play an important role in regulating extracellular pH in the retinal synaptic layers and by extension regulate neuronal communication. In order to better understand the K^+-induced extracellular acidification, we examined the dose-dependency of the acidification to K^+, the spatial profile of the effects on the Muller cell, and the role of extracellular CA in shaping the pH around the Muller cell. Previous work (Karwoski et al., 1985) showed increased activity in the retina leads to an elevation in extracellular K^+ levels. In order to associate increasing levels of activity to the level of acidification through the HCO_3^- -transport mechanism, we measured a dose-dependent K^+-induced acidification. Although our previous work suggested a greater acidification to K^+ at the endfoot of the Muller cell (near IPL) and a diminished acidification at the apical end (near OPL), it is possible that the source of the apical acidification was diffusion from the endfoot. The regional acidification response holds physiological significance, as it will affect synaptic transmission of specific retinal layers. The K^+-induced acidification persisted, although diminished from Muller cells with truncated endfeet. We also observed regulation of CA effects the HCO_3^--mediated acidification. Inhibiting extracellular CA significantly increased the magnitude of the acidification, indicating a role of CA in buffering pH outside the Muller cell. These findings extend previous work strongly implicating an important role for CA and regionally dependent HCO_3^--transport in shaping extracellular pH by Müller cells in the retina. They warrant future studies to characterize whether these bicarbonate-mediated alterations in pH contribute in a significant way to the processing of visual signals in retinal tissue.

F12 UG

ROLE OF Slp4 IN NEUROENDOCRINE VESICLE DOCKING AND FUSION

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Syntaptotagmin-like protein 4-a (Slp4-a)/granuphilin-a is a Rab27 effector protein that has been shown to play an integral role in the regulation of secretory vesicle docking and exocytotic fusion at the plasma membrane. Yet, the mechanism by which Slp4-a specifically regulates transition from stable vesicle docking to exocytosis is largely unknown. Here we test the hypothesis that Slp4-a regulates vesicle docking/priming and fusion through interaction of its N-terminal motif with the SM protein Munc18-1, which then participates in interaction with syntaxin1a on the plasma membrane. To test this hypothesis we initially defined the effects of various mutants of Slp4-a on exocytotic activity in primary cultures of mouse adrenal medulla chromaffin cells. Exocytotic activity was measured by monitoring changes in membrane capacitance under whole-cell patch clamp following UV flash uncaging of Ca^{2+} from NP-EGTA. Results demonstrated that overexpression of wild type Slp4-a, as well as a deletion mutant comprised of only the N-terminal Rab27A binding domain (Slp4-a (1-143)), led to a selective loss of the initial exocytotic component associated with the readily releasable vesicle pool (RRP). Notably, Rab27a interaction with Slp4-a was not required for promoting this secretory deficit suggesting that Slp4-a interaction with other effectors may be responsible. Slp4-a has been reported to interact with the Munc18-1/Syntaxin-1a complex to promote docking of dense-core vesicles to the plasma membrane as well as to inhibit vesicle exocytosis. However, the specific domain of Slp4-a that is responsible for this interaction and effects on the RRP have not been determined. Notably, the Rab27 binding domain (SHD1 and SHD2) at the N-terminus of Slp4-a is separated by a zinc finger region that may bind additional effectors. To investigate selective binding relationships between the N-terminus of Slp4-a and various effector proteins, GST-Slp4-a(1-143) was bacterially overexpressed and purified for use in *in vitro* pull-downs from brain cortical lysate. Our results indicate that the purified N-terminal expressed Slp4-a (1-143) protein effectively pulled down Munc18-1. In summary, the zinc finger region of Slp4-a likely interacts with the Munc18-1/syntaxin-1a complex and this interaction appears to be associated with strongly a diminished RRP in exocytotic neurotransmitter release.

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THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1 PD

AXONAL OUTGROWTH RATES OF PRIMARY NEURONS USING CUSTOM MUTICOMPARTMENTALIZED MICROFLUIDIC CHAMBER SYSTEM

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Although a variety of *in vitro* microfluidic devices for studying neuronal culture systems are currently available, they contain limitations for studying specific features of functionality for projection neurons. We have bioengineered novel open-top multi-compartmentalized microfluidic chambers for primary neuron cultures that permit neuronal subcellular compartmentalization (somatodendritic, axonal, and axon terminal), long-term fluidic isolation between the different compartments, immunocytochemistry, cellular transfection, and live cell imaging studies. The design includes ~90 microchannels located between the somatodendritic and axon terminal compartments. The small diameter of each microchannel permits the growth of only 1 or 2 axons, thereby simplifying the visualization of each individual axon. The objective of the current study was to optimize parameters using our microfluidic chambers for the determination of axonal outgrowth rates in primary neurons from fluorescent protein expressing transgenic embryos and naïve primary neurons transfected with fluorescent protein DNA constructs. Specific brain regions (cortex, hippocampus, striatum) were collected from E16 murine embryos and each dissected embryonic tissue sample was cryopreserved individually. The cryopreservation technique was implemented in order to separate the embryo tissue samples of differing genotypes. Axonal outgrowth rates were determined for transgenic neurons over-expressing tdTomato and for naïve neurons transfected after 2 days *in vitro* with mCherry-synaptophysin. In addition, we have utilized our refined model to investigate the effects of pathogenic proteins associated with neurodegenerative diseases on axonal outgrowth rates *via* transgenic expression and DNA transfection. Live cell fluorescent microscopy captured photomicrographs of each microchannel in its entirety, and individual axons were traced from entry into the microchannel from the somatodendritic compartment until they reached the axon terminal compartment using Zeiss Zen imaging analysis software. The axonal outgrowth length was measured for each individual axon over-time, generally 10-16 days *in vitro*, to calculate the axonal outgrowth rate. Axonal outgrowth measurements of axons emerging from the same somatodendritic compartment were averaged for each time-point, and axonal outgrowth rate (m) was defined by the linear trendline ($y = mx+b$) applied to the average outgrowth lengths.

G2 PD

CHARACTERIZING DEMYELINATION AND REMYELINATION IN ANIMAL MODELS OF DEMYELINATION

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Characterizing cells of the oligodendrocyte lineage is crucial for understanding demyelination and therapeutic benefit in demyelinating diseases of the central nervous system (CNS). We have recently optimized a novel method for the rapid, unbiased analysis of oligodendrocyte lineage cells (OLCs) using flow cytometry, a routine immunological technique for quantifying proteins on the cellular level. We have assembled panels of up to eight markers to characterize OLCs and conjugated them to specific fluorophores allowing for the entire panel to be run from a single tube on the cytometer. To definitively identify OLCs throughout the lineage, populations were defined by double positive staining− early OPCs: A2B5+/PDGFRa+, intermediate OPCs: A2B5+/NG2+, late OPCs: NG2+/O4+, pre-myelinating oligodendrocytes: O4+/GALC+, and mature myelin-forming oligodendrocytes: GALC+/MOG+. To further assess OLC properties in vivo, we stained for proliferation, necrosis/apoptosis, and chemotactic molecules. We next employed the assay to detect changes in OLC populations from whole brain and applied the method to the experimental autoimmune encephalomyelitis (EAE) model of demyelination. EAE produces multifocal inflammatory lesions of demyelination, and, in SJL/J mice immunized with PLP139-151, a clearly defined relapsing-remitting disease course similar to relapsing-remitting multiple sclerosis. OLC populations in the CNS were quantified by flow cytometry throughout an EAE disease course. To prevent the large infiltration of immune cells from skewing resident CNS cell analysis, we incorporated an antibody against the hematopoietic marker CD45 into the panel and gated out those cells in OLC analysis. Flow cytometry results demonstrated a robust loss of oligodendrocytes during onset of EAE and an early expansion of OPCs. By disease peak the early OPCs expressed more mature markers of OLCs but never fully differentiated into mature myelin-forming oligodendrocytes throughout the rest of the disease course. The early expansion of OPCs was further associated with an increase in the chemotactic protein CD44 in OPCs from the brain. In summary we present here quantification of OLCs and functional global analysis of the myelin-producing cells in EAE mice by flow cytometry. Characterization in mouse models of human CNS disease presents a rapid means to evaluate potential therapeutic

interventions in vivo for direct and indirect effects on demyelination and myelin regeneration.

G3 G

EVALUATION OF LIPOSOMAL NANOCARRIERS LOADED WITH ET_B RECEPTOR AGONIST, IRL-1620, USING CELL BASED ASSAYS

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One common feature of most neurodegenerative diseases, including Alzheimer's disease (AD) and stroke, is the death of neuronal cells. The neuronal cell death is associated with apoptosis, generation of reactive oxygen species (ROS) and oxidative stress. These neuronal cell death pathways can be reversed by ET_B receptor agonist, IRL-1620, which was found to enhance neuroprotection by promoting vascular and neuronal growth in rodent stroke model. Previous studies conducted at our end indicated that the treatment with IRL-1620 had significantly improved neurological and motor function while reducing oxidative stress and overall infarct area. IRL-1620 is a hydrophilic, 15 amino acid peptide and high molecular weight (~1820 Da). In this study, we have encapsulated IRL-1620 in PEGylated liposomes in order to enhance its efficacy. The batches prepared for liposomes encapsulating IRL-1620 were evaluated for particle size, polydispersity index (PDI), and charge (zeta potential) over a period of time to determine their stability. The liposomes loaded with IRL-1620 was tested on differentiated neuronal PC-12 cells for their neuroprotective ability against apoptosis caused by removal of nerve growth factor (NGF) against free peptide. A dose response curve was plotted based on the effect of neuroprotection by free IRL-1620 on differentiated neuronal PC-12 cells. The liposomal IRL-1620 showed significant increase in neuronal PC-12 cell viability compared to IRL-1620 alone. Experiments are also underway to determine the apoptotic protein expression, BAX and BCL-2, and the anti-apoptotic efficacy by PC-12 cells after treatment with liposomal nanocarriers loaded with IRL-1620.

G4

DIRECT CONVERSION OF RESIDENT OLIGODENDROCYTE PROGENITOR CELLS INTO MATURE NEURONS WITH MULTIPLE NEURONAL SUBTYPE SPECIFICATION

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Direct conversion of resident glia to neurons has emerged recently as a potential strategy for repair in the adult CNS. Oligodendrocyte Progenitor Cells (OPCs) are the most abundant proliferating resident neural cell population in the adult CNS. OPCs have not yet adopted a mature phenotype and represent a suitable cell population to recruit for neuronal repair by direct in vivo conversion. Furthermore, there is evidence that OPCs maintain population homeostasis, suggesting the functional population of resident OPCs would not be depleted following lineage respecification to neurons. Adult rat cortical OPCs were isolated using magnetic activated cell sorting for O4 antigen selection and maintained as a primary culture for screening combinations of putative neurogenic transcription factors including neurogenin2 (ngn2), ascl1, dlx2, sox2, neuroD1, pax6, and VP16Olig2. Beta-III-tubulin-expressing cells were observed by 10 days post transduction (dpt) of OPCs with retroviral supernatants of ngn2, ascl1, ascl1/dlx2, or neuroD1, with ngn2 exhibiting the most robust response. Ngn2- transduced cell expressed the mature neuronal markers, MAP2 and NeuN, and the post-mitotic projection neuron marker, tbr1, at 7dpt, suggesting successful neuronal subtype specification. Ngn2-transduced cells generated action potentials upon stimulation and displayed spontaneous activity and received synaptophysin-labeled connections from co-cultured postnatal primary neurons. OPCs transduced with the combination of ascl1 and dlx2 expressed inhibitory neuron marker, GAD67, demonstrating the generation of multiple neuronal subtypes from delivery of specific transcription factors. Direct in vivo delivery of retroviral neurogenin2 to the adult rat cortex demonstrated co-expression of immature neuronal marker, doublecortin, in transduced cells one week following gene delivery. Transduced cells expressed NeuN.

G5 PD

FLUORINATED 4-AMINOPYRDINES AS PET TRACERS FOR MULTIPLE SCLEROSIS

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Objectives: Multiple sclerosis (MS) is a common neurological disease for which no PET tracers are available. Tracers are in development for inflammation (TSPO ligands) and myelin but no tracers for demyelinated axons, the hallmark of MS, exist. Potassium (K^+) channels in myelinated axons are

normally located beneath the myelin sheath. During MS, myelin becomes damaged leaving these channels exposed. K^+ channel blockers, such as 4-aminopyridine (4-AP), are used clinically to enhance axonal conduction and improve neurological function. Here, we explore the possibility that 4-AP analogs can be used to image demyelination. Our goals: 1) Show that 4-AP has higher uptake in demyelinated areas over myelinated areas in animal models of MS. 2) Develop fluorinated derivatives of 4-AP and routes to label these molecules with ^{18}F. 3) Conduct PET imaging studies using [^{18}F] 4-AP in rats and monkeys.

Methods: 1) [^{14}C] 4-AP was administered to live demyelinated and control mice and the uptake in white matter was measured using autoradiography. 2) Fluorinated derivatives of 4-AP were synthesized and their binding affinity compared with 4-AP. 3) A route for ^{18}F labeling of our lead compound was developed. 4) PET imaging studies in demyelinated rats and monkeys are ongoing.

Results: 4-AP and the fluorinated derivative 3-F-4-AP show significantly higher uptake in demyelinated areas over normally myelinated white matter. These molecules permit distinguishing demyelinated animals from controls using autoradiography. The SUV ratio in brain over blood for 3-F-4-AP 1h post injection is >2. A novel synthetic strategy for ^{18}F labeling of 3-F-4-AP has been developed comprising aromatic nucleophilic substitution followed by reduction. Non-invasive microPET imaging results are expected for mid 2015.

Conclusions: We have identified the first compound whose uptake increases upon demyelination, which is also brain permeable and metabolically stable. This compound is based on an approved drug for MS. This compound is a promising PET tracer for demyelinating conditions.

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G6 PD

ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF USHER SYNDROME

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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 profound hearing impairment and vestibular dysfunction from birth, and the development of retinitis pigmentosa (RP) in early adolescence that progresses to blindness. We developed antisense oligonucleotides (ASO) to target two different mutations in *USH1C* that cause Usher syndrome in humans. One mutation is the Acadian Usher syndrome mutation c.216G>A (p.V72V), and the other is c.238-239insC (p.R80fs). The ASOs block the deleterious effects of the mutations and partially restore *USH1C* gene expression *in vitro* and *in vivo* in transgenic mice engineered to have the *Ush1c*.216G>A mutation. These mice have profound hearing impairment, circling behavior indicative of severe vestibular dysfunction and retinal dysfunction early in life. Mice treated with a single dose of ASO shortly after birth had normal vestibular function and could hear for more than six months of age. Remarkably, systemic delivery of progressively lower doses of ASO, which yielded minimal recovery of gene expression in the cochlea, was sufficient for phenotypic rescue, and hearing thresholds were shifted in a dose-dependent manner at 1, 3 and 6 months of age. Threshold values in response to low, mid and high frequency stimulation were stable at 1 and 3 months of age for all doses tested. However, at 6 months of age hearing thresholds were elevated for all frequencies and doses tested. By 9 months of age, only the highest dose continued to show rescue of hearing in response to low frequency stimulation. These results demonstrate that the ASOs are a promising drug platform for the treatment of auditory and vestibular disorders.

G7

HUMAN IPSC-DERIVED NEURONS: A SUITABLE MODEL FOR TOXICOLOGICAL ASSAYS

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New standards are needed to address the drug development for neurological degenerative diseases (e.g. Parkinons disease, Alzheimer's disease) and neurotoxicological liability screens. Current drug development and toxicology screens employ classical animal derived *in vitro* and *in vivo* models, but lack human cell models until clinical trials.

To meet this need Axiogenesis AG developed different types of human induced pluripotent stem cell (iPSC) derived neurons (dopaminergic and peripheal neurons) to cover central nervous system as well as peripheral nervous system assays.

Here we show that Axiogenesis neurons are a suitable model to assess different neurotoxicological assays, such as 1) mitochondrial toxicity that has been assessed with the Seahorse technology, using a high throughput 96well plate. 2) Functional synaptic activity, measured using dopaminergic

neurons plated in 12 well Multi Electrode Arrays, showing a functional network after 7 days in culture. Additionally, dopaminergic burst patterns showed similarities to primary mouse midbrain neurons. 3) Neurite outgrowth analysis using peripheral neurons treated with Angiotensin II and db-cAMP.

The data show that Axiogenesis human iPSC-derived neuronal subtypes display a suitable and physiological relevant human cell model that can be employed for a variety of different already established animal based toxicological assays.

THEME H. SENSORY AND MOTOR SYSTEMS

H1 PD

A NOVEL RETINAL AMACRINE CELL MICROCIRCUIT

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At the frontier of systems neuroscience is the pursuit to place identified types of neurons in the context of functional circuits. It is also critical to understand the natural dynamics that alter circuit connectivity and function. This circuit-level comprehension of neural networks is paramount in creating new therapies to combat neurodegenerative disease. The neural circuits of the retina offer unique opportunities for circuit-level analysis because of the accessibility of the tissue and our advanced knowledge of cell typology. The research project proposed here will examine the light responses of a novel amacrine cell in the mouse retina and reveal the function of the circuit where this cell is embedded. Neural computation depends on interactions between excitatory and inhibitory synaptic input. Feedforward and feedback inhibition, carried out by inhibitory interneurons, are fundamental building blocks of neuronal processing. Inhibition is present throughout the nervous system and plays a critical role in tuning the responses of sensory neurons. One of the first descriptions of lateral inhibitory circuits in the central nervous system came from studies examining signal processing within the retina. Horizontal and amacrine cell types facilitate inhibition in the outer and inner retina, respectively. More than sixty years of research have focused on characterizing the structure and function of numerous retinal cell types, including the role of horizontal cell-mediated inhibition in the outer retina, but have left the encoding properties of retinal amacrine cells largely uncharted. Amacrine cells are the most numerous inhibitory interneuron in the retina yet remain the least understood retinal cell class. Of the roughly 30 amacrine cell types identified morphologically in the mammalian retina, only three (starburst, A17, AII) have been described functionally and placed in the context of a specific retinal circuit. Amacrine cells are known to be involved in other visual computations, like distinguishing an object from background motion, but the identity of the amacrine cell types involved remains unknown. Here, I introduce only the fourth amacrine cell to be functionally characterized and placed in a specific amacrine cell – ganglion cell circuit. We hypothesize that this amacrine cell mediates a unique contrast response function in the postsynaptic ganglion cell. In order to fully comprehend how visual processing takes place within the retina, we must elucidate the role of amacrine cell-driven inhibitory circuits.

H2

RHO GTPASES ARE REQUIRED FOR SMAD3-MEDIATED INDUCTION OF ET-1 IN HUMAN TRABECULAR MESHWORK CELLS

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Purpose: Elevated content of transforming growth factor (TGF)-β2 and endothelin-1 (ET-1) within the aqueous humor of affected patients is associated with the development of primary open-angle glaucoma (POAG). We have previously demonstrated that TGF-β2 markedly enhances ET-1 expression and secretion in human trabecular meshwork (TM) cells through activation of both canonical (Smad) and non-canonical (Rho GTPase) signaling pathways. Here, we examined whether functional cross-talk between Smads and Rho GTPases promotes TGF-β2 mediated induction of ET-1 expression.

Methods: Primary human TM cells were conditioned in serum-free media and incubated in the absence (vehicle) or presence of TGF-β2 (5 ng/ml). TGF-β2 signaling was blocked using SB-431542 (1 μM) or targeted siRNA knockdown of Smad2 or Smad3. Activation of Rho GTPases was blocked by pre-treatment with exoenzyme C3 transferase (10 μM). Relative changes in preproendothelin (ppET)-1 mRNA content and secreted ET-1 peptide were quantified by real-time PCR and ELISA, respectively. Content of phosphorylated or total Smad2 and Smad3 proteins was determined by Western immunoblot.

Results: Primary human TM cells incubated with TGF-β2 exhibit markedly enhanced ppET-1 mRNA expression and ET-

1 peptide secretion, with a concurrent increase in the content of phosphorylated Smad2/3, compared with vehicle-treated controls. TGF-β2 mediated increases in ET-1 were prevented by co-incubation with SB-431542 as well as targeted siRNA knockdown of Smad3, but not Smad2. Pre-treatment with C3 also prevented TGF-β2 mediated increases of ET-1 expression with no observed changes in the content of phosphorylated Smad3. **Conclusions:** This study demonstrates that TGF-β2 mediated activation of Smad3, but not Smad2, facilitates ET-1 expression and secretion in human TM cells. Blocking Rho GTPase signaling prevents TGF-β2 mediated enhancement of ET-1 expression, with no effect on Smad3 phosphorylation. These findings suggest that TGF-β2 mediated activation of Rho GTPase signaling is required for Smad3-mediated transcription of ppET-1. This study demonstrates for the first time a functional cross-talk between the canonical Smad and non-canonical Rho GTPase signaling pathways in human TM cells.

H3 G

TRANSFORMING GROWTH FACTOR-β2 ATTENUATES BRADYKININ B2 RECEPTOR EXPRESSION IN HUMAN TRABECULAR MESHWORK CELLS

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Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterized by loss of peripheral vision secondarily associated with elevated intraocular pressure (IOP). Although the cause of POAG remains unclear, elevated levels of TGF-β2 in aqueous humor (AH) of affected patients is strongly implicated in the pathophysiology of enhanced AH outflow resistance. Despite recent advancements, the mechanism(s) by which TGF-β2 elevates IOP remains unknown. Bradykinin, a potent vasodilator, is currently under investigation as an alternative therapeutic strategy for the management of IOP in affected POAG patients. Here, we investigated the effects of TGF-β2 on bradykinin B2 receptor expression and signaling in primary and transformed human trabecular meshwork (TM) cells. In agreement with previously reported findings, porcine anterior segments chronically perfused with TGF-β2 (10 ng/ml) exhibited a sustained increase in IOP compared to vehicle-treated matched segments. TGF-β2 dependent changes in bradykinin signaling were subsequently determined using cultured primary or transformed human TM cells. Quiescent TM cells expressed measurable levels of bradykinin B2 receptor mRNA and protein. In contrast, TM cells cultured overnight in the presence of TGF-β2 (5 ng/ml) exhibited a marked 40-70% reduction in B2 receptor mRNA and protein expression, respectively. Interestingly, siRNA-targeted disruption of the canonical (Smad2, Smad3) signaling pathway prevented TGF-β2 mediated attenuation of B2 receptor expression in TM cells. In contrast, disrupting the non-canonical signaling pathway with either Y-27632 or with C3 exoenzyme did not prevent TGF-β2 mediated attenuation of B2 receptor expression in TM cells. Together, these findings suggest that elevated content of TGF-β2 in the AH of POAG patients may elevate IOP, in part, by attenuating constitutive B2 receptor expression within the conventional outflow pathway. 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.

H4 G

DOPAMINE DEPLETION RESULTS IN FREQUENCY-DEPENDENT DISINHIBITION OF CORTICOSTRIATAL TRANSMISSION *IN VIVO*: ROLE OF LOCAL STRIATAL CGMP AND GABAERGIC SIGNALING

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Parkinson's disease is strongly associated with the emergence of increased oscillatory activity within the cortico-basal ganglia loop, which is thought to reflect a disruption of corticostriatal transmission, and thereby exacerbate motor deficits associated with this disease. The precise neurobiological mechanisms underlying the development of increased synchronous activity resulting from dopamine depletion in the striatum however, remains poorly understood. It has previously been shown that following chronic nigrostriatal dopamine lesion there are adaptations to non-dopaminergic components within the striatal network. Of particular interest are the elevated cGMP signaling and impaired GABAergic function that emerge in the dopamine-depleted striatum. From a mechanistic point of view, it is therefore likely that in addition to dopamine, local striatal cGMP and GABA signaling contribute to fine-tune striatal responses to synchronous cortical inputs. The aim of this study is to determine the role of dopamine, GABA and cGMP signaling in the parkinsonian striatum in promoting increased corticostriatal synchrony at specific frequencies. Towards this goal, we employed local field potential recordings to first assess the pattern of cortical-evoked responses in the dopamine-intact striatum using trains of pulses delivered at

10, 20, and 40 Hz. We then determined if the pattern of striatal response is impaired following chronic nigrostriatal dopamine lesion and used pharmacological tools to identify the roles of striatal GABA and cGMP signaling in mediating corticostriatal transmission. We found a frequency-dependent incremental suppression of cortically-evoked striatal LFP *in vivo* that is disrupted following chronic lesion of the nigrostriatal DA pathway. Disruptions to dopamine, cGMP and, GABAergic signaling appear to play differential roles in the disinhibition of corticostriatal transmission in the parkinsonian brain. This study is supported by Rosalind Franklin University, PRI Innovation Grant, Ply donation, the Parkinson's Disease Foundation, and NIH-NINDS grant R03-NS088502.

H5 UG

CONCENTRATION AND PATTERN-DEPENDENT DOPAMINE NEUROMODULATION OF MOTOR PATTERNS

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Neuromodulators are chemical messengers in the nervous system that are either released from modulatory neurons or are present in the blood stream (as hormones). They modify neuronal properties and interactions and can alter the activity of whole networks of neurons1. The biogenic amine Dopamine (DA) plays a pivotal role in modulating locomotor activity2 and in humans, the loss of the dopaminergic neurons causes a number of pathologies including Parkinsons Disease. DA also directly targets motor circuits in both vertebrates and invertebrates. Its effects on these circuits are variable within a given species and system, a fact likely due to the dynamics of the involved receptors, making DA signaling contingent on the state of the neuron or network being modulated. We are studying the actions of DA on two central pattern generators in the stomatogastric ganglion (STG) of the crab, Cancer borealis. STG neurons produce the fast and spontaneously active pyloric rhythm and the slower episodic gastric mill rhythm. Both pyloric and gastric mill neurons are under descending modulatory control from anteriorly located extrinsic projection neurons. DA is a transmitter of a subset of these neurons and STG neurons possess DA GPCRs3 that affect several ionic conductances that influence spike and burst timing of the motor neurons. Yet DA has very little influence on network output. It is unknown whether this is also true at different DA concentrations and/or for the gastric mill rhythm and its interactions with the pyloric pattern. **We hypothesize that Dopamine has both concentration and pattern-dependent effects on the STG motor patterns.** To test this hypothesis we extracellularly recorded the activity of pyloric and gastric mill neurons in different DA concentrations. Our results show that despite the presence of DA receptors in pyloric neurons, ongoing pyloric rhythms are unaffected by all applied DA concentrations (N=4). This was different for the gastric mill rhythm: The burst durations of the main CPG neurons lateral gastric (LG) and dorsal gastric (DG) were differentially affected by increasing concentrations of DA (N=3). Our preliminary data shows that different types of gastric mill rhythms elicited opposite responses. Specifically, in one version of the rhythm DA increased LG burst duration with increasing DA concentrations, while in the other version LG burst duration decreased. This indicates that the effects of Dopamine are not only dependent on concentration, but also specific to the currently present motor pattern.

H6 G

DOPAMINERGIC NEUROMODULATION OF THE SUBTHALAMIC NUCLEUS

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Nigrostriatal neurons that degenerate in Parkinson's disease (PD) also innervate the subthalamic nucleus (STN). In order to determine the impact of dopaminergic neuromodulation and dopamine denervation on autonomous and synaptically patterned STN activity, we are studying the effects of dopamine receptor-selective drugs and optogenetically stimulated dopamine release in mouse brain slices.

Exogenous dopamine (0.1-10 µM) elicited a dose-dependent (up to 2-fold) increase in autonomous STN activity, which was reproduced by co- but not individual application of D1-like (SKF81297) and D2-like (quinpirole) receptor agonists. These data are consistent with the expression of postsynaptic D5 and D2 receptors, respectively. We are currently working to validate these findings through optogenetic stimulation of ChR2(H134)-expressing dopaminergic axon terminals in the STN. Exogenous dopamine also reduced the amplitude of the first electrically stimulated glutamatergic EPSC and increased the ratio of EPSC2:EPSC1, an effect mimicked by application of a D4 receptor agonist (PD168077). These data suggest that dopamine reduces the initial probability of glutamatergic transmission through activation of presynaptic D4 receptors.

In PD, the motor cortex (M1) and STN exhibit abnormal, synchronous beta band activity. In order to test the impact of dopaminergic neuromodulation on cortical patterning of STN activity, M1-STN axon terminals were optogenetically stimulated at 20 Hz for 1 second in the presence and absence of dopamine. Dopamine profoundly reduced cortical excitation of STN neurons (control = 7.1 spikes;

dopamine = 1.9 spikes; n = 6; $p < 0.05$). Together, these findings demonstrate that dopamine is a potent neuromodulator of autonomous activity, synaptic transmission and synaptic integration in the STN. Furthermore, loss of dopaminergic modulation in the STN may contribute to abnormal cortical patterning of STN activity in PD.

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H7 PD

FUNCTIONAL CHARACTERIZATION OF TWENTY TYPES OF RETINAL GANGLION CELLS AND THEIR SPIKING SIGNALS IN THE MOUSE RETINA

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Classification of neurons into distinct, functional, morphological, and genetic classes is essential in extending our understanding of the nervous system to the level of individual circuits. We have developed a novel strategy for classifying retinal ganglion cells (RGCs) which form the parallel outputs of the retina, carrying all visual information to the rest of the brain.

Far from the textbook camera-like representation of the visual world, in recent years it has been found that intricate computational processing already occurs in the retina. Parallel information channels, carried by the different RGC types, each extract specific features from the visual scene, including contrast, motion, orientation and color. A necessary step in understanding the different computations done in the retina, and characterizing the circuits responsible for them, is classification of RGCs into their different types. Previous attempts to classify RGC types have relied on unique gene expression profiles of subsets of RGCs or on large-scale clustering of dendritic morphology or electrophysiological properties. The different classification schemes have yet to arrive at a definitive, unified typology, and less than half of the ~20 RGC types suggested by morphological studies have been found in functional classifications.

Here we present a novel functional classification of RGCs in the mouse retina, using spiking response to a set of light stimuli. Rather than commonly used clustering and principal component analysis techniques, we use an efficient method based on a 'decision tree' to probe a large number of parameters of the light response. We have achieved reliable, online classification of 20 RGC types, and our algorithm can be used across labs to standardize RGC typology. Our classification includes all functional RGC types previously identified in mouse, as well as types previously identified only in other species, and types that were previously unknown in any mammalian retina.

H8

MODELING AMYOTROPHIC LATERAL SCLEROSIS IN C. ELEGANS: EVALUATING HOW TDP-43 EXPRESSION IMPACTS MOTOR AND SENSORY NEURON FUNCTION

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder. Mutations in the gene that expresses a 43 kD TAR DNA-binding protein (TDP-43) have been linked to ALS. This gene encodes a nuclear localized RNA binding protein, which, in its mutated form, becomes inappropriately cleaved, enters the cytoplasm, and becomes toxic. The toxicity may be caused by TDP-43 protein misfolding and aggregate formation, resulting in neuronal dysfunction. Cells have evolved a quality control system called proteostasis, which consists of a suite of molecules that monitor and adjust protein folding, maintaining a functional proteome. Failure of specific components of proteostasis may be associated with TDP-43 aggregation and neurodegeneration. To study the effects of TDP-43 on neuronal function, we generated a *C. elegans* model expressing a human TDP-43::YFP gene fusion in neurons. In our model, TDP-43 expression disrupts GABAergic motor neuron function, leading to motility deficits. Furthermore, behavioral assays on the chemosensory neuron AWC and the sensory neuron ASH reveal that TDP-43 expression has significant negative effects on the animal's ability to sense chemical odors and to respond to mechanical stimuli. These results demonstrate that the presence of TDP-43 leads to both sensory and GABAergic motor neuron dysfunction, suggesting that a common mechanism, proteostasis imbalance, may lead to neural dysfunction.

H9 G

TEMPERATURE REPRESENTATION IN THE *DROSOPHILA* BRAIN

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We are interested in the neurobiology of thermosensation, an indispensable sensory modality in all animals. How are hot and cold stimuli detected at the periphery? How are they processed in the brain? How are they integrated to produce behaviors such as temperature preference or avoidance of noxious extremes? We recently showed that

temperature stimuli are represented by a spatial map of activity in the Drosophila brain. First, we identified hot- and cold-sensing neurons in the fly antenna and showed that hot and cold receptor cells project onto distinct, but adjacent glomeruli in the Proximal-Antennal-Protocerebrum (PAP), forming a 'thermotopic' map. We used two-photon imaging to reveal the functional segregation of hot and cold responses in the PAP, and showed that silencing the hot- or cold-sensing neurons produces animals with distinct and discrete deficits in their behavioral responses to thermal stimuli. Together, these results demonstrated that dedicated populations of cells orchestrate behavioral responses to different temperature stimuli, and revealed a labeled-line logic for the coding of temperature stimuli. Our current work aims at identifying the central neural mechanisms that shape the behavioral responses to thermal stimuli, and how these become integrated with additional internal and external cues to orchestrate behavior.

H10 G

MECHANISMS UNDERLYING ORIENTATION SELECTIVITY IN THE MOUSE RETINA

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Orientation selectivity (OS) is well known in the visual cortex for decades and has recently been found in mouse lateral geniculate nucleus (Marshel, 2012; Zhao et. al. 2013; Piscopo, 2013). Does this property primarily arise in these regions or is there an orientation selective input from the retina via retinal ganglion cells (RGCs)? Orientation selective RGCs have been reported in the rabbit retina (Levick, 1967; Caldwell et. al. 1978; Amthor, 1989; Bloomfield 1994; Venkataramani and Taylor, 2010) but the underlying neural mechanisms remain unclear.

The goal of our research was to find and characterize OS cells in the mouse retina and probe the circuit mechanisms that underlie orientation selectivity. We probed RGCs with both flashed and moving bars in an ex vivo preparation of the intact retina. We characterized light responses in both cell-attached and whole-cell electrophysiological recordings. To correlate physiology with morphology, we imaged cells with two photon and confocal microscopy.

We found OS RGCs aligned with the two cardinal axes of the mouse visual system, and we observed OS in both excitatory and inhibitory synaptic inputs to RGCs, in contrast with previous reports (Levick, 1967; Caldwell et. al. 1978; Bloomfield, 1994). With our combination of physiological and anatomical measurements, we hope to reveal the circuit mechanisms of OS in the retina. With the power of genetic tools available in mouse, our identification of OS RGCs in this species will lead to future work on the processing of OS information throughout the visual system.

H11 G

HIGH-INTENSITY EXERCISE AUGMENTS SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR IN HUMANS WITH INCOMPLETE SPINAL CORD INJURY

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Research performed in animal models of spinal cord injury (SCI) suggests that exercise-dependent changes in the expression of brain-derived neurotrophic factor (BDNF) are related to the recovery of stepping after injury. Studies also demonstrate that exercise-dependent expression of BDNF is proportional to the intensity of the exercise. In the current study, the effect of exercise intensity on peripheral levels of neurotrophic proteins was assessed in 11 individuals with motor incomplete SCI. Changes in serum concentrations of BDNF and insulin-like growth factor-1 (IGF-1) were evaluated across different levels of exercise intensity achieved during a graded-intensity locomotor exercise paradigm. Levels of intensity were defined as percentages of the peak gait speed reached during testing (low= 33%, moderate=67%, and high= 100% of peak gait speed). In addition, the impact of the Val66Met single nucleotide polymorphism on the BDNF gene on exercise-dependent changes was examined. To our knowledge, this is the first study to evaluate exercise intensity-dependent changes in peripheral BDNF and the potential impact of the Val66Met SNP in individuals with motor incomplete SCI. Our results demonstrated a significant increase in serum BDNF at high exercise intensity as compared to moderate intensity ($p=0.01$) and 15 and 30 minutes post exercise ($p<0.01$ for both), with comparison to changes at low intensity approaching significance ($p=0.05$). Serum IGF-1 demonstrated no significant intensity-dependent changes. Positive correlations between changes in BDNF and various measures of exercise intensity (heart rate; $R=0.35$ $p=0.04$, oxygen consumption; $R=0.37$ $p=0.03$, and rating of perceived exertion; $R=0.43$ $p=0.02$) further indicate that exercise-induced changes in serum BDNF are related to exercise intensity. Additionally, the data suggest that carriers of the Val66Met SNP may not exhibit intensity-dependent changes in serum BDNF concentration. Given the known role of BDNF in experience-dependent neuroplasticity, these preliminary results suggest intensity of exercise may be an important parameter of physical rehabilitation interventions following neurologic injury.

H12 G

ENHANCED ACTIVITY FOR SEARCH TARGETS IN FRONTAL EYE FIELD DEPENDS ON TARGET AWARENESS

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Finding targets in complex, natural scenes is critical in the real world. Cells in Frontal Eye Field (FEF) show enhanced responses to search targets in paradigms using artificial arrays with small numbers of easily localizable stimuli. However, recent work using natural scenes, where increased complexity makes the location of the search target less obvious, suggests this enhancement is absent during search behavior. Why have enhanced FEF responses to targets been found in artificial tasks but not in natural scene search? Here, we recorded from single neurons in monkeys while they performed a natural scene search task. We found that the target enhances FEF activity in a specific manner: only prior to when the monkey knowingly moves to the search target, and only when this eye movement (and thus also the target) is near the neuron's receptive field. When monkeys accidentally made eye movements to the target, enhancement was absent. Moreover, we found that neurons' tuning curves sharpened and the gain increased when knowingly moving to the target compared to other areas in the scene. These effects suggest that awareness of the target's location is critical for an enhanced FEF response.

H13 G

INVOLVEMENT OF CAMKII ALPHA IN MULTIPLE SCLEROSIS-ASSOCIATED PAIN

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Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, with manifestations of neuroinflammation and demyelination. Pain in MS patients, with remarkable prevalence up to ~90%, significantly reduce quality of life. Over past decades, advances have been made in understanding the neurobiological mechanisms of motor dysfunction in MS, but to a much lesser extent, MS-associated pain. In this study, we tested the hypothesis that Ca2+/calmodulin-dependent protein kinase II (CaMKIIα) plays a critical role in the development and maintenance of pain and neuropathy in MS. We established a widely used animal model, experimental autoimmune encephalomyelitis (EAE), to study the pain mechanism in mice. We found that spinal CaMKIIα activities were increased, correlating with the development of mechanical allodynia and thermal hyperalgesia, in EAE mice. Prophylactic and acute 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, siRNA targeting CaMKIIα 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. Inhibiting CaMKIIα may offer potentially new pharmacological interventions to prevent or attenuate multiple sclerosis-associated pain.

H14

CENTRAL PROJECTIONS OF NERVES INNERVATING THE NASAL PASSAGES OF THE RAT

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The purpose of this research was to determine the central projections of nerves innervating the nasal passage of rats that may be involved in initiating the autonomic cardiorespiratory reflex known as the diving response. The anterior ethmoidal nerve (AEN), a branch of the ophthalmic division of the trigeminal nerve that innervates the nasal passages, was thought to provide the afferent signal that initiates the apnea, bradycardia, and selective increase in peripheral vascular resistance that occurs in response to underwater submersion. However recent research has indicated that rats retain the complete diving response even after bilateral AEN sectioning, suggesting that other nasal nerves can also provide the afferent signal to initiate this response. The transganglionic tracer WGA-HRP was directly injected into the left AEN in 4 rats. After immunohistological processing and brainstem tissue visualization with a Nikon AR1 confocal microscope, central tracer terminations were found in the ventral tip of the spinal trigeminal nucleus caudalis (medullary dorsal horn; MDH) and in the ventral trigeminal tract. This MDH location has previously been shown to contain secondary neurons that become activated during diving, presumably after afferent stimulation provided by the AEN. The nasal passages of an additional 8 rats were then injected with WGA-HRP; in 4 rats the AENs were intact, in 4 rats the AENs had been sectioned bilaterally. In these 8 rats tracer terminations were found in the ventral tip of the MDH, dorsal trigeminal tract, and

nucleus tractus solitarius. Results indicate that, in addition to the AEN, other nerves that innervate the nasal passages project to the ventral tip of the MDH and therefore could possibly provide the afferent information necessary to initiate the diving response, especially in the absence of the AEN. This research was supported by a CCOM Suarez Summer Research Fellowship awarded to KL, and MWU Intramural funding awarded to PFM.

H15

DIFFERENTIAL MODES OF SYNAPTIC TRANSMISSION WITHIN FAST SPINAL LOCOMOTOR CIRCUITRY

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Different speeds of locomotion are produced by the coordinated activation of spinal premotor networks and motoneurons. However, it is unclear if differences in excitatory network connectivity related to movement speed exist. In zebrafish, different speeds of swimming are generated by excitatory premotor neurons called V2a cells. We have recently reported two morphologically distinct classes; ones with bifurcating axons (V2a-B) and ones that only descend (V2a-D). Their different morphologies suggest differences in their connectivity within the spinal network. Here, we have tested this idea by focusing on cells within the two populations that should have similar functional roles, namely the most dorsal cells that are engaged during fast swimming. By performing simultaneous whole-cell somatic and extracellular axon recordings, we find that V2a-B cells have faster conduction velocities than V2a-D cells. To assess synaptic connectivity, we then performed dual whole-cell recordings from V2a neurons and the large, dorsal motoneurons recruited at the fastest speeds, namely primary motoneurons (pMNs). We find that the faster-conducting V2a-B/pMN connection is a mixed (electrical and chemical) synapse, while the slower-conducting V2a-D/pMN connection is purely chemical. In addition, we observe responses that are not phase locked to presynaptic spiking in either class, which suggests interactions via local gap junctional coupling within the motor pool and polysynaptic pathways converging onto pMNs. Our findings demonstrate that in addition to differences in morphology, there are differences in the speed and reliability of connections to motoneurons. They also reveal unexpected heterogeneity in the operation of spinal locomotor circuits driving fast movements. This study is supported by National Institutes of Health grant R01-NS067299 (D.L.M).

H16 PD

STRUCTURES OF SYNAPTIC DRIVE UNDERLYING SELF-SUSTAINED MOTOR UNIT DISCHARGE IN THE DECEREBRATE CAT

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The self-sustained discharge of spinal motoneurons can be observed in both animals and humans. Though often pronounced following neurological injury, the origins of this tonic motor output are not fully understood. Self-sustained motor unit activity often manifests as a relatively slow and steady discharge, consistent with minimal underlying synaptic drive. Indeed, evidence from animal preparations demonstrates that self-sustained discharge can be mediated through persistent inward Ca^{2+} and Na^{+} currents, intrinsic to the motoneuron and sensitive to monoamines, such as norepinephrine (NE). If the self-sustained discharge were generated exclusively through an intrinsic mechanism, the discharge of motor units would be independent of one another. Here we assess this mechanism by quantifying potential correlated and synchronous activity underlying self-sustained motor units discharge from the hind limb of the decerebrate cat. Electromyographic activity of the left soleus and/or medial gastrocnemius was collected from 11 animals using a custom 64 channel electrode grid placed directly on the isolated muscle. Offline, self-sustained EMG activity was isolated and decomposed into an average of 21 motor unit spike trains per recording. Consistent with previous reports, the self-sustained discharge of motor units occurred at low mean discharge rates, (7.4 ± 1.4 pps), with low interspike variability (14 ± 4.0% CoV). In these trials, significant low frequency coherence (<2 Hz) was observed in 7/11 preparations, while minimal degrees of coherence was inconsistently observed in higher frequency bands. A majority of these preparations demonstrate either narrow- or broad-peak short-term synchronization. Following intrathecal administration of methoxamine, a NEα1 agonist, self-sustained discharge was observed to a greater extent and motor unit discharge rates are increased significantly to 11.0 ± 4.3 pps, though no change in discharge variability is observed. Activation of spinal NEα1 receptors increased the prevalence and magnitude of low-frequency coherence and produced coherence in the 15-30 Hz sub-band (beta band) in 7/10 experiments. Further, short-term synchronization became more evident and ripples at ~50 ms were often observed in the cross correlation histogram, in agreement

with the findings from the coherence function. These data demonstrate that multiple structures of synaptic drive may underlie self-sustained discharge of motor units. Understanding the mechanisms underlying pathological motor output will allow us to develop targeted therapies to lessen disability and improve function in individuals with neurological injury.

H17

DEVELOPMENTAL MODIFICATIONS OF PREMOTOR EXCITATORY DRIVE MATCH CHANGES IN MOTONEURON PROPERTIES

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The first behavior zebrafish embryos produce is spontaneous 'coiling', involving bends of the entire body. This behavior is generated by spinal circuits that ultimately control fast escapes in larvae after they hatch. During this period, the earliest born axial 'primary' motoneurons (pMNs) migrate dorsally in the spinal cord and nearly double in size, resulting in substantial decreases in excitability. One question that arises is how the early premotor elements responsible for driving movements adjust to these changes to allow for continued expression of motor behavior through life. Here, we have focused on changes in a major source of premotor excitatory drive in all vertebrates, which arises from Chx10-positive V2a neurons. Using *in vivo* time-lapse imaging of stochastically-labeled V2a cells in a transgenic line labeling the motoneuron pool, we find that the earliest born V2a cells, which will ultimately occupy the dorsal-most positions in the larval spinal cord (dV2a), are initially ventrally located. At this early embryonic stage, putative connections to pMNs at the same ventral location arise from *en passant* synapses along the main axon. As dV2as and pMNs migrate dorsally during development, this initial contact is apparently maintained locally by secondary axonal branching from the initial site of contact with the main axon. Next, to examine the potential functional impact of this maintained connection, we performed whole-cell voltage clamp recordings of excitatory drive to pMNs during 'fictive' swimming in 2-day old embryos and 4-day old larvae. At both stages, pMNs received phasic excitation driving the cyclical bursts of motor activity and tonic excitation providing a background source of depolarizing drive. However, there was a substantial increase in both phasic and tonic drive commensurate with a decrease in input resistance (Rin) from day 2 to 4, consistent with the idea that synaptic inputs compensate for decreases in cellular excitability to maintain functional output. To examine the contribution of cellular excitability to this process, we are using the bacterial voltage-gated sodium channel, NaChBac, and the inward-rectifying potassium channel, Kir2.1, to provide genetically-targeted increases and decreases in cell excitability, respectively. Whole-cell patch clamp recordings from individual pMNs expressing these constructs have confirmed their utility. Our work thus suggests there are changes in dV2a morphology and excitatory drive that compensate for changes in pMN location, size and Rin, and we are now in a position to examine the contribution of cell autonomous features, like excitability, to this process.

H18 UG

COMPLEX AND NON-REDUNDANT SIGNALS FROM INDIVIDUAL ODOR RECEPTORS THAT UNDERLIE CHEMOTAXIS BEHAVIOR IN DROSOPHILA MELANOGASTER LARVAE

Jeewanjot S. Grewal, Christina Cho, Karolina Kir, Nicole Fledderman, Kathryn Swain, Scott A. Kreher
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The rules by which odor receptors encode odors and allow behavior are still largely unexplored. Although large data sets of electrophysiological responses of receptors to odors have been generated, few hypotheses have been tested with behavioral assays. We use a data set on odor responses of Drosophila larval odor receptors coupled with chemotaxis behavioral assays to examine rules of odor coding. Using mutants of odor receptors, we have found that odor receptors with similar electrophysiological responses to odors across concentrations play non-redundant roles in odor coding at specific odor concentrations. We have also found that high affinity receptors for odors determine behavioral response thresholds, but the rules for determining peak behavioral responses are more complex. While receptor mutants typically show loss of attraction to odors, some receptor mutants result in increased attraction at specific odor concentrations. The odor receptor mutants were rescued using transgenic expression of odor receptors, validating assignment of phenotypes to the alleles. Vapor pressures alone cannot fully explain behavior in our assay. Finally, some odors that did not elicit strong electrophysiological responses are associated with behavioral phenotypes upon examination of odor receptor mutants. This result is consistent with the role of sensory neurons in lateral inhibition via local interneurons in the antennal lobe. Taken together, our results suggest a complexity of odor coding rules even in a simple olfactory sensory system.

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