Chicago Chapter of the Society for Neuroscience 2017 Scientific Meeting

Friday, March 31st, 2017
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.

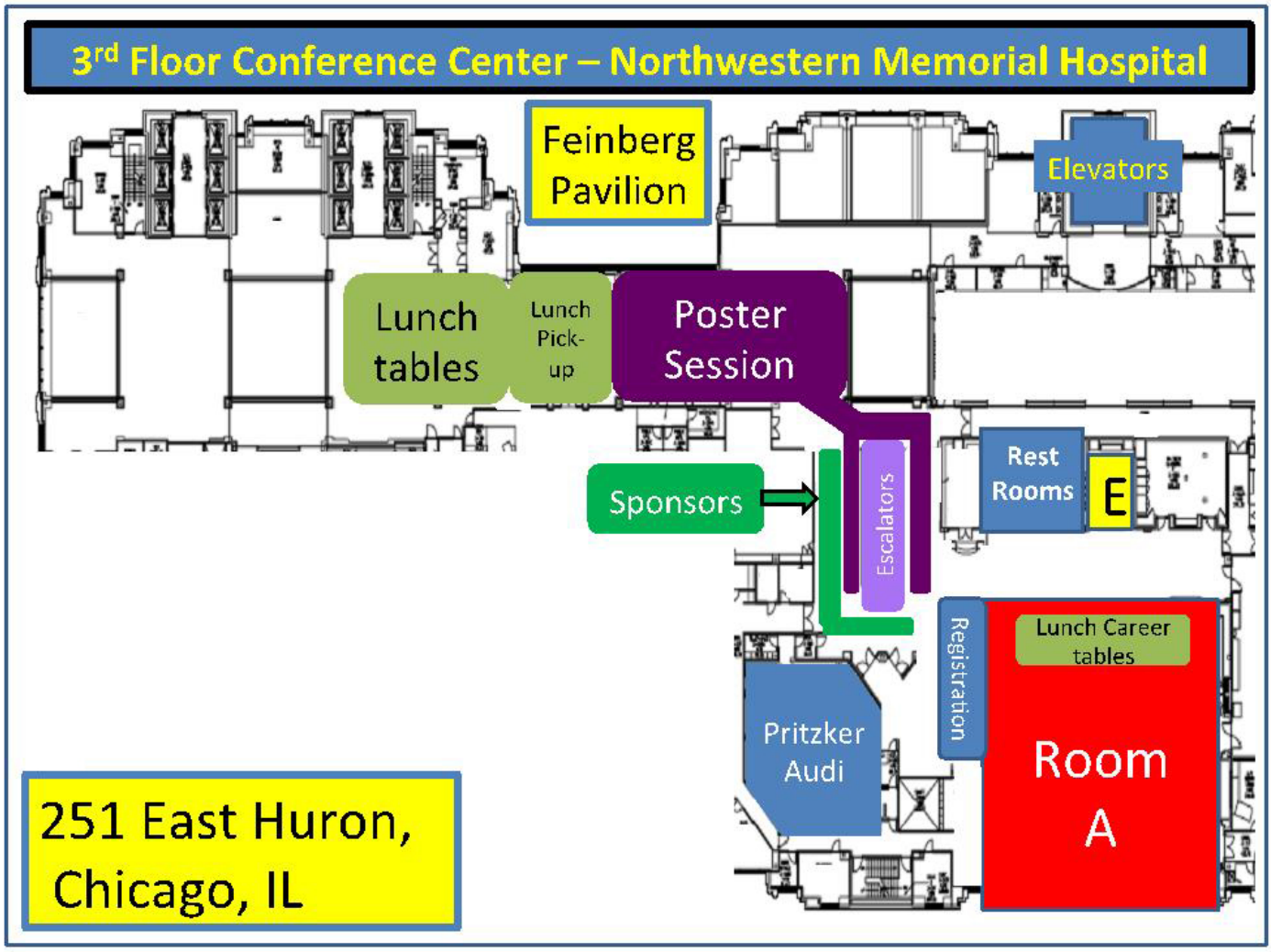
Vote for next year's Chicago Chapter SfN Officers and Councilors
.https://www.surveymonkey.com/r/XSVLTRJ

-
- 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 Photo:
"The bean has come to be a symbol of Chicago but also captures the shape of the human brain." Jennifer Schreiber, 3rd Year Ph.D. Candidate from Loyola University Chicago. Ms Schreiber is a member of Dr. Michael Collin's lab.


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

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DEPAUL UNIVERSITY
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RUSH UNIVERSITY


Northwestern
Neurobiology


DOMINICAN
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COLLEGE OF PHARMACY
CHICAGO
ROCKFORD

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1890

MIDWESTERN UNIVERSITY
1900

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UNIVERSITY CHICAGO
1870
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NUIN Northwestern University Interdepartmental Neuroscience

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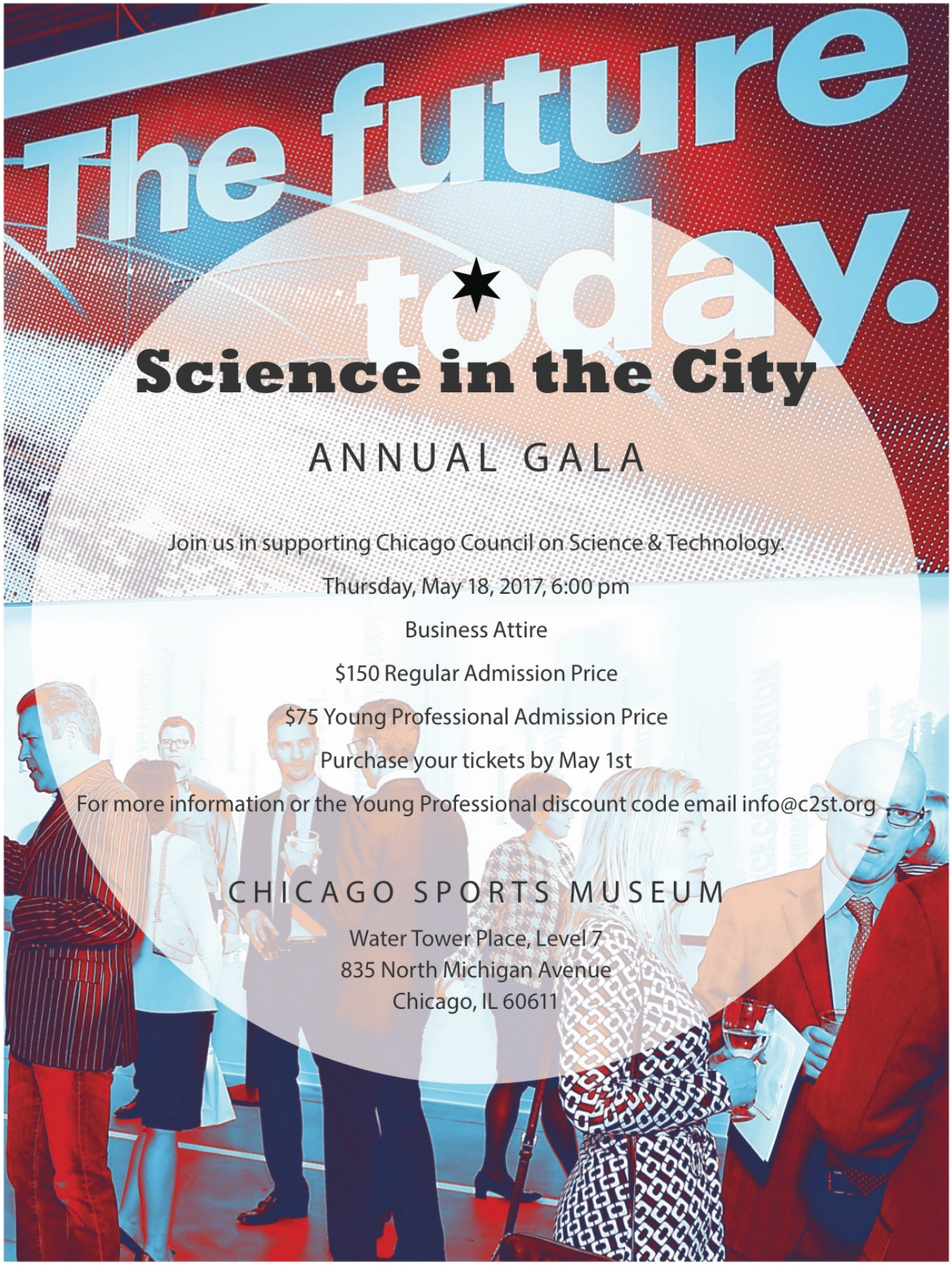
Chicago Society for Neuroscience Career Achievement Award 2017

Marina Wolf, Ph.D.

Dr. Wolf is Professor and Chair of the Department of Neuroscience at the Chicago Medical School of Rosalind Franklin University of Medicine and Science. Dr. Wolf has made outstanding contributions not only to neuroscience education and the advancement of neuroscience research, but also, in the area of public education and outreach in the greater Chicago community and beyond. She has been the recipient of numerous prestigious awards including a Merit Award and a Senior Scientist Research and Mentorship Award from National Institute on Drug Abuse (NIDA). Dr. Wolf has served as a member of the NIDA Advisory Council and the NIH Council of Councils. She presently chairs a NIH study section, serves on the NIDA Board of Scientific Counselors and on the Council of the American College of Neuropsychopharmacology. Dr. Wolf's pioneering research investigating the role of neuronal plasticity in drug addiction has garnered support from the National Institute of Mental Health, the Pharmaceutical Manufacturer's Association Foundation (PMAF), and the National Alliance for Research on Schizophrenia and Depression (NARSAD) and has resulted in over 100 publications in top-tier journals. She has mentored an impressive number of undergraduates, graduate students and post-doctoral fellows and is recognized as an exceptional mentor by her students at every stage of academic development. Dr. Wolf has been a tremendous asset to the Neuroscience community in Chicago and we are pleased to honor her with this award.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Science in the City
ANNUAL GALA
Join us in supporting Chicago Council on Science & Technology.
Thursday, May 18, 2017, 6:00 pm
Business Attire
$150 Regular Admission Price
$75 Young Professional Admission Price
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For more information or the Young Professional discount code email info@c2st.org
CHICAGO SPORTS MUSEUM
Water Tower Place, Level 7
835 North Michigan Avenue
Chicago, IL 60611

SCHEDULE OF EVENTS - OVERVIEW

7:30-10:00 AM	**Registration/Continental Breakfast**	***3rd Floor***
8:00-8:45 AM	**Mentoring Panel & Breakfast (with Conference Speakers)** Moderators: Drs. Simon Kaja and VIrgine Mansuy-Aubert	***Pritzker Aud.***
8:00-4:00 PM	**Poster Viewing and Vendor Display**	***Atrium, 3rd Floor***
9:00-9:15 AM	**2017 Chicago Career Achievement in Neuroscience Award** Presented by Dr. Cindy Voisine & Dr. Dorothy Kozlowski	***Room A***
	PRESIDENTIAL SYMPOSIUM – Sponsored by Stoelting	
9:00-10:30 AM	**Using Biomarkers and Neuroimaging to Diagnose Neural Disease and Injury** Chaired by Dorothy Kozlowski, Ph.D.	
	"Diffusion tensor imaging of structural connectivity in Alzheimer's Disease." **Kejal Kantarci MD.**, Professor of Radiology, Mayo Clinic College of Medicine	
	"***Rehabilomics Research: A biomarkers based approach to assessing multimodal outcomes after TBI."*** ***A*my Wagner MD** Associate Professor of Physical Medicine and Rehabilitation, University of Pittsburgh	
	KEYNOTE SPEAKER	***Room A***
10:30-11:30 AM	***"Football and the Brain"*** **Ann McKee MD** Professor of Neurology and Pathology, Director of Boston University's CTE Center and Chief of Neuropathology at the Boston VA Medical Center. Boston University	
	POSTER COMPETITIONS AND LUNCH BREAK	
11:30-2:00 PM	Graduate, Undergraduate and Postdoctoral Poster Competitions *"Diversity in Careers"* Lunch tables	***Atrium, 3rd Floor***
12:15-1:15 PM	Dr. McKee and Graduate Student Symposium participants lunch	***Room E***
	GRADUATE STUDENT SYMPOSIUM	***Room A***
2:00- 3:35 PM	Selected Graduate Student Talks	
	PLENARY AFTERNOON SYMPOSIUM	***Room A***
3:45- 5:30 PM	***Social Neuroscience*** Chaired by Drs. John Cacioppo & Stephanie Cacioppo **Molecular Roots of the Social Brain** Gene Robinson, Ph.D., University of Illinois at Urbana-Champaign **The Healing Power of Love: An Oxytocin Hypothesis** Sue Carter, Ph.D., Kinsey Institute **How The Human Brain Forms Salutary Connections With Other Brains** Stephanie Cacioppo, Ph.D., The University of Chicago **Social Isolation and Behavioral Deficits: A Translational Pharmacological Approach for PSI, PTSD and Depression Treatment** Graziano Pinna, Ph.D., University of Illinois at Chicago	
5:45-7:00PM	**AWARDS CEREMONY, RECEPTION AND BUSINESS MEETING** Social and announcement of awards, recognition, election results	***Room A***

MORNING PROGRAM

8:00-8:45 AM **Mentoring Panel** ***Pritzker Auditorium***
(with Keynote Speaker and Presidential Symposium Speakers)
Moderated by: Drs. Simon Kaja and VIrgine Mansuy-Auber

9:00-9:15 AM **2017 Chicago Career Achievement in Neuroscience Award** ***Room A***
Recipient: Marina Wolf, Ph.D. Rosalind Franklin
Presented by Dr. Cindy Voisine and Dr. Dorothy Kozlowski

PRESIDENTIAL SYMPOSIUM ***Room A***

9:15-10:30 AM **"Using Biomarkers and Neuroimaging to Diagnose Neural Disease and Injury"**
Chaired by Dorothy Kozlowski, Ph.D.

9:15-9:30 AM *Welcoming Remarks*

9:30-10:00 AM **PSA** **Diffusion tensor imaging of structural connectivity in Alzheimer's Disease** *(Abstract p. 23)*
Kejal Kantarci, M.D.
Professor of Radiology, Mayo Clinic, College of Medicine

10:00-10:30 AM **PSB** **Rehabilomics Research: A biomarkers based approach to assessing multimodal outcomes after TBI** *(Abstract p. 23)*
Amy Wagner, M.D.
Associate Professor of Physical Medicine and Rehabilitation, University of Pittsburgh

KEYNOTE SPEAKER ***Room A***

10:30-11:30 AM **Football and the Brain** *(Abstract p. 22)*
Ann McKee, M.D.
Professor of Neurology and Pathology, Director of Boston University's CTE Center and Chief of Neuropathology at the Boston VA Medical Center. Boston University

LUNCH BREAK

11:30-2:00 PM **Poster Viewing & Vendor Tables** ***Atrium, 3rd Floor***

12:00-12:15 PM **Poster Competitions**

12:00-12:45 PM Authors in group A present for competition
12:45-1:30 PM Authors in group B present for competition

Post-doctoral Poster Competition
Chaired by **Irina Calin-Jageman, PhD, Dominican University**

Graduate Student Poster Competition
Chaired by **Joanna Dabrowska, PhD, Rosalind Franklin University**

Undergraduate Student Poster Competition
Chaired by **Naomi Wentworth, PhD, Lake Forest College**

For poster titles and abstracts, go to pages 28 and 36, respectively.

12:00-1:00 PM **Themed Lunch Tables (open to all Trainees)** ***Room A***

Chaired by Cindy Voisine, PhD, Northeastern Illinois University and Thomas Macek, Pharm.D., Ph.D. Takeda Pharmaceuticals

"Diversity in Careers"
Know more about your professional options

Table 1 ***Research and Teaching in Academia- Undergraduate Institutions***
Margaret Bell, Ph.D. Assistant Professor, Biological and Health Sciences Departments, DePaul University
Eiron Cudaback, Ph.D., Assistant Professor, Department of Health Sciences, DePaul University

Table 2 ***Corporate – Takeda***
Eileen Burkart-Hartman, Ph.D., Associate Director, Medical Communications Medical Affairs, US Region, Takeda Pharmaceuticals U.S.A. Inc
Maggie McCue, M.S., R.D., Clinical Science Director, US Medical Affairs, Takeda Pharmaceuticals U.S.A., Inc

Table 3 ***Corporate – AbbVie***
Ana M. Basso, Ph.D., Principal Research Scientist, AbbVie/Calico Collaboration
Chang Zhu, MD, Msc, Senior Research Scientist II, Neuroscience Research, AbbVie Inc.

Table 4 ***Alternative Careers***
Katie Youmans-Kidder, Ph.D., Medical Science Liaison, CNS-Movement Disorders, Teva Pharmaceuticals
Abby Stayart, Ph.D., Program Director, my CHicago Options In Career Empowerment, Biological Sciences Division
University of Chicago
Michelle Wright, Ph.D., Associate Director Research Program Development, Biological Sciences Division, University of Chicago

12:15-1:15 PM **Dr. McKee and Graduate Student Symposium participants lunch** ***Room E***

AFTERNOON PROGRAM

GRADUATE STUDENT SYMPOSIUM *(For abstracts see p. 24)* ***Room A***

2:00- 3:35 PM Chaired by Stephanie Cacioppo, Ph.D., University of Chicago

2:00-2:05 PM **Introduction**
Stephanie Cacioppo, Ph.D., University of Chicago

2:05-2:20 PM ***Npy-Induced Stress Resilience And Down-Regulation Of Hcn1 Channels Modifies Expression Of Conditioned Fear***
GS1 Maria Bompolaki
Physiology and Biophysics; Rosalind Franklin University
Advisor: Janice H. Urban, PhD

2:20-2:35 PM **UBQLN2-Dependent Regulation Of Mtor Kinase In Neuronal Development And Neurodegeneration**
GS2 Brittany Edens
Departments of Pediatrics, Neurology and Physiology, Northwestern University
Advisor: Yong-Chao Ma

2:35-2:50 PM **Physiological state modulates real-time dopamine responses to taste stimuli**
GS3 Samantha Fortin
University of Illinois at Chicago
Advisor: Mitch Roitman

2:50-3:05 PM **Biomarker Discovery In Fragile X-Associated Tremor/Ataxia Syndrome Using Mass Spectrometry Based Proteomics**
GS4 Amber Orcutt
Department of Neurological Sciences, Rush University
Advisor: Stephanie Cologna & Liz Berry Kravis

3:05-3:20 PM **Deficits In Cerebellar Synapse And Circuit Function In An Autism Mouse Model For The Human 15q11-13 Duplication**
GS5 Dana Simmons
Department of Neurobiology, University of Chicago
Advisor: Christian Hansel

3:20-3:35 PM **Elevated Hydrostatic Pressure Selectively Increases Matricellular Gene Expression in Human Trabecular Meshwork Cells**
GS6 Jonathan Lautz
Program in Neuroscience, Loyola University Chicago
Advisor: Evan B. Stubbs, Jr.

PLENARY AFTERNOON SYMPOSIUM

Room A

(for abstracts, see p. 23)

3:45-5:30 PM ***"SOCIAL NEUROSCIENCE"***
Chaired by Drs. John & Stephanie Cacioppo

3:45-3:50 PM ***INTRODUCTION***
Dr. John Cacioppo

3:50-4:15 PM **Molecular Roots of the Social Brain**
PAS1 Gene Robinson, Ph.D.,
University of Illinois at Urbana-Champaign

4:15-4:40 PM **The Healing Power Of Love: An Oxytocin Hypothesis**
PAS2 Sue Carter, Ph.D.,
Kinsey Institute

4:40-5:05 PM **How The Human Brain Forms Salutary Connections With Other Brains**
PAS3 Stephanie Cacioppo, Ph.D.,
The University of Chicago Pritzker School of Medicine

5:05-5:30 PM **Social Isolation And Behavioral Deficits: A Translational Pharmacological Approach For PSI, PTSD And Depression Treatment**
PAS4 Graziano Pinna, Ph.D.
University of Illinois at Chicago

AWARD CEREMONY, BUSINESS MEETING AND SOCIAL

Atrium, Room A

5:40-7:00 PM **Wine and Cheese Social ("EtOH Receptor Binding Study")**

Election Results
Recognition of Councilors

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

2017 Chicago Brain Bee winners
2017 Lake Forest College Neuroscience Student Organization SYNAPSE
2017 Northwestern University Brain Awareness Organization (NUBAO)

Announcement of prize winners

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

Graduate Student Poster Competition
Presented by Joanna Dabrowska, Ph.D., Rosalind Franklin University

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

Graduate Student Symposium
Presented by Stephani Cacioppo, Ph.D., The University of Chicago

ABSTRACTS

KEYNOTE LECTURE

CLINICOPATHOLOGICAL CORRELATIONS IN A LARGE CASE SERIES OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Ann C. McKee, Jesse Mez, Daniel H. Daneshvar, Patrick T. Kiernan, Bobak Abdolmohammadi, Victor E. Alvarez, Bertrand R. Huber, Michael L. Alosco, Todd M. Solomon, Christopher J. Nowinski, Lisa McHale, Kerry A. Cormier, Caroline A. Kubilus, Brett M. Martin, Lauren A. Murphy, Christine M. Baugh, Christine E. Chaisson, Robert A. Stern, Robert C. Cantu, Neil W. Kowall, Douglas I. Katz, Lee E. Goldstein, Thor D. Stein

Professor of Neurology and Pathology, Director of Boston University's CTE Center and Chief of Neuropathology at the Boston VA Medical Center. Boston University

There are growing concerns that cumulative repetitive head impact (RHI) exposure is associated with increased risk of long-term problems, including the development of chronic traumatic encephalopathy (CTE). CTE is a distinctive neurodegenerative disease that can only be diagnosed by neuropathologic examination of brain tissue. Recently a panel of experienced neuropathologists defined the pathological criteria for the diagnosis of CTE and delineated the pathognomonic lesion of CTE - a perivascular accumulation of hyperphosphorylated tau protein in neurons and astrocytes, most prominent at the cortical sulcal depths. From 2008–2016, the families of 326 contact sport athletes and military veterans donated their brains to the VA-Boston University–Concussion Legacy Foundation brain bank. The brains were neuropathologically evaluated blinded to clinical findings and an independent team of clinicians performed retrospective telephone clinical assessments blinded to neuropathology. Online surveys with informants ascertained additional demographic, athletic, military, and head trauma history. CTE was neuropathologically diagnosed in 237 brain donors, including 190 former American football players, 14 boxers, 10 ice hockey players, 4 rugby players, 3 soccer players, 2 professional wrestlers, 54 veteran-athletes and 10 veterans. CTE-related ptau pathology followed an age-dependent evolution from focal cortical lesions in teenagers and young adults to a severe neurofibrillary neurodegeneration at mid-life involving the medial temporal lobes and widespread brain regions. The neurofibrillary degeneration advanced with increased age in concert with deposition of beta amyloid, alpha-synuclein, and TDP-43. Clinically, CTE was associated with violent behaviors, explosivity, loss of control, depression, memory loss and cognitive changes. While the exact incidence and prevalence of CTE remain unknown, given that millions of contact sport athletes and military service members are exposed to RHI each year, there is an urgent need to advance CTE research. Critical areas of research focus include identification of CTE during life, improved understanding of the epidemiology and pathobiology of CTE, and the development of effective prevention and treatment strategies for CTE.

This work was supported by the National Institute of Neurological Disorders and Stroke (grants U01 NS086659, R01 NS078337, R56 NS078337, U01 NS093334, F32 NS096803), the National Institute on Aging (grants K23 AG046377, P30AG13846; supplement 0572063345-5, R01 AG1649), the U.S. Department of Defense (grant W81XWH-13-2-0064), the U.S. Department of Veterans Affairs (I01 CX001038, the National Operating Committee on Standards for Athletic Equipment, the Alzheimer's Association (grants NIRG-15-362697, NIRG-305779), the Concussion Legacy Foundation, the Andlinger Family Foundation, WWE, and the NFL.

PRESIDENTIAL SYMPOSIUM

USING BIOMARKERS AND NEUROIMAGING TO DIAGNOSE NEURAL DISEASE AND INJURY

PSA

DIFFUSION TENSOR IMAGING OF STRUCTURAL CONNECTIVITY IN ALZHEIMER'S DISEASE

Kejal Kantarci MD, MS

Mayo Clinic, Rochester MN

With advances in acquisition and analysis methods, DTI is gaining acceptance as the preferred quantitative technique for assessing the white matter integrity and structural connectivity in aging and dementia. The microstructural changes identified through DTI in the brain may be critical for early diagnosis and disease characterization in AD. Although the biological underpinnings of the DTI changes in the AD brain is yet unknown, significant abnormalities have been identified in the diffusion indices of patients with AD and patients with and mild cognitive impairment (MCI) many of whom have prodromal AD and are destined to progress to AD in the future. DTI has demonstrated that the integrity of white matter is disrupted as early as the preclinical stages of Alzheimer's disease (AD). These white matter alterations on DTI are initially localized to the medial temporal limbic association tracts, and tend to spread to the temporal and parietal white matter as the clinical symptoms progress. This anatomic concordance between gray and white matter degeneration in AD suggest that the disruption in white matter tracts is associated with the cortical

AD pathology, particularly the neurofibrillary tangle (NFT) tau pathology of AD. Structural connectomics of the brain may open new frontiers in understanding the cognitive decline, brain reserve and progression of the cortical pathology in AD. Future studies on understanding the pathophysiological basis of these changes are warranted.

PSB
REHABILOMICS RESEARCH: A BIOMARKERS BASED APPROACH TO ASSESSING MULTIMODAL OUTCOMES AFTER TBI

Amy K. Wagner, MD

Department of Physical Medicine and Rehabilitation Department of Neuroscience Safar Center for Resuscitation Research Center for Neuroscience at the University of Pittsburgh

Traumatic brain injury (TBI) is challenging to manage clinically, as people with similar injury profiles often experience different functional, cognitive, and emotional and behavioral outcomes. To date, prognostic models for post-TBI outcomes have primarily focused on clinical and biomarker measures of injury severity (e.g. Glasgow Coma Scale score, S100B) as predictors and survival or global disability. However, to effectively manage TBI symptoms and complications across the whole recovery trajectory, further consideration should include other personal (e.g. premorbid characteristics and conditions, genetics) and biological factors (e.g. hormonal changes, inflammation) present at injury and during recovery that influence common long-term cognitive, emotional, and behavioral symptoms that can persist for decades post-injury. The Rehabilomics model is a conceptual framework from which to investigate diverse outcomes, such as those found with TBI recovery, by examining the complex interplay between personal, biological, and psychosocial factors and by providing a foundation for personalized clinical care and management. Our work supports variation in dopamine systems as a promising biological factor that 1) is susceptible to dysfunction following TBI, 2) is heavily influenced by genetics and other individual factors, and 3) has been shown in our initial work to be predictive of later cognitive and behavioral outcomes post-TBI. The presentation will overview of the Rehabilomics model, the cognitive/behavioral interplay modulated by dopamine systems, and the neurobiological changes in dopamine systems after TBI. The clinical implications of these findings, and the potential for personalizing clinical management, will be discussed.

PLENARY AFTERNOON SYMPOSIUM
SOCIAL NEUROSCIENCE

PAS1
MOLECULAR ROOTS OF THE SOCIAL BRAIN

Gene E. Robinson

*Carl R. Woese Institute for Genomic Biology, Department of Entomology and Neuroscience Program
University of Illinois at Urbana-Champaign*

Studies of genes and social behavior, aided by new genomic resources, are revealing new insights into the social brain. Here, I highlight two insights: 1) Nature builds diverse social brains from common genetic blocks in insects and vertebrates, including those related to metabolism and transcriptional regulation; and 2) The social brain is addicted to altruism.

PAS2
THE HEALING POWER OF LOVE: AN OXYTOCIN HYPOTHESIS

Sue Carter, PhD

Director, Kinsey Institute and Rudy Professor of Biology Indiana University, Bloomington, IN 47405

This presentation will discuss the hormonal and neural mechanisms that support the beneficial and healing effects of loving relationships. Love is deeply biological. Love also has profound effects on our mental and physical state, pervading every aspect of our lives. Without loving relationships or in isolation, humans fail to flourish, even if all of their other basic needs are met. As such, love is clearly not just an emotion. Research in animals including humans is now revealing the basic biology of love. Comparisons among species and across various paradigms provide an overview of the mechanisms underlying the evolution and development of social behavior. Of particular importance is the neuropeptide, oxytocin and related molecules, including vasopressin, which provide biological substrates for love. Oxytocin and vasopressin engage in a dynamic dance, which helps to explain the consequences of the presence or absence of relationships. These ancient hormones and their receptors are capable of regulating the capacity for a sense of safety, which in turn allows social cognition, social bonding, social support, growth and restoration. Oxytocin also regulates the functions of the autonomic nervous system, with effects on vagal and sympathetic pathways. Oxytocin is protective against stress, with direct antioxidant and anti-inflammatory consequences for tissues throughout the body. The oxytocin system is influenced by early experience, and oxytocin can epigenetically alter the expression of its own receptors. The

capacity of oxytocin to regulate these systems helps to explain the pervasive adaptive consequences of social experiences for emotional and physical health across the lifespan. Knowledge of the pathways through which oxytocin and vasopressin act offers a new perspective on the healing power of love.

PAS3
HOW THE HUMAN FORMS SALUTARY CONNECTIONS WITH OTHER BRAINS

Stephanie Cacioppo, Ph.D.

Department of Psychiatry and Behavioral Neuroscience
University of Chicago

Social relationships endow health and fitness benefits, especially when these relationships are successful and lasting i.e., when there is long-term parity between an individual's preferred and actual social relationship with a significant other. Although bonds such as friendship has traditionally been conceptualized as a uniquely human phenomenon, there is ample evidence demonstrating how non-human primates form lasting emotional and social bonds with specific significant companions. Bridging the bonding research gap between human and non-human primates has much to contribute to our understanding of the neural and hormonal mechanisms of lasting salutary relationships. Here, I'll present the current state of knowledge of the brain mechanisms and neuroendocrinological correlates underlying salutary, long-term bonds. The better our understanding of lasting companionship across phylogeny, the greater should be our understanding of the mechanisms underlying human bonds and their significance for health and well-being.

PAS4
BIOLOGIC EMBEDDING OF STRESS AND TRAUMA IN AN URBAN, POPULATION-BASED SAMPLE

Monica Uddin, PhD

Associate Professor, Psychology, University of Illinois Urbana Champaign

Lifetime experiences have long been recognized as important determinants of mental health and illness; however, the biological mechanisms through which social exposures influence mental health, and how these mechanisms interact with underlying genetic variation to become physiologically and psychologically manifest have, until recently, remained unknown. Epigenetic modifications made throughout the lifecourse provide a plausible and, increasingly, empirically supported explanatory model. The goal of this presentation is to provide an overview of how stressful and traumatic events, experienced throughout the lifecourse, have biological consequences at the molecular level with implications for subsequent mental health. The objectives are to: (i) illustrate how both molecular and environmental variation shape risk of mental illness, using post-traumatic stress disorder and major depressive disorder as an examples; (ii) define DNA methylation and show how it can translate social experiences into risk for, or resilience to, mental illness; and (iii) provide evidence that adverse early life experiences impact stress-relevant molecular phenotypes into adulthood. Examples will be drawn from previous and ongoing research drawn from the Detroit Neighborhood Health Study, an urban, population based cohort of adult residents of Detroit sampled from 2008-2014.
Support: R01DA022720, R01DA022720-S1, RC1MH088283

GRADUATE STUDENT SYMPOSIUM

GS1
NPY-INDUCED STRESS RESILIENCE AND DOWN-REGULATION OF HCN1 CHANNELS MODIFIES EXPRESSION OF CONDITIONED FEAR

M. Bompolaki[1], J. A. Rosenkranz[2], W. F. Colmers[3], J. H. Urban[1]

[1]Physiology & Biophysics, [2]Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, [3]Pharmacology, University of Alberta, Edmonton, AB, Canada

The anxiolytic and stress-buffering properties of neuropeptide Y (NPY) in the basolateral amygdala (BLA) have long been established in animal models as well as in humans. Repeated injections of NPY into the BLA promote long-lasting resilience to restraint stress (Sadjyk et al., 2008), which is associated with down-regulation of HCN1 (hyperpolarization activated cyclic nucleotide gated) channels. In addition to inducing stress resilience, we hypothesize that repeated injections of NPY and down-regulation of HCN1 subunits in the BLA will ameliorate freezing behavior in a cued fear conditioning paradigm.
Male rats received bilateral infusions of 10pmol NPY or vehicle (100nl; 0.1M PBS) into the BLA repeated daily for 5 days. Two weeks after the injections, animals underwent a cued fear conditioning protocol: On day 1, animals were placed in chamber 1 and received 4 pairings of a tone (1500Hz, 85dB) with a foot shock (0.4mA; fear acquisition). The following day the rats were placed in novel chamber 2 and received 15 trials of the tone without a foot shock at 60s inter-trial intervals (fear extinction) and freezing behavior was monitored (Anymaze software). Both vehicle- and NPY-treated rats displayed similar rates and amplitudes of fear acquisition on day 1. On day 2, NPY-treated rats exhibited significantly lower freezing in the first five sessions of the extinction phase. Additionally, at the time point we performed

the fear conditioning experiment, we observed an induction of LC3B expression (an autophagy marker) and down-regulation of brain-derived neurotrophic factor (BDNF), however down-regulation of the HCN1 protein is not seen until 4 weeks after the NPY treatment.

Lastly, to test the involvement of HCN1 subunits in fear conditioning, HCN1 protein was knocked-down in the BLA using lentiviral delivery of HCN1-shRNA. Four weeks after the surgery, the rats underwent the same cued fear conditioning protocol as described above and freezing behavior was monitored. HCN1-knockdown animals expressed reduced freezing on the acquisition day.

This work indicates that the induction and maintenance of NPY-induced stress resilience is associated with differential changes in protein expression over time. NPY-induced resilience is correlated with BDNF down-regulation and induction of autophagic pathways at early time points, while HCN1 down-regulation later consolidates a new stress-relieving baseline in NPY-treated animals. These findings can be of great importance for the way anxiety disorders like post-traumatic stress disorder are viewed and treated.

Work supported by MH090292 (JHU;WFC).

GS2
UBQLN2-DEPENDENT REGULATION OF mTOR KINASE IN NEURONAL DEVELOPMENT AND NEURODEGENERATION

Brittany M. Edens[1], Han-Xiang Deng[2], Teepu Siddique[2], and Yong-Chao Ma[1]

[1] Departments of Pediatrics, Neurology and Physiology, Northwestern University Feinberg School of Medicine, Lurie Children's Hospital of Chicago, Chicago, IL 60611
[2] Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611

Tightly regulated protein turnover is essential for virtually all cell biological processes. In particular, proteolytic pathways are critical for the regulation of signal transduction through receptors and kinases, whose protein levels are kept in check by targeted degradation. Ubiquilins—encoded by *UBQLN* genes—belong to the ubiquitin-like family of proteins and act as key regulators of protein degradation through both lysosomal and ubiquitin pathways. *UBQLN* variants have become widely associated with neuropathology. Most notably, mutations in *UBQLN2* have been reported in patients afflicted with familial ALS with or without dementia, and ubiquilin2 inclusion pathology is characteristic of even unrelated forms of ALS. We identified mTOR kinase, a master regulator of aging with implications in neurodegeneration, as a ubiquilin2-interacting protein. In a mouse model of *UBQLN2*-associated ALS/FTD, TG-h*UBQLN2*^{P497H}, substrates of mTOR show hyperactivation, and cell morphological features of hippocampal neurons are altered in ways consistent with heightened mTOR activity. Rescue of such morphological phenotypes with the mTOR inhibitor rapamycin further suggests heightened kinase activity in the disease mice. Given the regulatory roles ubiquilins play in protein degradation pathways, we considered that these effects might arise from impaired degradation of mTOR kinase in the context of *UBQLN2*^{P497H} expression. Indeed, comparison of mTOR protein levels between TG-h*UBQLN2*^{P497H} and wild-type mice revealed a notable accumulation of the kinase in mutant brain tissue, suggesting impaired degradation. We further noted prolonged mTOR half-life in *UBQLN2*^{P497H}-expressing cells in cycloheximide pulse-chase assays, confirming a role for ALS-associated *UBQLN2* in mTOR retention. There are several mechanisms through which ubiquilin2 may facilitate mTOR kinase degradation, one of which being chaperone-mediated autophagy. Consistent with this possibility, we identified several KFERQ-like motifs in mTOR's primary sequence, and verified its interaction with the chaperone-mediated autophagy adaptor LAMP2A. Altogether, we provide evidence of a novel regulatory mechanism balancing mTOR kinase activity through ubiquilin2-dependent targeting. Because this mechanism plays a role in setting up the developmental synaptic landscape, perturbations to this process may confer vulnerability to degeneration in neurological disease states.

GS3
PHYSIOLOGICAL STATE MODULATES REAL-TIME DOPAMINE RESPONSES TO TASTE STIMULI

Fortin SM[1], Roitman MF[1]

[1]University of Illinois, Chicago

The consumption of nutritive stimuli is thought to result from homeostatic challenge or, in the absence of need, hedonic value. However, perturbations of homeostasis alter the hedonic value of a stimulus. This is perhaps best illustrated in sodium appetite, when a concentrated sodium solution is avidly consumed only after sodium depletion. We hypothesized that challenges to body fluid homeostasis by sodium depletion would recruit nucleus accumbens dopamine signaling - thought to participate in hedonic encoding - in response to sodium. We used fast-scan cyclic voltammetry to measure subsecond changes in dopamine concentration in the nucleus accumbens shell of both sodium deplete and replete rats during intraoral delivery of either a hypertonic (0.45 M) NaCl solution or distilled water. A robust increase in dopamine concentration (41.0 ± 6.27 nM) from baseline (9.1 ± 0.21 nM; $p<0.05$) was evoked by intraoral infusions of NaCl in furosemide-induced sodium depleted rats. Conversely, in sodium replete animals, intraoral infusion of NaCl evoked a decrease in dopamine concentration (0.4 ± 2.97 nM) from baseline (15.9 ± 0.20 nM; $p<0.05$). The dopamine increase in

sodium deplete rats was selective for a salt solution containing the sodium ion, as both potassium chloride and water infusions were without effect. Thus, dopamine neurons track fluid balance and respond to sodium stimuli in a state-dependent manner. The state-dependency of phasic dopamine signaling likely serves to provide a reinforcement signal only when the ingested stimulus satisfies the need state of the animal. Moreover, the data emphasize the participation of mesolimbic dopamine signaling in homeostatic-driven ingestive behavior.

GS4
***UBQLN2*-DEPENDENT REGULATION OF mTOR KINASE IN NEURONAL DEVELOPMENT AND NEURODEGENERATION**

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Tightly regulated protein turnover is essential for virtually all cell biological processes. In particular, proteolytic pathways are critical for the regulation of signal transduction through receptors and kinases, whose protein levels are kept in check by targeted degradation. Ubiquilins—encoded by *UBQLN* genes—belong to the ubiquitin-like family of proteins and act as key regulators of protein degradation through both lysosomal and ubiquitin pathways. *UBQLN* variants have become widely associated with neuropathology. Most notably, mutations in *UBQLN2* have been reported in patients afflicted with familial ALS with or without dementia, and ubiquilin2 inclusion pathology is characteristic of even unrelated forms of ALS. We identified mTOR kinase, a master regulator of aging with implications in neurodegeneration, as a ubiquilin2-interacting protein. In a mouse model of *UBQLN2*-associated ALS/FTD, TG-h*UBQLN2*^{P497H}, substrates of mTOR show hyperactivation, and cell morphological features of hippocampal neurons are altered in ways consistent with heightened mTOR activity. Rescue of such morphological phenotypes with the mTOR inhibitor rapamycin further suggests heightened kinase activity in the disease mice. Given the regulatory roles ubiquilins play in protein degradation pathways, we considered that these effects might arise from impaired degradation of mTOR kinase in the context of *UBQLN2*^{P497H} expression. Indeed, comparison of mTOR protein levels between TG-h*UBQLN2*^{P497H} and wild-type mice revealed a notable accumulation of the kinase in mutant brain tissue, suggesting impaired degradation. We further noted prolonged mTOR half-life in *UBQLN2*^{P497H}-expressing cells in cycloheximide pulse-chase assays, confirming a role for ALS-associated *UBQLN2* in mTOR retention. There are several mechanisms through which ubiquilin2 may facilitate mTOR kinase degradation, one of which being chaperone-mediated autophagy. Consistent with this possibility, we identified several KFERQ-like motifs in mTOR's primary sequence, and verified its interaction with the chaperone-mediated autophagy adaptor LAMP2A. Altogether, we provide evidence of a novel regulatory mechanism balancing mTOR kinase activity through ubiquilin2-dependent targeting. Because this mechanism plays a role in setting up the developmental synaptic landscape, perturbations to this process may confer vulnerability to degeneration in neurological disease states.

GS5
DEFICITS IN CEREBELLAR SYNAPSE AND CIRCUIT FUNCTION IN AN AUTISM MOUSE MODEL FOR THE HUMAN 15Q11-13 DUPLICATION

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Autism Spectrum Disorder (ASD) is characterized by two hallmark symptoms: impaired social interaction and increased repetitive behaviors. While ASD is typically regarded as a social disorder, about 80% of patients also display motor learning deficits, suggesting involvement of the cerebellum in ASD pathology. We studied cerebellar physiology in the 15q11-13 copy number variation mouse model, which is the most frequent and penetrant genetic aberration seen in ASD. In these mice, genetic imprinting determines whether offspring will show pathology associated with the autistic-like phenotype. A mouse receiving the 15q11-13 duplication paternally (patDp/+), but not maternally (matDp/+), will show ASD-resembling behaviors (Nakatani et al., *Cell* 137, 2009). To investigate cerebellar abnormalities associated with this phenotype, including the known impairment of LTD-induction at parallel fiber (PF) – Purkinje cell synapses in patDp/+ mice (Piochon et al., *Nat. Commun*. 5, 2014), we studied climbing fiber (CF) – Purkinje cell and PF – Purkinje cell synaptic transmission. patDp/+ mice showed abnormally large amplitude CF-evoked excitatory postsynaptic currents, which led us to look for altered synaptic density between CFs and Purkinje cells. Immunohistochemistry with VGluT2, a marker for CF terminals, indicated that patDp/+ mice displayed increased density of CF terminals on both large-caliber and fine Purkinje cell dendrites, the latter of which are ordinarily considered PF input territory. We next examined calcium transients in spines, fine dendrites, and large-caliber

dendrites, evoked by paired stimulation of PF 100Hz with a single CF stimulation, a single CF stimulation, or PF 100Hz stimulation. Although the CF-evoked calcium transient was unaltered in patDp/+ and matDp/+ mice, our calcium imaging results revealed abnormally small amplitude calcium transients in response to paired stimulation and PF 100Hz stimulation in patDp/+ spines and fine branches. These data suggest that the underlying cause of the known LTD-induction impairment in patDp/+ mice may be due to weak, abnormally small calcium signaling at PF-Purkinje cell spines. It is possible that PFs, even with paired CF-stimulation, do not provide a sufficient calcium signal to induce LTD. The result of increased CF-Purkinje cell synapse density with reduced PF calcium transients raises the possibility that CF synapses are too abundant on Purkinje cell fine dendrites, and thereby invade territory typically reserved for PF-Purkinje cell synapses. Taken together, our findings highlight cerebellar physiological abnormalities that contribute to motor deficits in a mouse model of ASD.

GS6
ELEVATED HYDROSTATIC PRESSURE SELECTIVELY INCREASES MATRICELLULAR GENE EXPRESSION IN HUMAN TRABECULAR MESHWORK CELLS

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Purpose: Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterized by loss of peripheral vision secondarily associated with elevated intraocular pressure (IOP). Transforming growth factor (TGF)-β2 is markedly elevated in the AH of patients with POAG. We and others have previously shown that TGF-β2 increases IOP, in part, by inducing expression and release of endothelin-1 (ET-1) and connective tissue growth factor (CTGF) within the trabecular meshwork (TM). ET-1 and CTGF may ultimately lead to increases in IOP by enhancing TM cell contractility and extracellular matrix (ECM) deposition. Despite these advancements, the direct effect of elevated IOP on TM cell responsiveness remains unknown. Here we determined whether elevated hydrostatic pressure (HP) can selectively alter gene expression in a transformed human TM cell line.
Methods: Confluent cultures of primary and transformed human TM cells were serum-starved x 24h and subsequently cultured in the absence (ambient) or presence of elevated HP (+30 mmHg above ambient) for up to 24h. Changes in F-actin organization were visualized by confocal microscopy. Relative changes in ECM composition and the expression and/or release of TGF-β2, ET-1, and CTGF were quantified by qRT-PCR, Western immunoblot, or ELISA.
Results: Elevated hydrostatic pressure markedly altered F-actin organization in transformed TM cells. Both primary and transformed human TM cells exposed to elevated HP exhibited increased TGF-β2, ppET-1, and CTGF mRNA content in a time-dependent manner. Similarly, elevated HP induced a transient increase in ET-1 as well as a sustained increase in TGF-β2 and CTGF secretion. Additionally, ECM composition was markedly altered in response to elevated HP. No significant effect on the expression of 12 other genes implicated in the pathogenesis of POAG in response to elevated HP were observed.
Conclusion: Cultured human trabecular meshwork cells exposed to elevated HP exhibit marked and selective changes in the expression of genes associated with the pathogenesis of POAG. We propose that pressure-dependent changes in TM cell gene expression represent a feed-forward mechanism that exacerbates TGF-β2 associated increases in TM cell contractility and altered ECM synthesis and deposition in affected POAG patients.

G- GRADUATE STUDENT COMPETETION
PD- POSTODOCTORAL STUDENT COMPETITION
UG- UNDERGRADUATE STUDENT COMPETITION
A/B- JUDGING GROUP A OR JUDGING GROUP B

POSTER ABSTRACT TITLES

THEME A. COGNITION AND BEHAVIOR

A1 UG-B
IDENTIFICATION OF CIRCADIAN OUTPUT GENES THAT AFFECT REST:ACTIVITY RHYTHMS IN DROSOPHILA
S.T. Bajwa, T.A. Bajwa, and D.J. Cavanaugh
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A2 G-A
Impact of Emotional Contrast and Psychological Function on Response Inhibition to Threatening Faces
T. Greif, K. Dye, M. Masson, M. Pitchiah, and J.D. Waring
Saint Louis University

A3 UG-A
INVESTIGATING THE CONTRIBUTION OF ANATOMICALLY DISTINCT CLOCK NEURON POPULATIONS TO CIRCADIAN REST:ACTIVITY RHYTHMS
K.R. Spontak, B.A. Kleeman, A.P. Dreyer, and D.J. Cavanaugh
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A4 UG-A
VARIABILITY IN NORMAL HEARING THRESHOLDS, BUT NOT SYNAPTOPATHY, INFLUENCES HEARING IN NOISE
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A5 PD-A
NEUROSTEROID BIOSYNTHESIS MEDIATES THE ANXIOLYTIC AND ANTI-FEAR EFFECTS INDUCED BY THE ENDOCANNABINOID, N-PALMITOYLETHANOLAMINE (PEA)
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A6
THE EFFECTS OF EXERCISE SEQUENCE ON LEARNING AND MEMORY
Amanda S. Nazario & Rodney A. Swain
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A7 UG-A
PARTIALLY REINFORCED WISTAR-KYOTO FEMALE RATS SHOW AN INCREASE IN AVOIDANCE ACQUISITION COMPARED TO FULLY REINFORCED SPRAGUE DAWLEY RATS DURING A LEVER-PRESS AVOIDANCE TASK
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A8
EFFECTS OF CONCUSSION ON WORKING MEMORY AMONG COLLEGIATE CLUB ATHLETES
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A9 UG-A
MOLECULAR CORRELATES OF SAVINGS MEMORY IN THE MARINE MOLLUSK APLYSIA CALIFORNICA
Leticia Perez, Ushma Patel, Marissa Rivota, Catherine Conte, Jency Patel, Irina Calin-Jageman and Robert Calin-Jageman
Neuroscience Program, Dominican University

A10 UG-A
CAN MEMORY BE IMPROVED WITH OSCILLATING SOUNDS THAT PROMOTE BENEFICIAL BRAIN OSCILLATIONS DURING LEARNING?
Hadley C. Pfalzgraf, Jessica D. Creery, Ken A. Paller
Northwestern University

A11
CORTICOTROPIN-RELEASING FACTOR (CRF) NEURONS IN THE OVAL NUCLEUS OF THE BED NUCLEUS OF THE STRIA TERMINALIS (BNSTov) MODULATE FEAR AND ANXIETY IN MALE RATS
Alexandra Roman (1), Daisy Martinon (1), and Joanna Dabrowska (1,2)
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A12 G-B
NEURAL CORRELATES OF SLEEP-BASED OLFACTORY TARGETED MEMORY REACTIVATION IN THE HUMAN BRAIN
Laura K Shanahan, Eva Gjorgieva, Thorsten Kahnt, & Jay A Gottfried
Feinberg School of Medicine, Department of Neurology, Northwestern University

A13
EXERCISE-INDUCED APOPTOTIC CELL DEATH IN THE HIPPOCAMPUS
Morgan E. Stevenson & Rodney A. Swain
University of Wisconsin-Milwaukee

A14 G-A
OCULOMOTOR MEASURES, GREY MATTER DENSITY, AND SYMPTOM OUTCOMES IN COLLEGIATE ATHLETES WITH MTBI: A PILOT STUDY
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THEME B. DEVELOPMENT

B1
ASSESSING GLIOGENESIS IN A MURINE MULTIFACTORIAL BRAIN INJURY MODEL SYSTEM
Miriam S. Domowicz1, Natasha L. Wadlington1, Judith G. Henry1, Kasandra Diaz1, Miranda J. Munoz1, Nancy B. Schwartz1,2
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B2 G-B
ENDOTHELIN B RECEPTOR AGONIST IRL-1620 ENHANCES NEUROGENESIS IN AN EX VIVO MODEL OF ADULT MOUSE SPINAL CORD INJURY
Angela Chang, Denis Lawlor, Harsh Sharthiya, Seema Briyal, Anil Gulati, Michele Fornaro
Midwestern University

B3 UG-B
IDENTIFICATION OF A NOVEL REGULATOR OF GLIAL DEVELOPMENT
Diana Luong, Dr. Jennifer Jemc
Loyola University Chicago

B4 UG-A
THE FUNCTIONAL MATURATION OF THE FEMALE PREFRONTAL CORTEX THROUGH VENTRAL HIPPOCAMPAL STIMULATION
Lily Veldran, Daniel R. Thomases, Kuei-Yuan Tseng
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B5
THE EFFECTS OF MATERNAL SEPARATION ON STRESS-INDUCED ALCOHOL CONSUMPTION AND EMOTIONAL BEHAVIOR IN SPRAGUE-DAWLEY RATS
A. Wieker, J. Herba, C. Brashaw, K. Braun, B. Morrett, B. Sanders
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B6 UG-B
REGULATION OF NEURON-GLIA INTERACTIONS IN THE DEVELOPING EYE
Victoria Hans, Asma Patel, and Jennifer Jemc
Loyola University Chicago, Department of Biology

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 G-A
MECHANISMS FOR THE MODULATION OF STRIATONIGRAL AND STRIATOPALLIDAL NEURON ACTIVITY BY PHOSPHODIESTERASE 10A INHIBITION IN L-DOPA-INDUCED DYSKINESIA
Feras Altwal1, Nivea Falcao Voelkner1, Fernando Eduardo Padovan-Neto1, Chaya Tabas1, Nicole Cho1, Antoinette Wowolo1, Sumender Sharma1, Cheska Zoleta1, Reza Danesh1, and Anthony R. West1
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C2 G-A
A DUAL-HIT MODEL OF METHAMPHETAMINE-INDUCED VULNERABILITY FOR PARKINSON'S DISEASE.
Isadora Calma, Amanda Persons, Matthew Kase, and T. Celeste Napier
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C3 PD-B
INVESTIGATING THE ROLE OF HGF ON MOTOR NEURON SURVIVAL AND FUNCTION IN ALS
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C4
APP-CTF TARGETED AT THE MEMBRANE REDUCES Abeta BURDEN AND AMELIORATES COGNITIVE FONCTION IN ALZHEIMER'S DISEASE MOUSE MODELS
Carole Deyts1, Mary Clutter1, Paramita Chakrabarty2, Awilda M. Rosario2, Nicholas Pierce1, Anna Goddi1, Kulandaivelu Vetrivel1, Steven L. Wagner3, Gopal Thinakaran1, Todd E. Golde2, and Angèle T. Parent1
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C5 PD-A
CONTRIBUTION OF POSTNATAL CEREBELLAR STEM CELLS IN DEVELOPMENTAL NEURONAL NETWORK DYSFUNCTION OF SPINOCEREBELLAR ATAXIA TYPE 1
Chandrakanth Reddy Edamakanti 1, Jeeheah Doo 2, Alessandro Didonna 3, Marco Martina 2 and Puneet Opal1,4
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C6 G-B
ENDOCYTIC VESICLE RUPTURE BY AMYLOID PROTEINS PROMOTES INCLUSION FORMATION THROUGH DISRUPTION OF THE AUTOPHAGY-LYSOSOME DEGRADATION PATHWAY
W.P. Flavin1,2, Z.C. Green3, Y. Chu4, L. Bousset5, M.J. Chaney6, R. Melki5, J.H. Kordower4,7, E.M. Campbell2,3,6
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C7 PD-B
EMERGING ROLE OF ONE-CARBON METABOLISM IN THE EPIGENETIC DOWNREGULATION OF GABAA RECEPTOR DELTA SUBUNIT IN THE CEREBELLUM OF ALCOHOLIC SUBJECTS
E. Gatta1, J. Auta1, D.P. Gavin1, 2, D.K. Bhaumik1, D.R. Grayson1, S.C. Pandey1, 2, A. Guidotti1
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C8
ANALYSIS OF THE SWI1 PRION DOMAIN VIA MUTAGENESIS
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C9 PD-B
CAMKIIalpha CONTROLS THE BIOGENESIS OF LET-7 MICRORNAS IN OPIOID TOLERANCE
Ying He and Zaijie Jim Wang
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C10
UNDERSTANDING THE LINK BETWEEN CORTICAL INJURY AND ALS
Amiko K. B. Lagrimas1, Jodi L. Klessner1, Hande Ozdinler1,2,3, Dorothy A. Kozlowski2, P. and Javier H. Jara1
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C11 UG-B
STRUCTURAL CHARACTERIZATION OF ABOS
Erika Cline, Josette Kamel, Anthea Weng
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C12
EFFECTS OF CHRONIC PRAMIPEXOLE ON AMPA RECEPTOR TRAFFICKING AND AKT/GSK-3B SIGNALING IN A RAT MODEL OF PARKINSON'S DISEASE
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C13 G-B
DEFINING SYNAPTIC PATHOLOGY OF INFANTILE NEURONAL CEROID LIPOFUSCINOSIS
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C14 G-A
EFFECTS OF ANTERIOR CINGULATE CORTEX STIMULATION ON BASOLATERAL AMYGDALA INPUTS INTO NUCLEUS ACCUMBENS
M. K. Loh and J. A. Rosenkranz
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C15 G-B
PERIPHERAL INFLAMMATION, APOE4, AND AMYLOID-B SYNERGISTICALLY INTERACT TO COMPROMISE CEREBROVASCULAR INTEGRITY LEADING TO COGNITIVE DECLINE.
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C16
TAU PET, AMYLOID PET, AND STRUCTURAL IMAGING IN PRIMARY PROGRESSIVE APHASIA
Martersteck A., Mesulam M.-M., Rogalski E.
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C17 UG-A
EFFECTS OF TARGET ASO THERAPY ON MARKERS OF CHOLINERGIC FUNCTION ON USHER SYNDROME MICE
Adam M. McNeela, Tia N. Donaldson, Kelsey T. Jennings, Lucia A. Cherep, Frederic F. Depreux, Michelle L. Hastings, & Douglas G. Wallace
Northern Illinois University & Rosalind Franklin University and Medical Science

C18
PERIPHERAL IMMUNE CHALLENGE AFFECTS IN VIVO ELECTROPHYSIOLOGICAL PROPERTIES OF BASOLATERAL AMYGDALA NEURONS
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C19 G-B
IMPLICATIONS FOR LRRK2 AND AUXILIN IN PARKINSON'S DISEASE PATHOGENESIS
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C20 G-A
HIGH DENSITIES OF ACTIVATED MICROGLIA ARE PRESENT IN CORTICAL WHITE MATTER AND CORRESPOND TO REGIONS OF GREATEST ATROPHY IN PRIMARY PROGRESSIVE APHASIA
Daniel Ohm, Garam Kim, Tamar Gefen, Zach Parton, Eileen H. Bigio, Emily Rogalski, M.-Marsel Mesulam, Changiz Geula
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C21 UG-B
UNDERSTANDING THE NATURE OF TOXICITY OF PARKINSON'S DISEASE ASSOCIATED ALPHA-SYNUCLEIN FAMILIAL MUTANTS H50Q, G51D, AND A53E WITH YEAST MODELS
E. Ong, M. Tembo, C. Mwale, P. Jones, M. Marshall, C. Alvarado, M. Buabeng, N. Kukulka, and S. DebBurman
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C22 G-A
POTENTIAL PRECLINICAL GAIT AND BALANCE MARKERS FOR DEVELOPING FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)
E. Robertson 1, A. McAsey 1, M. Swanson 2, A. Bery 2, C. Huml 1, E. Berry-Kravis 3, D. A. Hall 3, and J. A. O'Keefe 1,3
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C23
IDENTIFYING SMALL MOLECULES THAT ANTAGONIZE PRIONS AND ALLEVIATE AMYLOID TOXICITY
Luzivette Robles-Cardona, Zhiqiang Du, Stephanie Valtierra, Liming Li
Department of Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Chicago, IL; Northwestern University Interdepartmental Neuroscience Program

C24 PD-A
HDAC6 INHIBITORS SHOW A CELLULAR ANTIDEPRESSANT SIGNATURE, TRANSLOCATING ACTIVATED Gαs FROM LIPID-RAFTS
Harinder Singh1, Jeffrey Schappi1, Mark Rasenick1,2
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C25 UG-B
STRIATAL TRANSCRIPTOME OF MICE SELECTIVELY BRED FOR INCREASED PHYSICAL ACTIVITY PROVIDES NOVEL INSIGHTS INTO THE MOLECULAR ETIOLOGY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER
Anastassia M. Sorokina, Michael C. Saul, Petra Majdak, Joseph V. Gogola, Justin S. Rhodes
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C26 UG-B
INSIGHT INTO PARKINSON'S DISEASE FROM YEASTS: GROWING EVIDENCE FOR SUMOYLATION AS A PROTECTIVE FACTOR AGAINST A-SYNUCLEIN TOXICITY
Rosemary Thomas, Paul Jones, Alexandra Roman, Morgan Marshall, Yoan Ganev, Galina Lipkin, and Shubhik K. DebBurman
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C27
DELTA OPIOID RECEPTOR AS A TARGET FOR MIGRAINE – CGRP CO-EXPRESSION AND INHIBITION OF MEDICATION OVERUSE HEADACHE
Alycia Tipton, Laura Segura, and Amynah A Pradhan
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C28 PD-A
THE COMBINATION OF IMMUNE TOLERANCE AND MYELIN REPAIR THERAPY TO EFFECTIVELY TARGET DISEASE COURSE AND SEVERITY IN MULTIPLE SCLEROSIS
Titus, H.E., Lis, C., Beddow, S., Eaton, V., Robinson, A.P., Miller, S.D.
Feinberg School of Medicine, Northwestern University

C29 UG-A
SPATIAL EFFECTS ON AβO AMOUNTS IN C57 5xFAD MICE
Anthea Weng, Erika Cline, Savio Chan, Ellie Hong, William L. Klein
Northwestern University (Evanston Campus) and Northwestern Feinberg

C30 G-B
ROLE OF GPCRS AND GAS IN THE ANTIDEPRESSANT ACTION OF KETAMINE
Nathan Wray, Jeffrey Schappi, Mark M. Rasenick
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THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1

ISOLATED BULLFROG ROSTRAL BRAINSTEMS EXHIBIT A DAMGO-INSENSITIVE LUNG-LIKE EPISODIC RHYTHM IN THE PRESENCE OF BICUCULLINE

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THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG-B

APOE GENOTYPE-DEPENDENT DIFFERENTIAL EXPRESSION OF GROWTH FACTORS IN BRAIN

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F2 UG-A

IMPROVING NEURITE OUTGROWTH IN STROKE USING A CELL CULTURE MODEL

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F3 G-A

INDUCTION OF LYSOSOMAL BIOGENESIS BY CINNAMIC ACID: IMPLICATIONS FOR LYSOSOMAL CLEARANCE IN NEURODEGENERATIVE DISORDERS

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F4 G-A

REGULATION OF NMDAR TRAFFICKING BY PROTEIN PHOSPHATASE 1

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F5 UG-B

NG2 KNOCK-OUT IN NEU7 AND A7 ASTROCYTE CELL LINES TO PROMOTE NEURONAL REGENERATION

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F6 G-B

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F7 G-A

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F8 UG-B

TRANSPORT AND DEGRADATION OF THE SLO-1 BK CHANNEL IN C. ELEGANS

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F9 PD-A

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F10 UG-B

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Department of Physiology, Northwestern University

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O. López-Ramírez, R. A. Eatock
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H. D. Samberg1, J. E. Vantrease1, S. R. Blume3, J. H. Urban2, J. A. Rosenkranz1
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F17 PD-B
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Department of Neurosurgery, NorthShore University Health System

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1,Department of Neurosurgery, and 2,Center for Basic M.R. Research, Department of Radiology, NorthShore University HealthSystem, Evanston, IL

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Laura S Moye, Madeline Novack, Harish R Krishnan, Subhash C Pandey, Amynah AA Pradhan
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H1 UG-A

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Casey Gährs, Carola Städele, Abigail Benson, Wolfgang Stein, and Andrés Vidal-Gadea
ALL authors have affiliation with School of Biological Sciences, Illinois State University. Carola Staedele also is affiliated with Department of Integrative Biology and Physiology, UCLA.

H2 UG-A

CRISTAE IN INNER HAIR CELL MITOCHONDRIA ARE POLARIZED TOWARD CUTICULAR PLATE

Kevin Arias
University of Illinois at Chicago

H3 G-A

STIMULUS-DEPENDENT RECRUITMENT OF LATERAL INHIBITION UNDERLIES RETINAL MOTION COMPUTATION

Qiang Chen, Zhe Pei, David Koren, and Wei Wei
QC: Committee on Computation Neuroscience, Univ. of Chicago QC, ZP,DK,WW: Department of Neurobiology, Univ. of Chicago

H4 PD-A

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H5 PD-B

DIVERSITY OF M1 INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS

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H6 UG-A

STRUCTURAL ANALYSIS OF INNER EAR HAIR CELL MITOCHONDRIA NEAR THE STRIATED ORGANELLE

STRUCTURAL ANALYSIS OF INNER EAR HAIR CELL MITOCHONDRIA NEAR THE STRIATED ORGANELLE

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H7

STIMULATION OF THE INTERNAL NASAL PASSAGES PROVIDES THE AFFERENT SIGNAL THAT INITIATES THE DIVING RESPONSE IN VOLUNTARILY DIVING RATS

P.F. McCulloch, K.A. Lahrman, E.A. Warren, and K.M. DiNovo
Department of Physiology, Chicago College of Osteopathic Medicine, Midwestern University, Downers Grove IL

H8 UG-B

CRISTAE ALIGN ACROSS MITOCHONDRIAL MEMBRANES IN VESTIBULAR HAIR CELLS TO POSSIBLY INCREASE ATP OUTPUT

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Supported by NIH R21-DC013181 (AL) and P41-RR004050 (GP, ME).

H9 UG-B

FUNCTIONAL AND MORPHOLOGICAL CHARACTERISTICS OF EFFERENT BOUTON MITOCHONDRIA OF THE INNER EAR

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H10 G-B

MELANOPSIN SETS THE CONTRAST DETECTION THRESHOLD OF ON-ALPHA RETINAL GANGLION CELLS IN THE MOUSE RETINA

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H11 UG-A

ASSESSING THE ASYMMETRICAL DISTRIBUTION OF CRISTA JUNCTIONS IN TUBULAR MITOCHONDRIA LOCATED ADJACENT TO A POST-SYNAPTIC DENSITY OF A VESTIBULAR HAIR CELL RIBBON SYNAPSE

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POSTER ABSTRACTS

THEME A. COGNITION AND BEHAVIOR

A1 UG-B
IDENTIFICATION OF CIRCADIAN OUTPUT GENES THAT AFFECT REST:ACTIVITY RHYTHMS IN DROSOPHILA

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Most organisms have endogenous circadian clocks that produce behavioral and physiological rhythms. The circadian system has three main parts: input pathways, core clock cells, and output pathways. The core clock in the fruit fly, *Drosophila melanogaster*, is comprised on several populations of neurons in the brain that keep time through a cell-autonomous molecular clock. These cells are synchronized by input pathways that provide information about environmental cues such as light and temperature, and they control behavioral and physiological processes via output pathways. Although much is known about the input pathways and the molecular clock, little is known about the output pathways. We recently identified the *Drosophila* pars intercerebralis (PI) as a major circadian output center that lies downstream of the core clock cells in a circuit controlling rest:activity rhythms, and used single-cell RNA sequencing to identify genes expressed by PI cells. Here we use cell-specific RNA interference (RNAi) to knock down expression of >30 candidate genes within the PI. We reasoned that if the gene was involved in the ability of cells to communicate circadian information to downstream output pathway neurons, then knockdown would reduce behavioral rhythmicity. We have identified two genes whose knockdown reliably decreases circadian rhythm strength: *slowpoke* (*slo*) and *sleepless* (*sss*). Interestingly, these genes encode for a potassium ion channel and a potassium channel regulatory protein, and could have a role in setting neuronal activity levels in PI output cells. Our experiments demonstrate that expression of these genes in the PI is vital in the production of circadian rhythms and suggest that regulation of output cell activity is a mechanism through which circadian information is transmitted across output circuits.

A2 G-A
IMPACT OF EMOTIONAL CONTRAST AND PSYCHOLOGICAL FUNCTION ON RESPONSE INHIBITION TO THREATENING FACES

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Threatening stimuli are negatively-valenced signals predictive of adverse physical or emotional effects. Poor inhibitory control over responses to such negative emotional information and biased attention toward negative information may be the root of affective disorders like depression and anxiety. Specifically, young adults with higher trait anxiety demonstrate difficulty disengaging from both fearful and angry faces, although there may be differences in attentional motivation for fearful versus angry faces related to their different environmental signals. While fearful faces signal an indirect threat in the environment, angry or dominant faces signal a direct threat to the receiver. The effect of fearful versus angry faces on response inhibition remains an open question. For the present study, young adult participants completed an emotional go/no-go task involving happy, neutral, and either fearful or angry faces. We investigated differences in response inhibition accuracy (false alarms to nontargets) and speed (response time to targets) as a function of condition (fearful v. angry) and block (threatening face target with happy v. neutral face nontarget, and happy v. neutral face target with threatening face nontarget). We also tested relationships between task performance and self-reported measures of depressive and anxious symptoms. Results showed no differences between angry and fearful face conditions for accuracy or speed. However, within-subject effects demonstrated a pattern of slower response times and more false alarms in blocks where threatening faces were paired with happy, versus neutral faces. These results may reflect degree of emotional contrast, such that higher contrast blocks (containing threatening with happy faces) produce more conflict and require more elaborative processing than lower contrast blocks (containing threatening with neutral faces). We also observed higher self-reported depressive and anxious symptoms were related to slower response times and more false alarms in blocks containing lower but not higher contrast. This may be a result of the lower contrast blocks involving neutral (rather than happy) faces, which individuals with depression/anxiety tend to perceive as more negative, therefore impacting task performance more than blocks with happy faces.

A3 UG-A
INVESTIGATING THE CONTRIBUTION OF ANATOMICALLY DISTINCT CLOCK NEURON POPULATIONS TO CIRCADIAN REST:ACTIVITY RHYTHMS

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Most physiological processes exhibit daily oscillations under the control of an endogenous circadian clock, which allows animals to anticipate and adapt to 24-hr rhythms of light and temperature. The circadian system consists of a central clock,

input pathways that transmit environmental signals to the clock, and output pathways that connect the clock to behavioral outputs. Although much progress has been made in research of the circadian clock in *Drosophila melanogaster*, knowledge of output circuits remains the most limited of the three components. The central clock in *Drosophila* is comprised of ~150 clock neurons that each contains a cell-autonomous molecular clock. These are divided into distinct subpopulations based on anatomical and functional properties. Our aim was to elucidate the mechanisms by which circadian information is coordinated across neuronal populations within the clock network and translated into coherent behavioral outputs. We used restricted GAL4 lines to drive expression of a dominant negative construct that shut off the molecular clock in specific clock cell populations, and measured locomotor activity rhythms to assess circadian control of behavior. These studies demonstrated that the dorsal lateral clock neurons play a more significant role in the clock than previously thought, and we hypothesize that they may be especially important for transmitting circadian information from the clock network to downstream output circuits. We are conducting ongoing studies to further test this hypothesis.

A4 UG-A

VARIABILITY IN NORMAL HEARING THRESHOLDS, BUT NOT SYNAPTOPATHY, INFLUENCES HEARING IN NOISE

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Even within a healthy, young population, there is a wide range of speech-in-noise abilities. Why some young listeners with normal hearing have greater difficulty understanding speech in noise relative to their peers is unknown. Studies in animal models suggest that degeneration of auditory nerve fibers following moderate noise exposure, a phenomenon known as synaptopathy, could account for this hearing in noise difficulty. Though it affects the auditory nerve, synaptopathy is believed to leave cochlear hair cells intact, suggesting it would not impair hearing threshold. Therefore, synaptopathy should be undetectable by conventional audiometry, but reflected through electrophysiological responses that assess neural processing along the auditory pathway (i.e. Auditory Brainstem Response or ABR). Specifically, synaptopathy should be observed as a reduction of the suprathreshold wave I amplitude, as the size of this ABR peak reflects the health and integrity of the auditory nerve. While animal work supports this assumption, its validity in humans has yet to be tested. Thus, the current understanding of synaptopathy leaves two predictions to be tested: 1) hearing thresholds do not correlate with wave I amplitude; and, 2) wave I amplitude, but not hearing thresholds, relate to hearing-in-noise abilities in normal hearing individuals. We tested these predictions by analyzing wave I amplitude, hearing thresholds from .125 – 14 kHz, and hearing-in-noise performance in 121 normal-hearing adolescents (aged 15 to 16 years). In contrast to the synaptopathy hypothesis, we found correlations between wave I amplitude and hearing thresholds. Furthermore, while we did not observe any relationships between wave I amplitude and hearing-in-noise abilities, hearing thresholds did relate to hearing-in-noise abilities. These results fail to support current assumptions about synaptopathy's independence from hearing thresholds and the role of synaptopathy in hearing-in-noise difficulties. Instead, these results demonstrate that in a normal-hearing population, variability in hearing sensitivity can be detected by conventional audiometry and impacts real-world listening.

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A5 PD-A

NEUROSTEROID BIOSYNTHESIS MEDIATES THE ANXIOLYTIC AND ANTI-FEAR EFFECTS INDUCED BY THE ENDOCANNABINOID, N-PALMITOYLETHANOLAMINE (PEA)

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Post-traumatic stress disorder (PTSD) is a debilitating condition that affects 8-13% of the general population and 1 in 5 veterans. Current medication is inadequate due to the inefficacy of some antidepressants and benzodiazepines in the treatment of PTSD. SSRIs remain the drugs of choice but with high rates of resistance. Low non-serotonergic doses of fluoxetine (FLX) increase the corticolimbic levels of the GABA-A receptor-active neurosteroid, allopregnanolone and improve fear responses in socially isolated (SI) mice, which is a mouse model of PTSD. The endocannabinoid (eCB) system regulates emotions and stress responses and new cannabinoid ligands have become a major focus for anxiety and PTSD treatment. Disruption of the eCB system enhances fear acquisition and impairs fear extinction while activation of peroxisome proliferator-activated receptor (PPAR)-alpha by the endocannabinoid, N-palmitoylethanolamine (PEA), induces antidepressant effects comparable to those elicited by FLX. Like FLX, PEA induces allopregnanolone biosynthesis in cell cultures and spinal cord. Thus, these findings suggest that PEA may also induce allopregnanolone biosynthesis in corticolimbic areas and improve anxiety and fear responses. Our results show that PEA treatment resulted in a significant increase of allopregnanolone levels in the hippocampus, amygdala and olfactory bulb of SI mice at the doses of 5, 10

and 20 mg/kg and in the frontal cortex levels at the dose of 20 mg/kg. The same treatment did not modify allopregnanolone levels in the striatum. PEA, by a reconsolidation blockade, facilitated fear extinction and also prevented the spontaneous recovery of fear memory in SI mice. Furthermore, PEA induced a marked anxiolytic and antiaggressive effect, which was mimicked by the PPAR-alpha agonist, GW7647 and prevented by GW6471, a potent PPAR-alpha inhibitor. Locomotor activity was not altered by these treatments. Our results suggest that PPAR-alpha receptors may be an important neural target to regulate emotions by stimulation of neurosteroid biosynthesis and, therefore, may be useful for PTSD therapy.
Funded by DOD award W81XWH-15-1-0521.

A6

THE EFFECTS OF EXERCISE SEQUENCE ON LEARNING AND MEMORY

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The University of Wisconsin-Milwaukee, 2017

Aerobic exercise promotes enhanced learning and memory in both human and non-human animals. Structurally, exercise improves blood perfusion, vascularization, and neurogenesis in brain structures associated with learning and memory. Behaviorally, exercise facilitates acquisition and improves retention on a variety of learning tasks. Numerous studies have shown that an animal that exercises prior to learning a task exhibits faster learning and better recall of the task when compared to sedentary controls. However, it is not well-known what effect exercise has on learning and memory if exercise occurs after learning. Some studies have indicated that exercise training presented after initially learning a task impedes the recall of that task. However, this has only been shown in mice and dogs. The present study aimed to examine what behavioral effects the sequencing of seven days of voluntary exercise had on acquisition and retention in rodents. Long Evans rats were divided into three groups. The first group was allowed seven days of access to a voluntary running wheel prior to training on a difficult version of the Morris Water Maze (MWM). A probe trial followed a week after the last day of training. The second group was trained on the MWM, given seven days of voluntary exercise, and then subjected to a probe test. The third group was the inactive controls and remained sedentary with the exception of training on the MWM and a probe a week after the completion of training. It was hypothesized that animals that voluntarily exercise before learning would acquire the MWM faster than the sedentary controls and those animals that exercised after learning. Our results indicate that animals that exercised prior to learning acquired the task faster than inactive controls and animals that exercised after learning.

A7 UG-A

PARTIALLY REINFORCED WISTAR-KYOTO FEMALE RATS SHOW AN INCREASE IN AVOIDANCE ACQUISITION COMPARED TO FULLY REINFORCED SPRAGUE DAWLEY RATS DURING A LEVER-PRESS AVOIDANCE TASK

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The behaviorally inhibited Wistar-Kyoto (WKY) strain has been studied extensively as a model for anxiety vulnerability. WKY rats acquire signaled lever-press avoidance more rapidly and they are resistant to extinguishing the avoidance response when compared to Sprague Dawley (SD) rats (e.g., Servatius et al, 2008). Recently it was demonstrated that learning in behaviorally inhibited humans was less affected by partial reinforcement during Pavlovian eye blink conditioning (Allen et al., 2014). In the present study, we questioned how behaviorally inhibited WKY rats will react to complete or partial reinforcement in a lever-press avoidance paradigm. We compared avoidance acquisition in female WKY versus female SD rats receiving either 100% reinforcement of paired tone-shock trials or 50% partial reinforcement with inconsistent tone only trials. WKY rats receiving 100% reinforcement showed the highest levels of acquisition followed by WKY rats receiving 50% reinforcement. SD rats receiving 100% reinforcement showed lower rates of acquisition than either of the WKY rat contingencies, and WKY rats receiving 50% reinforcement had very little avoidance acquisition. Our results suggest that female WKY rats are extremely influenced by the tone-shock reinforcement even when it is inconsistent. Such enhanced associative learning in vulnerable populations could be a major factor in the development of anxiety and stress disorders. To further study this relationship, we are performing immunohistochemical screens to identify differentially activated circuits underlying avoidance learning in WKY and SD rats.

A8

EFFECTS OF CONCUSSION ON WORKING MEMORY AMONG COLLEGIATE CLUB ATHLETES

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Objective: Mild traumatic brain injury (mTBI/concussion), as experienced through sports, combat, falls and automobile accidents, has emerged as a major public health issue. Most concussions, such as those related to sports injury, appear to exhibit good recovery within days or a few weeks, based on current neuropsychological and neurological evaluation. However, the actual long-term negative outcomes of one or

more concussions can be significant. Working Memory (WM), the ability to mentally hold and manipulate information over a brief period of time, is a common deficit following concussion and is a critical cognitive ability that matures during adolescence and provides a basis for other higher-ordered cognitive functions.

Methods: We used a computerized task to assess spatial WM at variable cognitive load levels that implements signal detection theory in order to obtain measures of WM sub-processes, d' and β. d' measures ability to distinguish signal from noise and β indicates the allowance of a False Alarm to increase correct responses. We compared performance on this WM task between demographically matched concussed/injured (n=4) and non-injured control (n=4) collegiate club athletes. Concussed athletes were studied within 7 days of symptom resolution.

Results: Concussed athletes trended towards lower d' (1.800±0.323) compared to non-injured control athletes across loads (2.15±0.284) with a large effect size (p=.151; *d*= 1.16). In terms of β, there were no changes between groups and no significant effect across loads.

Discussion: These pilot data suggest that adolescents who sustain concussion may demonstrate residual impairment in component WM processes, specifically the ability to distinguish signal from noise, despite resolution of clinical symptoms. Thus, impairment in this core cognitive ability may persist beyond clinical recovery as assessed by standard neuropsychological and neurological evaluations. Given our small sample size, replication of these findings in a larger cohort is needed.

A9 UG-A

MOLECULAR CORRELATES OF SAVINGS MEMORY IN THE MARINE MOLLUSK APLYSIA CALIFORNICA

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Most long-term memories fade. Even after recall becomes impossible, however, it can be easier to re-learn "forgotten" information, a phenomenon known as savings memory (Ebbinghaus, 1885). Even though savings memory occurs across the animal kingdom, the mechanisms mediating savings remain shrouded in mystery.

Here we describe the first molecular correlates of savings memory using the long-term sensitization paradigm in the marine mollusk *Aplysia californica.* First, we confirmed savings memory in this paradigm. *Aplysia* received long-term sensitization training—a series of noxious shocks to one side of the body. This produced long-term sensitization memory, expressed as a long-lasting increase in reflex responsiveness on the side of training. One week after training, sensitization memory seemed to have faded, as reflex responsiveness had returned to within 1% of baseline. A weak reminder shock, however, revealed savings memory, producing a much stronger change in reflex duration on the previously trained side.

To identify the molecular correlates of savings memory we conducted microarray analysis on CNS samples harvested 1 and 7 days after training, time points associated with strong memory and apparent forgetting. We found over 1,000 strongly-regulated transcripts 1 day after training. One week later, most of these changes had relapsed to baseline. Notably, however, we identified a small set of transcripts which remain strongly regulated after apparent forgetting. We confirmed several of these with qPCR in independent samples. Identified changes include down-regulation of spectrin, a protein implicated in meta-plasticity of LTP, and up-regulation of FMRF-amide, a peptide neurotransmitter thought to function as a memory repressor. These results suggest the intriguing possibility that savings memory may be a consequence of active forgetting mechanisms.

A10 UG-A

CAN MEMORY BE IMPROVED WITH OSCILLATING SOUNDS THAT PROMOTE BENEFICIAL BRAIN OSCILLATIONS DURING LEARNING?

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Rhythms observed in electrophysiological recordings from the brain are thought to reflect important neural processing relevant for cognitive function. For example, oscillations at theta and beta frequencies (3-7 Hz and 13-30 Hz, respectively) have often been observed during memory processing. Various speculations about beta and theta rhythms have been made in relation to memory functions, but a clear picture linking these rhythms to neural mechanisms of memory storage has yet to emerge. In particular, it is unknown if beta and theta oscillations are merely a byproduct of information processing or if they reflect causal stages in the process of memory encoding. If these oscillations are causal in memory processing, inducing them at the proper moment during memory formation might beneficially influence subsequent memory performance. In the current study, we attempt to examine the importance of brain activity at theta and beta frequencies by pairing sounds at corresponding frequencies with to-be-remembered objects shown to participants in a spatial memory task. Participants learned the screen locations of 60 objects while each object was paired with one of three different types of pink noise (20 objects each). Noise modulated at 6 Hz was intended to induce theta oscillations, noise modulated at 15 Hz was intended to induce beta oscillations, and constant noise was included as a control condition. Each object was paired with the same sound throughout the study. After a 10-min break, participants

attempted to recall the location of each object. The distance between the recalled location and the correct location (recall error) was compared across conditions. Spatial memory was found to be superior for objects learned in conjunction with beta-modulated sound, implicating beta brain rhythms in memory formation. Future analyses of EEG oscillations may provide additional substantiation of this link between beta activity and memory processing. This approach of facilitating learning using auditory entrainment at beta frequencies may thus yield a noninvasive strategy for memory improvement and also a useful tool for investigating neural mechanisms of memory storage.

A11

CORTICOTROPIN-RELEASING FACTOR (CRF) NEURONS IN THE OVAL NUCLEUS OF THE BED NUCLEUS OF THE STRIA TERMINALIS ($BNST_{OV}$) MODULATE FEAR AND ANXIETY IN MALE RATS

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Corticotropin-releasing factor (CRF) is a neuropeptide responsible for regulating the autonomic, endocrine, and behavioral responses to stress. One significant population of CRF cell bodies is located within the bed nucleus of the stria terminalis (BNST), a region of the brain that mediates adaptive responses to stressors, such as fear and anxiety. This research investigates the role of these CRF neurons in the BNST regarding the acquisition of conditioned fear and background anxiety. We used designer receptors exclusively activated by designer drugs (DREADDs) within adult male transgenic CRF-Cre rats (developed by Pomrenze et al., 2015) to modulate this system. In this model, Cre recombinase is exclusively expressed by central CRF neurons. We performed bilateral BNST injections of viral vectors driving Cre-dependent expression of DREADDs and reporter protein, mCherry, in both Cre+ and Cre- rats. Viruses used encoded either DREADDs-Gi (pAAV-hSyn-DIO-hM4D(Gi)-mCherry(AAV8)) to silence CRF neurons or DREADDs-Gq (pAAV-hSyn-DIO-hM43(Gq)-mCherry(AAV8)) to activate them. Four weeks after stereotaxic AAVs injections, we measured baseline acoustic startle reactivity of all rats. Then, we used a fear-potentiated startle (FPS) paradigm to determine if inhibition or activation of the CRF neurons in the BNST affects acquisition and recall of cued fear or background anxiety. Animals were injected with the DREADDs selective ligand, clozapine-N-oxide (CNO, 1 mg/kg/mL, IP), 45 min before fear conditioning and tested for FPS expression 24 hours later. We found that activating CRF neurons in the BNST reduces the acquisition of background anxiety measured in FPS and completely eliminates the recall of cued fear. We also confirmed through fluorescent immunohistochemistry that mCherry was exclusively expressed on CRF neurons in the BNST. In light of this data, future experiments will aim to further elucidate the functional role of CRF neurons in the BNST and confirm the specificity of DREADDs expression in this promising rat model.

This work is supported by a National Institute of Mental Health grant (R00MH096746) and CMS RFUMS start-up funds to JD.

A12 G-B

NEURAL CORRELATES OF SLEEP-BASED OLFACTORY TARGETED MEMORY REACTIVATION IN THE HUMAN BRAIN

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Odors have been shown to be key agents in targeted memory reactivation (TMR), a technique used to manipulate sleep-based memory consolidation. During olfactory TMR, an odor is presented during learning, and then again during subsequent sleep (i.e., reactivation). TMR often results in enhanced performance for the associated memory task upon waking, but the neural mechanism underpinning these memory improvements is not well understood. Researchers speculate that reactivation cues bias memory replay toward associated memories. Here, we developed a novel olfactory TMR paradigm to test the hypothesis that odors evoke replay of associated memories in the sleeping human brain. First, subjects learn the locations of pictures belonging to specific categories during fMRI scanning. Next, subjects learn to associate each picture category with a unique odor. Then, half of the category-specific odors are presented in sleep during simultaneous EEG-fMRI recording. Our behavioral data suggests that reactivation improves memory performance for reactivated picture categories. Moreover, in an interference test following reactivation, reaction times for reactivated picture categories are increased, possibly reflecting a struggle to override the strengthened memory traces. Finally, we employ multivariate pattern classification of fMRI data to show that category-specific pictures elicit distinct ensemble patterns of neural activity during learning. In future analysis, we plan to directly test the hypothesis that odors promote replay of reactivated memory traces by searching for the re-emergence of category-specific fMRI activity during the reactivation phase.

A13

EXERCISE-INDUCED APOPTOTIC CELL DEATH IN THE HIPPOCAMPUS

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Exercise produces numerous benefits in the body and brain. In the brain, it is well established that exercise enhances cognition on tasks such as the Morris Water Maze. Exercise

may exert these effects in part through accelerating neurogenesis, the proliferation and migration of new neurons, in the hippocampus. To support the metabolic requirements of elevated neurogenesis, it is in turn necessary to increase angiogenesis, the sprouting of new vessels from preexisting capillaries. Interestingly, within 24 hours of the onset of aerobic exercise, a population of hippocampal cells undergoes apoptotic cell death. This cell death, although transient, may be an important signal for neurogenesis and angiogenesis, which temporally follow. This study aimed to identify whether newly birthed or adult hippocampal neurons were most vulnerable to this exercise-induced apoptotic cell death. Findings indicated the dentate gyrus (DG) and CA1 region of the hippocampus were most vulnerable to exercise-induced apoptosis. Unbiased stereology indicated a significant increase in caspase-3 immunohistochemical labeling in these regions when comparing animals that voluntarily exercised for 24 hours with inactive controls. Furthermore, newly migrating neurons were disproportionately affected by this exercise-induced cell death. Using immunofluorescence techniques, it was found that significantly more caspase-3 was colocalized with doublecortin (a marker of migrating neurons) in exercising animals compared to inactive controls. Interestingly, there was decreased cell death of adult neurons in exercising animals compared to inactive controls, as indicated by decreased caspase-3 and NeuN colocalization.

A14 G-A

OCULOMOTOR MEASURES, GREY MATTER DENSITY, AND SYMPTOM OUTCOMES IN COLLEGIATE ATHLETES WITH MTBI: A PILOT STUDY

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Background/Introduction: A concussion or mild Traumatic Brain Injury (mTBI) initiates a cascade of pathophysiological processes resulting in clinical symptoms such as headache, dizziness, cognitive difficulties, and emotional changes which persist to varying degrees across individuals (McCrory et al., 2013). Current standard neuropsychological tools have low specificity in distinguishing individuals with mTBI from those without mTBI and are not predictive of functional outcomes.

Objective: This pilot study aimed to: 1) evaluate whether oculomotor measures are predictive of clinical outcomes (symptom (sx) severity, length of recovery) in collegiate student athletes (SA) with mTBI; 2) evaluate group differences in oculomotor measures between athletes with mTBI versus controls (CON); and 3) evaluate group differences in gray matter (GM) density in ROIs associated with oculomotor performance.

Methods: Eight collegiate SA were recruited, 4 with sports-related mTBI and 4 demographically matched CON. mTBI SA completed the Post-Concussion Symptom Scale (PCSS) every 48 hours from time of injury until sx resolution. Oculomotor testing and neuroimaging were completed within 7 days of sx resolution; CON athletes were studied within 2 weeks of the mTBI athlete. Oculomotor testing consisted of pro-saccade (reflexive) and anti-saccade tasks.. Magnetic resonance imaging (MRI) was performed using a Siemens 3T Prisma scanner and T1-weighted anatomical images were acquired. T1 images were pre-processed and between group analyses were conducted using voxel-based morphometry (VBM8 for SPM8). Small volume correction ($p<0.01$) was used by applying an oculomotor control circuit mask comprised of the bilateral dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF) and supplementary motor areas (SMA).

Results: 1) Select oculomotor measures (reaction time, duration, and absolute velocity) were predictive of length of recovery and/or symptom severity on both the pro- and anti-saccade tasks ($p<.05$).

2) mTBI significantly differed from the CON on anti-saccade error rate such that mTBI group was 1.889x more likely to make a pro-saccade error than the CON group ($\chi^2=12.881$, $p<.001$).

3) Between group differences in GM density were found across several ROIs ($p<.01$), where mTBI showed lower GM density compared to CON in regions associated with the oculomotor control circuit.

Conclusion: This pilot study provides initial support for the use of oculomotor measures to predict functional outcomes following mTBI in SA and to detect group differences between mTBI and CON. Further, reduced GM across an oculomotor control circuit was observed in athletes with mTBI.

THEME B. DEVELOPMENT

B1

ASSESSING GLIOGENESIS IN A MURINE MULTIFACTORIAL BRAIN INJURY MODEL SYSTEM

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Brain injury in humans caused by trauma, intrauterine infections, hypoxia and/or ischemia, pre-maturity or low birth weight, during the perinatal period which coincides with glial cell (astrocyte and oligodendrocyte) maturation in the brain, often has devastating neurological consequences such as epilepsy, cerebral palsy, and behavioral and cognitive problems. Due to the variety of risk factors associated with these neurodevelopmental disorders, we are using a multifactorial injury model to examine the effects on

differentiation and maturation of the two glial subtypes. The model consists of penetrating perinatal traumatic brain injury, with or without intraperitoneal injection of lipopolysaccharide (LPS) as a model of remote pathogen exposure. Postnatal-day-6 (P6) mouse pups underwent sham, LPS-alone, stab-alone, or stab-plus-LPS treatments. At different ages after injury, the pups were harvested and gene-expression changes for astrocyte, neuron, oligodendrocyte, and precursor-cell markers were assessed using mRNA *in situ* hybridization (ISH) and qPCR. In general, the injured (ipsilateral) side exhibited enlarged ventricles, occasional disruption of the cortex structure and sporadic cysts; whereas the uninjured (contralateral) side remained unaffected overall, comparable to sham-treated animals. Astrocyte-precursor and mature-astrocyte marker mRNA levels increased in the stab-alone and stab-plus-LPS treated animals. Microglial/macrophage markers CD208 and CD68 levels, increased in the ipsilateral sides of stab and stab-plus LPS animals by P10, but the differences resolved by P15. Decreased mRNA expression of mature oligodendrocyte markers, proteolipid protein 1 (PLP) and myelin basic protein (MBP) and the neuronal marker Class III beta-tubulin (TUBB3), was observed only on the ipsilateral side in stab-treated pups by ISH. Interestingly, ectopic expression of the neural stem cell marker SRY(sex-determining region Y)-box 2 (SOX2), astrocyte precursor SOX9, and the oligodendrocyte precursor marker oligodendrocyte transcription factor (OLIG2) mRNAs were observed in the ipsilateral side following stab injuries with or without LPS treatment at P10. By fluorescent ISH, partial colocalization of SOX2, OLIG2 and SOX9 mRNAs with GFAP-positive cells was confirmed. These data suggest that shortly following traumatic injury, concomitant with the decrease in mature oligodendrocyte and neuronal marker expression, neural stem cells and glial precursor populations may be attempting to repopulate the injury region.

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B2 G-B

ENDOTHELIN-B RECEPTOR AGONIST IRL-1620, ENHANCES NEUROGENESIS IN AN *EX VIVO* MODEL OF ADULT MOUSE SPINAL CORD INJURY.

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Spinal cord injury (SCI) is a devastating condition that causes substantial damage to the tissue due to an increase in vascular permeability, infiltration of inflammatory cells, focal edema and apoptosis—with apoptosis being the most prominent event in chronic SCI. Adult SCI is often mentioned among the first conditions for which stem cells might provide a new therapeutic strategy. Recent discovery of niches of endogenous multi-potent neural stem/progenitor cells (NSPCs) within the adult spinal cord has shed light on stem cell therapies for SCI. If undifferentiated stem cells are present within the spinal cord, their activation may lead to the generation of mature neurons with the ability to re-network the lost circuitry after lesion. Our group previously demonstrated that stimulation of Endothelin-B (ET_B) receptors with an ETB receptor agonist, IRL-1620, limits apoptosis and increases the expression of VEGF and NGF in both stroke and Alzheimer's disease in animal models. In our study, we focused on the neurogenic effect of IRL-1620 in an *ex vivo* mouse spinal cord model by investigating specific neurogenic markers expressed along the neuronal lineage. Our confocal images of transverse spinal cord sections localized the presence of NSPCs and its potential to migrate from their neurogenic niches towards their final destinations. Our Western blots show an increased expression in various neurogenic markers in the IRL-1620 treated explant cultures following 1 day of injury. Furthermore, we utilized a microarray analysis the follow the up- and down-regulation of gene expressions involved in neurogenesis. Taken together, our results indicate that the treatment of IRL-1620 following SCI enhances the expression of neurogenic markers that promotes the entry of NSPCs into the neuronal lineage. If the beneficial effects of IRL-1620 are proven significant, this agonist will have profound clinical impact on the recovery following

B3 UG-B

IDENTIFICATION OF A NOVEL REGULATOR OF GLIAL DEVELOPMENT

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Glial cells serve numerous roles in nervous system development, from providing contact mediated guidance cues to acting as intermediates for axonal path finding. When fully differentiated they promote proper neuron function by maintaining ionic homeostasis, ensheathing axons via myelination, and facilitating synapse formation and maturation. In vertebrates defective glial cells have been linked to neurodegeneration and neurological diseases like schizophrenia. Our lab uses *Drosophila melanogaster* to examine the genetic basis of glial development, as glial function is conserved from mammals to fruit flies. We have found the *raw* gene to be required in glia, as reducing *raw* levels in glial cells by RNAi results in lethality. Due to the lethality observed when *raw* is removed from glia we have examined the effect of reducing *raw* levels on the developing nervous system. Upon *raw* reduction, we have observed morphological defects in the brain and ventral nerve cord and

a reduced number of glia along the peripheral nerves. Further examination of peripheral nerve structure by transmission electron microscopy reveals significant changes in nerve morphology when *raw* levels are reduced. These phenotypes suggest a defect in glial specification, proliferation or survival. While glia appear to be specified normally in *raw* mutants and do not undergo cell death, we observe fewer proliferating glia upon *raw* knockdown. Current work focuses on identifying the specific glial subtypes that require Raw to promote glial proliferation. These studies have resulted in the identification of a novel regulator of glial development, and are likely to yield novel molecular mechanisms underlying the establishment of neuron-glia interactions during development.

B4 UG-A

THE FUNCTIONAL MATURATION OF THE FEMALE PREFRONTAL CORTEX THROUGH VENTRAL HIPPOCAMPAL STIMULATION

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The World Health Organization defines adolescence as the time after childhood, but before adulthood, which correlate around ages 10-19 Years old. The adolescent period includes many life evens that can evoke strong emotional responses that are not typically seen in adulthood, such as engaging in behaviors to better oneself (e.g. making friends) and risky behaviors (e.g. drugs, unsafe driving, sexual activity). Adolescence is also a time period where the brain continues to mature. Specifically the prefrontal cortex (PFC) goes through a process of disinhibition to inhibition as we age. This region receives many inputs to drive this process. One of these is the ventral hippocampus (vHipp).The Tseng lab has previously shown that inputs from this region has a frequency dependent maturation pattern in male rats. However, this same maturation pattern has yet to be tested in female rats. In this present study, we focus on frequency dependent responses in the medial PFC that are evoked in the ventral hippocampal region. This is done by measuring Local Field Potential (LFP) responses in the medial PFC by means of *in vivo* electrophysiology. We found that evoking a 10 Hz train response showed no difference females postnatal day 30 (P30) to P35, P40-45, and P50 and older. A 20 Hz (beta frequency) train stimulation showed a transient facilitation P30-35, a null response P40-45, and a transient suppression at P50 and older. Finally, a 40 Hz (gamma frequency) train stimulation evoked suppression in all three age groups, but there was significantly more suppression of the response in females P50 and older. This study shows a frequency dependent, maturation pattern for the medial PFC from juvenile (P30-35), through adolescence (P40-45), and into adulthood (P50 and older). With these established patterns we can compare a normal PFC maturation with factors such as chronic drug use and stress. Supported by Rosalind Franklin University of Medicine and Science, the Brain Research Foundation and NIH Grant R01-MH086507 to KYT.

B5

THE EFFECTS OF MATERNAL SEPARATION ON STRESS-INDUCED ALCOHOL CONSUMPTION AND EMOTIONAL BEHAVIOR IN SPRAGUE DAWLEY RATS

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Neuropsychological conditions such as drug and alcohol dependence, anxiety and depression are highly prevalent conditions that negatively affect the physical, psychological and social well-being of those afflicted. These disorders have etiologies and that include complex interactions between, among other influences, environmental and genetic factors. Research in humans has shown that adverse childhood experiences (ACE) significantly increases the risk of developing later neuropsychiatric and physical illness. Early life trauma is frequently modeled in rodents using maternal separation (MS) in the post-natal period, resulting in increased anxiety- and depressive-like behaviors, as well as disrupted HPA regulation. The purpose of these experiments using rodents was to explore the extent to which MS influences: 1) voluntary alcohol consumption and depressive-like symptoms in response to adult stress, and 2) cardiovascular and behavioral responses to contextual fear conditioning. Sprague-Dawley pups were maternally separated for 3 hours/day from PD 1-14; controls remained undisturbed during this period. In the first study, voluntary consumption of 10% ethanol was assessed while animals were being exposed to three different acute stressors (two times each) over 6 days: 1) elevated platform, 2) restraint stress, and 3) mild foot shock. To measure depressive-like behavior following the acute stress period, rats were subjected to a 10 minute forced swim test. Rats were then maintained on 10% ethanol for 30 days followed by 14 days of alcohol deprivation. A novelty suppressed feeding test (NSF) was administered to test for anxiety-like behaviors. Results indicate that MS rats had higher levels of immobility and reduced intake of and preference for alcohol, the latter of which was particularly pronounced in MS female subjects. Although no differences were observed in anxiety-like behavior as measured by latency to eat in the NSF, MS animals made more entries into the center of the arena. In the second study, blood pressure was measured in MS and control male animals during rest and 24h after being exposed to contextual fear conditioning. Freezing behavior was measured as an indication of fear. MS animals had significantly higher resting blood pressure and freezing responses upon being reintroduced to the context

chamber. Taken together, these results suggest that early life trauma can have an enduring, sometimes gender specific, effect on future biobehavioral responses to stressful and emotional stimuli.

B6 UG-B

REGULATION OF NEURON-GLIA INTERACTIONS IN THE DEVELOPING EYE

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Glial cells in vertebrates have numerous functions, including ensheathment of neuronal axons, regulation of axon targeting, enhancement of synaptic transmission, and providing metabolic support. These glial functions are conserved from mammals to fruit flies. Recent studies in our lab have demonstrated that the novel gene *raw* is required for glial development. When *raw* expression is reduced in glia by RNAi, the result is pupal lethality, leading us to ask what the role of Raw is in glia during development. The developing eye of *Drosophila* provides an excellent system for studying the role of Raw in glia due to its well-characterized glial subtypes and well-described development. Subperineurial glia form a carpet along which perineurial glia migrate from the brain and optic stalk into the developing eye imaginal disc in third instar larvae, where they make contact with photoreceptor cells. Following contact with neurons, perineurial glia differentiate into wrapping glia and ensheath photoreceptor axons. Axons then extend along glia to the optic lobe of the brain. Our studies have revealed a reduction in the number of glia in the third instar eye imaginal disc when Raw levels are reduced in glial cells using the Gal4/UAS system to produce Raw RNAi. While we observe a reduction in the number of glia, it is unclear if the reduction of glia is due to cell death or reduced proliferation. To determine if the reduction arises from an increase in cell death, we have performed acridine orange as well as immunostaining for activated Caspase and do not observe an increase in cell death, nor is there an obvious increase in glial proliferation. However, it appears that subperineurial glia may fail to alter their morphology to provide a carpet for glial migration. Therefore, we are currently exploring the requirement for Raw in specific glial subtypes. Lastly, as glia are important for proper axon targeting to the optic lobe of the brain, we have examined the effects of reducing *raw* levels on photoreceptor axon targeting. In larvae with reduced *raw* levels in glia, we observe axon mistargeting in the brain, suggesting that Raw functions indirectly to regulate axon targeting as well. Thus, we have identified a new regulatory protein that functions in glia during development. Ongoing studies of the molecular basis of Raw function will provide valuable insight into the molecular mechanisms regulating glia-neuron interactions.

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1 G-A

MECHANISMS FOR THE MODULATION OF STRIATONIGRAL AND STRIATOPALLIDAL NEURON ACTIVITY BY PHOSPHODIESTERASE 10A INHIBITION IN L-DOPA-INDUCED DYSKINESIA

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L-DOPA remains the gold standard treatment for Parkinson's disease (PD). However, with repeated administration, L-DOPA can cause abnormal involuntary movements (AIMs, e.g. L-DOPA-induced dyskinesia; LID). Substantial research efforts have been conducted to understand the molecular mechanisms that underlie the development and expression of LID (Huot et al., 2013). There is a clear need for novel preclinical and clinical research to identify an effective antidyskinetic intervention that provides PD patients with a better quality of life during the on-state of L-DOPA treatment. LID expression is thought to depend on both pre- and postsynaptic disruption of dopaminergic transmission as well as downstream non-dopaminergic mechanisms. Therefore, there is clearly a necessity to identify novel non-dopaminergic targets as new therapeutic strategies for PD.

Towards this effort, inhibitors of cAMP/cGMP metabolizing phosphodiesterases (PDEs) are emerging as promising candidates for restoring striatal dysfunction in patients with LID. Thus, systemic (Giorgi et al., 2008) or intrastriatal (Picconi et al., 2011) administration of PDE inhibitors (zaprinast or UK-343664) reduced the incidence of LID in parkinsonian rats by preventing both the L-DOPA-induced decrease of cyclic nucleotides and rescuing striatal long-term depression (LTD). These results suggest that PDE inhibitors could be useful therapeutic agents in the treatment of LID due to their ability to restore abnormal modulation of glutamatergic transmission. Since cyclic nucleotide production occurs downstream of dopamine (DA) receptor stimulation, our goal was to determine the effects of the PDE10A inhibitor TP-10 and L-DOPA co-treatment, together with a cocktail combination of either D1 or D2 antagonists (SCH-23390 or eticlopride, respectively) on LID. The clinical implications of this discovery are expected to advance the treatment options for patients with PD suffering from LID.

C2G-A

A DUAL-HIT MODEL OF METHAMPHETAMINE-INDUCED VULNERABILITY FOR PARKINSON'S DISEASE.

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Methamphetamine (meth) abusers are at risk for developing Parkinson's disease (PD). We revealed that rats self-administering (SA) meth exhibit an abstinence time-dependent reduction in striatal and nigral tyrosine hydroxylase (TH) (Kousik et al., Eur J Neurosci. 40, 2014). These findings led to our hypotheses that (i) meth initiates a pathological trajectory that may result in PD and (ii) the meth-compromised state would be vulnerable to a secondary dopaminergic insult. To test these hypotheses, we administered a subthreshold dose of rotenone, a dopaminergic toxin, to meth-SA rats and controls; we measured brain and behavioral markers of PD. Male Sprague-Dawley rats (n=64) self-administered meth (0.1mg/kg/0.1mL infusions) or were saline-yoked for 14 days, 3h per day. After the last operant session, rats were randomly assigned to receive vehicle or rotenone (1mg/kg/day) via subcutaneous osmotic minipumps for 6 days. Rats were sacrificed 1 or ~56 days after the rotenone treatment. PD-like motor assessments (forelimb akinesia, rearing) were performed throughout the study. Biomarkers for PD-like pathology were assessed in the striatum using immunohistochemistry (TH) or immunoblotting (VMAT-2) at 1 and ~56 days post-treatment. Statistical analyses were performed using GraphPad 6. Behavioral and biochemical markers were not altered by saline+rotenone. In the meth-SA rats, rearing was not altered, but by 36 days, akinesia developed ($p=0.0002$). By 50 days, meth+rotenone rats exhibited greater akinesia ($p<0.0001$). None of the treatment groups showed changes in VMAT-2, but there was a 50% TH reduction in meth-SA rats compared to saline-yoked rats 56 days after rotenone ($p=0.02$), but was not exacerbated in meth+rotenone rats. Thus, a subthreshold dose of rotenone was sufficient to exacerbate the emerging akinesia effects of meth-SA, but not dopamine terminal markers. Support provided by NIH ES02592, and the Rush University Medical Center for NIH ES02592

C3 PD-B

INVESTIGATING THE ROLE OF HGF ON MOTOR NEURON SURVIVAL AND FUNCTION IN ALS

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Hepatocyte growth factor (HGF) was first discovered as a hepatocyte mitogen and its role in angiogenesis, fibrosis, muscle regeneration, apoptosis and neurodegeneration has been studied. Recent evidence suggests that HGF has a supportive role for motor neuron survival. ALS is a progressive neurodegenerative motor neuron disease involving both the upper and lower motor neurons. Therefore, HGF treatment has been considered as a potential option for ALS disease. VM 202 is a plasmid DNA containing HGF-x7, which encodes two isoforms of HGF, and allows production of HGF in the introduced cells and neurons.

We initially investigated the expression patterns of HGF-receptor (c-Met) and HGF in the neuromuscular junction, spinal cord and the motor cortex of hSOD1^{G93A}-UeGFP mice, in which both the upper and the spinal motor neurons are genetically labeled with eGFP expression that is stable and long-lasting, allowing visualization and cellular analysis of different components of the motor-neuron circuitry.

We detect HGFR (HGF receptor) at the neuromuscular junction, spinal cord and the motor cortex. Interestingly, CSMN displayed selectively high levels of HGFR expression at P80 and P120. Our initial studies suggest that astrocytes are the primary source of HGF in the spinal cord, and that spinal cord has higher levels of HGF than that of the cortex. Interestingly, especially towards end-stage, HGFR levels were increased in diseased mice. These results suggest that both upper and lower motor neurons would respond to HGF treatment.

Our goal is to investigate whether constant supply of HGF would have an impact on degenerating motor neurons. Current experiments involve biweekly intramuscular injections of the VM202 plasmid into 4 different muscles in the leg of hSOD1^{G93A}-UeGFP mice, at P60, – a time of disease onset, and investigate the correlation between motor function improvements and motor neuron survival with respect to disease progression. Upon completion, we will have a better understanding for the correlation between HGF treatment and improved motor neuron health and motor function, an important preclinical assessment in ALS therapies.

Viromed Inc

C4

APP-CTF TARGETED AT THE MEMBRANE REDUCES Abeta BURDEN AND AMELIORATES COGNITIVE FONCTION IN ALZHEIMER'S DISEASE MOUSE MODELS

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Alzheimer's disease (AD) is a progressive neurodegenerative disease pathologically characterized by the cerebral deposition of β–amyloid peptides (Aβ) in senile plaques that is believed to contribute to the cognitive deficits associated with the disorder. Targeting Aβ reduction is therefore of great interest as a potential therapeutic strategy. Our studies investigate the contribution of APP molecule as a whole cellular component that could modulate brain function and memory process and have consequences on the course of AD. We previously reported that an *in vitro* accumulation of APP-derived C-terminal fragments (APP-CTF) promote axodendritic outgrowth and dendritic-spine formation through intracellular cAMP/PKA signaling. Indeed, APP-mediated cAMP signaling was enhanced when γ-secretase cleavage of the APP-CTF was inhibited or when the APP intracellular domain (AICD) was tethered to the membrane via a lipid anchor domain (mAICD). Using recombinant adeno-associated virus (AAV) brain delivery in neonatal AD mouse models, we explored the *in vivo* significance of AAV-mediated expression of mAICD and its associated signaling cascade on brain function. We found that mAICD could rescue memory deficit in 5XFAD and knock-in mice expressing familial AD-linked PS1-M146V mutation suggesting that APP-CTF metabolites might possess mnemonic properties. Concurrently, we also observed that mAICD decreases Aβ burden in 5XFAD mouse brains, especially in the hippocampal brain area that is associated with memory formation. We observed that mAICD expression in cell lines promotes the non-amyloidogenic processing of APP through the accumulation of APP at the cell surface. Our findings strongly support a novel role of membrane-bound APP-CTF in regulating Aβ production and strengthening memory formation. This study was supported by NIH, BrightFocus foundation, IDPH, ITM, and Alzheimer's Association grants.

C5 PD-A

CONTRIBUTION OF POSTNATAL CEREBELLAR STEM CELLS IN DEVELOPMENTAL NEURONAL NETWORK DYSFUNCTION OF SPINOCEREBELLAR ATAXIA TYPE 1

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Spinocerebellar ataxia type1 (SCA1) is an adult onset neurodegenerative disease caused by a pathogenic polyglutamine expansion in the protein ataxin-1 (Atxn1). Despite its late onset, recent studies in genetically engineered mice demonstrate that pathological changes begin in the first few weeks of life. Since Purkinje cells bear the brunt of the pathology in SCA1, scientific investigations have focused on characterizing intrinsic deficits within these neurons. In this study, using SCA1 knock-in mice model, we demonstrate a surprising finding that the mutant Atxn1 disrupts yet earlier steps in the development of the cerebellar neuronal circuitry by altering the proliferation and fate of postnatal stem cells (Prominin-1/CD133 expressing cells) that are known to generate GABAergic interneurons and astrocytes. When mutated, Atxn-1 acts in cell-autonomous manner within these stem cells to increase the proliferation, there by causes gain in GABAergic interneuron lineage and concomitant loss of astrocyte lineage. Gain in GABAergic interneurons contribute numeric increase in density of inhibitory synapse formation with Purkinje cells and corresponding suppression of Purkinje cell firing activity. Observations on human patient samples parallel the data obtained in mouse, as evidenced by the dense basket phenotype. The reduction in number of astrocytes could lead to loss of metabolic support to the Purkinje neurons during development. Overall, our results demonstrate that late onset neurodegeneration may have its earliest underpinnings in non-cell autonomous inhibition of Purkinje neurons by GABAergic interneurons and astrocytes. These results pave a way to test the novel therapeutic implications in SCA1 by reinstating aberrant cerebellar stem cell fate and function.

C6 G-B

ENDOCYTIC VESICLE RUPTURE BY AMYLOID PROTEINS PROMOTES INCLUSION FORMATION THROUGH DISRUPTION OF THE AUTOPHAGY-LYSOSOME DEGRADATION PATHWAY

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Numerous pathological amyloid proteins spread from cell to cell during neurodegenerative disease, facilitating the propagation of cellular pathology and disease progression. Understanding the mechanism by which disease-associated amyloid protein assemblies enter target cells and induce cellular dysfunction is therefore key to understanding the

progressive nature of such neurodegenerative diseases. In this study, we utilized an imaging-based assay to monitor the ability of disease-associated amyloid assemblies to induce the rupture of intracellular vesicles following endocytosis, as well as to elucidate the cellular consequences of this damaging mechanism of invasion. We observe that the ability to induce vesicle rupture is a conserved feature of fibrillar amyloid assemblies of α-synuclein (α-syn), tau, and huntingtin Exon1 with pathologic polyglutamine repeats. Immunostaining analysis revealed that vesicles ruptured by α-syn are lysosomes, but the observation that many ruptured vesicles are positive for the autophagic marker LC3 and re-establish a low intravesicular pH suggests that ruptured lysosomes become targeted to the autophagic degradation pathway. We further note a pathological enlargement of low pH compartments containing α-syn and damaged vesicular debris, which may be due to a loss of proteolytic enzymes following lysosomal rupture and a resulting inability of autophagy to degrade the cellular burden of misfolded proteins and damaged vesicles. We observe that vesicles ruptured by α-syn can accumulate and fuse into large, intracellular structures resembling Lewy bodies in vitro, and show that the same markers of vesicle rupture surround Lewy bodies in brain sections from PD patients. These data underscore the importance of this conserved endocytic vesicle rupture event as a damaging mechanism of cellular invasion by amyloid assemblies of multiple neurodegenerative disease-associated proteins, and suggest that proteinaceous inclusions such as Lewy bodies form as a consequence of continued fusion of autophagic vesicles in cells unable to degrade ruptured vesicles and their amyloid contents.

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C7 PD-B

EMERGING ROLE OF ONE-CARBON METABOLISM IN THE EPIGENETIC DOWNREGULATION OF $GABA_A$ RECEPTOR DELTA SUBUNIT IN THE CEREBELLUM OF ALCOHOLIC SUBJECTS

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Regulation of gene expression within the CNS is a dynamically controlled mechanism critical for brain function that involves epigenetic modifications such as DNA methylation. The addition of a methyl group to cytosines is catalyzed by DNA-methyltransferases (DNMTs). This reaction is dependent on levels of S-adenosylmethionine (SAM), which is synthesized in the brain by methionine-adenosyl-transferase (MAT) 2a/b, part of the one-carbon metabolism pathway. This pathway is sensitive to chronic ethanol exposure leading to aberrant levels of DNA methylation in the liver. To the best of our knowledge, there are no detailed studies showing a link between methylation and SAM levels or levels of transmethylation enzymes and their consequences on the epigenome of the cerebellum of alcoholic subjects. The cerebellum exerts a strong control on posture, motor balance and cognitive function. Alcohol exposure inhibits cerebellar function by increasing GABA release from Golgi cells and potentiating extrasynaptic (α_6/δ) $GABA_A$ receptor function on granule cells. To investigate the effect of chronic alcohol drinking on the dynamic state of DNA methylation in the cerebellum, we used a cohort (New South Wales Tissue Resource Center) of post-mortem brains from 25 controls and 25 uncomplicated chronic alcoholics (35±1.8 drinking years; 189.5±30g EtOH/day). While the levels of various DNMTs (mRNA and protein) were similar in controls and alcoholics, we found increased expression of one-carbon metabolism enzymes, including MAT2b that positively correlated with drinking behavior. These changes were associated with an increased SAM/S-adenosyl-homocysteine (SAH) ratio, which may facilitate transmethylation reactions and influence DNA methylation patterns of GABA neurotransmission components. We found a reduced expression of the $GABA_A$ receptor δ subunit, which correlated with drinking behavior, while no changes were observed in the other synaptic plasticity genes investigated, including the $GABA_A$ receptor α_1 and α_6 subunits. Accordingly, methylation levels were higher at the $GABA_A$ receptor δ subunit promoter regions (from -633 to -414bp and -346 to -153bp) in alcoholic patients as compared with controls. These data provide novel evidence for a central role of transmethylation reactions to produce neuroadaptive changes in GABA neurotransmitter function that may occur in the alcoholic brain particularly in the cerebellum.

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C8

ANALYSIS OF THE SWI1 PRION DOMAIN VIA MUTAGENESIS

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Prions are proteins capable of adopting altered, transmissible conformations implicated in numerous diseases. The namesake prion protein typically adopts a normal fold, PrP^{C} but may also adopt a toxic alternative conformation PrP^{Sc} that leads to neurodegenerative diseases termed transmissible spongiform encephalopathies. Other illnesses including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis have proteins implicated to act as prions. Prions have been identified in mammals as well as plants, *Drosophila*, *Aplysia*, and fungi such as the budding yeast, *Saccharomyces cerevisiae*. In fact, *S. cerevisiae* has at least nine identified yeast prions – endogenous proteins that can adopt altered conformations, aggregate, and act as epigenetic elements. Many yeast prion proteins (and some human prion-like proteins) are highly enriched in glutamine (Q) and/or asparagine (N) residues; however, the effects of various amino-acids on prion characteristics are only partially understood. Our lab discovered the yeast prion [*SWI*$^{+}$] whose protein determinant, Swi1 consists of three domains – an N-terminal N-rich domain, a Q-rich domain, and a functional C-terminal domain. We previously demonstrated that the first 38 amino acids of Swi1 are necessary and sufficient for prionization and maintenance and propagation of [*SWI*$^{+}$]. This prion domain (PrD) of Swi1 remains the smallest PrD described and uniquely contains a high number of N residues without any Q residues. Within this PrD, we have conducted site-directed mutagenesis to elucidate how the various amino-acid residues contribute towards the prion properties of the Swi1 PrD and characteristics of [*SWI*$^{+}$]. Using the robust yeast system, we have analyzed the ability for these mutants to aggregate with wild-type Swi1 as well as maintain [*SWI*$^{+}$] in the absence of full-length Swi1. Initial results suggest differing contributions to aggregation of the two N-terminal phenylalanine residues as well as lack of importance for the lone C-terminal threonine residues. Additional analysis via a saturated random mutagenesis approach will provide further unbiased insight. The combined efforts of these experiments shall increase understanding of what makes a protein capable of forming, maintaining, and propagating a prion.

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C9 PD-B

CAMKIIα CONTROLS THE BIOGENESIS OF LET-7 MICRORNAS IN OPIOID TOLERANCE

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Emerging evidence suggests that microRNAs (miRNAs) – mediated cellular adaptations are critical for drug addiction. We previously reported that let-7 family miRNAs contribute to the development of opioid tolerance by targeting the μ opioid receptor. Chronic morphine treatment induced a marked increase of let-7 expression, which functionally correlated with the development of opioid tolerance.

The aim of this study was to understand the mechanisms how let-7 is regulated by opioids. We first determined the transcription status of let-7 and found that the expression of primary let-7 (pri-let-7) remained unchanged in SH-SY5Y cells that were treated with morphine (1 μM, for 48 h). In agreement with the *in vitro* observation, morphine pellet implantation (one 75 mg morphine pellet/mouse, *s.c.*) did not alter the level of pri-let-7 in mouse brain front cortex region. These findings suggested that the robust elevation of let-7 occurred at the post-transcriptional level. Of interest, in the presence of KN93, inhibitor of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), chronic morphine treatment failed to generate let-7 up-regulation in SH-SY5Y cells. We further determined whether inactivation of CaMKIIα by T286A point mutation would affect let-7 expression and opioid tolerance. Indeed, antinociceptive tolerance was absent in $CaMKII\alpha^{T286A}$ mutant mice. Meanwhile, the level of let-7 in $CaMKII\alpha^{T286A}$ mutant mice was much lower than that in wild-type mice, and was resistant to chronic morphine stimulation. Taken together, these data suggested that the activity of CaMKIIα was required for the biogenesis of let-7 in opioid tolerance.

C10

UNDERSTANDING THE LINK BETWEEN CORTICAL INJURY AND ALS

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Traumatic brain injury (TBI) is linked to the development of neurodegenerative diseases in which motor neuron circuitry is impaired. In particular, professional athletes with concussion history and military veterans are in greater risk of developing motor neuron diseases. Corticospinal motor neurons (CSMN) are located in the cerebral cortex and therefore more susceptible to TBI. CSMN are a key component of the motor neuron circuitry and play a role in ALS pathology. CSMN can be studied using UCHL1-eGFP (U-eGFP) transgenic line, in

which CSMN are genetically labeled with eGFP. By crossing U-eGFP mice with ALS mouse models a distinct vacuolation pattern in the CSMN apical dendrite is observed. In addition, the immune response also plays a role in CSMN degeneration. Microglia activation correlates with CSMN deficits in patients and is present in the vicinity of diseased CSMN. Among the neuroinflammatory components observed, MCP1/CCR2 is a chemokine/receptor system critically involved in both in ALS and TBI. In an effort to study the link between TBI and neurodegenerative diseases we developed a mild cortical injury model to study its effect on CSMN degeneration and neuroinflammation. We assessed and visualized CSMN degeneration and microglia/infiltrating monocyte presence after mild cortical injury in U-eGFP and MCP-CCR2 reporter mice. A mild cortical injury using 0.3mm depth at a speed of 3m/s produced a small contusion cavity after 72 hrs. in both U-eGFP and MCP1-CCR2 mice. Our results show CSMN with vacuolated apical dendrites underneath the contusion cavity and decreased numbers in layer V of the motor cortex. CSMN degeneration and death was confirmed at 10 days and evidenced by TUNEL staining. On the contrary, CSMN in the contralateral side of the cortex or sham controls do not present a vacuolated pattern. Microgliosis and astrogliosis is increased after 72hrs. throughout the motor cortex and MCP1+ and CCR2+ cells are identified as microglia and infiltrating monocytes, respectively. The mechanisms that lead to CSMN degeneration and neuroinflammation are not completely understood. Our preliminary results demonstrate the possible activation of MAPK signaling pathways after mild cortical injury, offering a mechanistic target. Our studies allow for the development of a mild cortical injury model in which CSMN have a common pattern of degeneration previously observed in ALS mouse models. Moreover, the fact that immune response is increasingly present after TBI and during ALS pathology opens a venue for exploration to understand the basis of common neuroinflammation mechanisms in both contexts. This study is funded by ALS Association (JHJ) and Les Turner and Wenske Foundation (PHO).

ALS Association, Les Turner ALS Foundation

C11 UG-B

STRUCTURAL CHARACTERIZATION OF ABOS

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Alzheimer's disease (AD) is an irreversible, progressive brain disorder characterized by the loss of cognitive functioning. AD is ranked as the sixth leading cause of death, affecting more than 5 million Americans. Of the top ten leading causes of death, it is the only one that cannot be cured, prevented or slowed down. In the United States, the cost of AD is estimated at 180 billion per year and affects almost fifty percent of the population over the age of 85, making it the third costliest disease. The search for toxins implicated in AD pathogenesis has shifted from the amyloid plaque hypothesis, which attributes nerve cell death to the accumulation of amyloid plaques, to the oligomer hypothesis, characterized by the buildup of small soluble Aβ oligomers. Aβ oligomers (AβOs) have been found to inhibit long-term potentiation, cause neural degeneration, and are believed to act in AD pathology by targeting synapses and disrupting synaptic communication. AβOs are also better correlated with AD onset than plaques and neurofibrillary tangles. Despite advances in the field identifying amyloid beta oligomers as critical in AD pathogenesis, the exact structure of toxic oligomers is unknown, and a range of differentially sized species have been identified as critical for AD pathogenesis in the literature. For example, some groups have identified dimers and tetramers as the most critical species whereas others have implicated higher order oligomers such as dodecamers. This uncertainty is partially due to insufficient methods to measure oligomer size, which is usually performed by Western Blot and SDS-PAGE. My project aims to structurally characterize Aβ oligomers by Size Exclusion Chromatography (SEC)—a chromatographic method for separating molecules by size—and determine the immunoreactivity of these fractionated oligomers to a set of AβO-specific antibodies, shown in the literature to target different AβO species, using an enzyme-linked immunosorbent assay (ELISA) assay. Based on current published and unpublished data, we hypothesize that oligomers with a critical role in AD pathogenesis will be greater than 50 kDa.

C12

EFFECTS OF CHRONIC PRAMIPEXOLE ON AMPA RECEPTOR TRAFFICKING AND AKT/GSK-3B SIGNALING IN A RAT MODEL OF PARKINSON'S DISEASE

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The D3 receptor (D3R)-preferring agonist pramipexole (PPX) is an effective treatment for motor symptoms in Parkinson's disease (PD). However, behavioral addictions associated with limbic systems emerge following chronic PPX administration. The D3R is involved in the addiction process, and one D3R-mediated signaling cascade involves the Akt/GSK-3β pathway. We previously demonstrated in limbic brain regions that acute PPX dephosphorylated Akt, which prevented phosphorylation of constitutively active GSK-3β. Un-phosphorylated GSK-3β strengthens glutamatergic synapses *via* insertion of AMPA receptors (AMPAR) in neuronal membranes; a phenomenon associated with addiction. However, the effects of chronic PPX on this pathway remain unknown. Because PPX is often used as a therapeutic in early-stage PD, clarification of these neuronal processes is highly relevant to clinicians. Here, we tested the

hypothesis that chronic PPX can increase AMPAR surface expression in limbic brain regions of PD-like rats. The neurotoxin 6OHDA was injected bilaterally into the dorsolateral striatum of rats to model PD (4µg/2µl); sham-lesioned controls were injected with ascorbic acid vehicle (2µl). Twenty-one days post-lesion, rats were subcutaneously implanted with osmotic minipumps containing vehicle or PPX (1.2 mg/kg/day). The forelimb akinesia task was used to confirm PD-like motor deficits and PPX efficacy in lesioned rats. After 14 days of PPX treatment, brain tissue was harvested. Modified Western blot protocols determined surface and intracellular levels of GluA1 (an AMPAR subunit), as well as ratios of pAkt/Akt and pGSK3β/GSK3β. In the nucleus accumbens and ventral pallidum, there was no effect of chronic PPX on pAkt/Akt or pGSK/GSK-3β. In the medial prefrontal cortex, the ratios of pAkt/Akt and pGSK-3β/GSK-3β were significantly increased in PPX-treated, PD-like rats (ANOVA; p=0.0161 and p=0.0119, respectively), but surface/intracellular GluA1 was unchanged. Thus, while acute PPX promoted AMPAR trafficking, AMPAR surface expression appeared to normalize with chronic PPX. In addition to AMPAR, adaptation of excitatory synapses can be regulated by GSK-3β-linked changes in NMDA receptors. Thus, it is possible that changes in NMDA receptors may contribute to PPX-induced behavioral addictions. Future studies will make this determination.

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C13 G-B

DEFINING SYNAPTIC PATHOLOGY OF INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

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Infantile neuronal ceroid lipofuscinosis (CLN1) is a pediatric neurodegenerative, lysosomal storage disorder. CLN1 causes visual failure, seizures, and cognitive impairment, resulting in developmental regression and death by age 10. CLN1 is an autosomal recessive disorder caused by mutations in palmitoyl protein thioesterase 1 (PPT1), a depalmitoylating enzyme. Consequently, protein metabolism is dysregulated, leading to the accumulation of proteolipid material, lipofuscin. Importantly, lipofuscin is the cardinal neuropathological finding of all CLNs, each of which leads to cognitive decline and death, and is identified in many prominent neurodegenerative disorders, including Alzheimer's disease. Under a fluorescent microscope, these proteolipid materials are readily visible as autofluorescent lipopigments (ALs). Deposition of these pathological aggregates correlates with progression of CLN symptoms. While protein palmitoylation directly modulates the localization and activity of canonical synaptic proteins, it remains unclear whether AL accumulation correlates with impaired synaptic functions in CLN1. Among the first clinical symptoms of CLN1 is progressive visual failure, occurring between 5-12 months of age. This visual failure is associated with loss of visual evoked potential, an indication of neuronal dysfunction. Therefore, we study abnormal synapse formation in the visual cortex (VC) of PPT1-knockout (KO) mice. While previous studies have documented AL deposition in adult PPT1-KO mice (≥P60), we demonstrate the accumulation of AL immediately after eye opening at post-natal day (P) 14 in the PPT1-KO VC. Remarkably, the AL accumulation started in layer IV of the VC, the termination site of thalamocortical projections, and plateaued by P42. Next, we investigated AL accumulation in dissociated primary neuronal cultures and found: 1) ALs accumulate in PPT1-KO cells immediately following the formation of mature synapses, and 2) that increasing neuronal excitability increases AL in PPT1-KO cells. Lastly, in immunoblotting analyses of VC tissues, N-methyl-D-aspartate (NMDA) receptor subunit composition is altered, exhibiting a higher GluN2B/2A ratio, which suggests increased excitability and higher susceptibility to apoptosis. Together, these results suggest that AL accumulation is activity-dependent. In the future, we will examine if correcting abnormal glutamate receptor function will mitigate synaptic dysfunction and cell death in CLN1. Importantly, novel therapeutic strategies for this monogenic disorder will have a broader implication for adult-onset neurodegenerative disorders.

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C14 G-A

EFFECTS OF ANTERIOR CINGULATE CORTEX STIMULATION ON BASOLATERAL AMYGDALA INPUTS INTO NUCLEUS ACCUMBENS

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Bipolar disorder (BD) is a characterized by recurring, anti-phasic episodes of mania and depression. While the exact cause of BD is unclear, human diffusion tensor imaging (DTI) scans have shown greater white matter connectivity between basolateral amygdala (BLA) and nucleus accumbens (NAcc) in BD patients. These regions play a role in the production of mood and emotion. Understanding the neurobiology of BLA to NAcc projections, and the factors that modulate their activity, may provide information on changes that can lead to abnormal mood regulation. Different patterns of neural activation within the anterior cingulate cortex (ACC) shift preference for different facial expressions, indicating the ACC as a key player in switching between positive and negative moods. In addition, this activity of ACC is abnormal in BD. We hypothesize that different types of ACC activity may favor positive or negative moods by influencing the BLA to NAcc projection. In this current study, in vivo single-unit extracellular

electrophysiology is utilized to determine if ACC gates the BLA-NAcc interaction. It is hypothesized that different stimulation patterns of ACC, single or train, alter projection properties of NAcc respond to BLA input. Data illustrates no observable change in spontaneous NAcc activity that is altered by single-pulse ACC stimulation. Train stimulation of ACC did not significantly impact response probability of BLA-NAcc projections; however, it may dampen the influence of BLA on NAcc. In addition, a trend of decreased variability in latency is observed in BLA-NAcc responses post-ACC train stimulation. Together these data illustrate that the activity of ACC may play a role in the neurocircuitry that drives mood and should be further investigated. This study is funded by a National Institute Health grant (RO1 MK084970).

C15 G-B

PERIPHERAL INFLAMMATION, *APOE4*, AND AMYLOID-B SYNERGISTICALLY INTERACT TO COMPROMISE CEREBROVASCULAR INTEGRITY LEADING TO COGNITIVE DECLINE.

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Cerebrovascular (CV) dysfunction is being newly revisited as a critical pathological process in Alzheimer's disease (AD). As such, it is essential that the roles of AD risk factors in CV dysfunction are unraveled. *APOE4*, Aβ, and peripheral inflammation have all demonstrated an independent ability to compromise CV function. However, their synergistic interactions remain unknown. Therefore, the principal goal of this study was to delineate the interactive effects of *APOE4*, Aβ, and peripheral inflammation on CV and cognitive function *in vivo*. EFAD mice, a well-characterized mouse model expressing human *APOE3* (E3FAD) or *APOE4* (E4FAD) that overproduces Aβ42 via the 5 Familial AD (5xFAD) mutations, were utilized in this study. Comparing EFAD carriers [5xFAD+/-/APOE+/+ (EFAD+)] and non-carriers [5xFAD-/-/APOE+/+ (EFAD-)] enabled us to parse out the effects of peripheral inflammation both with and without the overproduction of Aβ. EFAD mice were treated with a low dose of lipopolysaccharide (LPS; 0.5 mg/kg/wk i.p.) from 4 to 6 months of age to mimic peripheral inflammation associated with peripheral AD risk factors (e.g. diabetes, hypertension, atherosclerosis, etc.). LPS-induced peripheral inflammation resulted in cognitive deficits, lower post-synaptic protein levels, and increased Aβ42 levels in 6-month-old male E4FAD+ mice. Notably, we observed CV deficits in LPS-challenged E4FAD+ mice, including higher leakiness, lower vessel coverage, and higher CAA-like Aβ deposition. Collectively, our data imply that *APOE4*, Aβ, and peripheral inflammation can synergistically induce CV deficits and cognitive dysfunction.

C16

TAU PET, AMYLOID PET, AND STRUCTURAL IMAGING IN PRIMARY PROGRESSIVE APHASIA

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Primary progressive aphasia (PPA) is a clinical dementia syndrome caused by neurodegenerative disease and characterized by asymmetric atrophy of the language-dominant (usually left) hemisphere. The most common neuropathologies reported for PPA are Alzheimer's disease (AD; ~40%), frontotemporal lobar degeneration with tauopathy (~30%), or with TDP-43 proteinopathy (~30%). Recent innovations in PET technology have allowed quantitation and spatial localization of amyloid and tau. These technologies are particularly promising in diseases such as PPA where there is no one-to-one relationship between clinical symptoms and underlying pathology. We used the tau ligand [^{18}F] AV-1451 to scan three PPA participants whom also underwent [^{18}F] AV-45 amyloid PET and structural MRI (sMRI). Two participants were diagnosed with the agrammatic subtype of PPA (PPA-G) and the other was diagnosed with the logopenic subtype (PPA-L). The sMRI was processed with FreeSurfer to derive measures of cortical atrophy. Amyloid was quantified using a previously described FreeSurfer method (Landau et al. J Nucl Med 2013). Two participants (1 PPA-L and 1 PPA-G) showed elevated amyloid binding (Aβ+; using the 1.11 whole cerebellar SUVR threshold), consistent with AD pathology. Both of these Aβ+ patients had elevated tau PET uptake patterns that mirrored the asymmetric left hemisphere atrophy, presumably reflecting the distribution of the neurofibrillary degeneration underlying the cortical atrophy. The amyloid-negative PPA-G patient had asymmetric left cortical atrophy and low tau PET binding. Longitudinal studies of neuropsychological performance, MR imaging, amyloid PET, and tau PET are needed in PPA to determine the temporal relationship among these measures and the usefulness of tau PET as biomarker for tracking the progression of disease.

T32 AG20506

C17 UG-A

EFFECTS OF TARGET ASO THERAPY ON MARKERS OF CHOLINERGIC FUNCTION ON USHER SYNDROME MICE

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Usher syndrome is an autosomal recessive genetic disorder that is associated with impaired visual, auditory and vestibular function. Previous studies have suggested that the vestibular system is important for self-movement cue processing and has an influence on hippocampal formation cholinergic function. Recent work has demonstrated that antisense oligonucleotide (ASO) therapy can attenuate behavioral and electrophysiological deficits associated with a mouse model of Usher syndrome; however, it remains to be determined whether Usher syndrome and ASO therapy influence hippocampal formation function. The current study investigates the relationship between hippocampal cholinergic function and ASO therapy in a mouse model of Usher syndrome. Heterozygous and mutant Usher mice received intraperitoneal injections of ASO or control treatment at postnatal day five. All mice were then tested in an exploration task at two and six months of age. Subsequent to the six month testing all mice were sacrificed and coronal sections at the level of the dorsal hippocampus were stained for acetylcholinesterase (AChE) a marker of cholinergic function. Optical densities were calculated for several hippocampal and cortical areas. No differences in AChE optical densities were observed between Usher and control mice. In contrast, significant increases in AChE optical density were observed in the several hippocampal regions in ASO treated Usher mice relative to the other groups. These results demonstrate that ASO therapy influences hippocampal function in an Usher mouse model and has implications for understanding neuropathology associated with genetic disorders.

C18

PERIPHERAL IMMUNE CHALLENGE AFFECTS IN VIVO ELECTROPHYSIOLOGICAL PROPERTIES OF BASOLATERAL AMYGDALA NEURONS

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Peripheral inflammation and infection are associated with changes in mood or affect, and are characterized by a group of physical manifestations including lethargy, malaise, anhedonia, listlessness, decreased appetite and fever. These changes in the neuro-physiologic and behavioral aspects seen with peripheral inflammation are known to be mediated at the molecular level by the pro-inflammatory cytokines like interleukin (IL)-1β, IL-6, TNF-α etc. The basolateral amygdala (BLA) is a key region involved in emotion and affects behavioral changes. However, it is unknown how the peripheral inflammatory state affects the BLA physiology at the level of the neuronal functions. In the present study, adult male Sprague-Dawley rats treated with intraperitoneal (i.p.) IL-1β were tested using behavioral and electrophysiological experiments in order to explore how peripheral inflammatory state affects BLA neuronal activity. Peripheral immune activation reduced locomotion in open-field test, reduced social interaction and also reduced home-cage mobility, consistent with sickness behavior caused by immune activation. Using *in vivo* single-unit extracellular electrophysiological recordings, spontaneous BLA neuronal firing rate was measured after IL-1β i.p. injection. Evoked local field potential (eLFP) in the BLA after stimulation of the medial prefrontal cortex was also measured. There was a significant decrease in the firing rate over time as well as a time-dependent change in the eLFP in IL-1β group compared to control. The findings suggest a significant link between the change in behavior and the BLA neuronal firing which might help us to understand the neuronal basis underlying the depressive-like behavior seen during infection and inflammation. The study was supported by NIH Grants MH084970 and MH109484 to JAR. SM received the GIAR award from the National Academy of Sciences, administered by the Sigma Xi, The Scientific Research Society (Grant ID G2016100191685784).
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C19 G-B

IMPLICATIONS FOR LRRK2 AND AUXILIN IN PARKINSON'S DISEASE PATHOGENESIS

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Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the dramatic loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. The majority of patient cases described arise sporadically. However, several monogenic forms of the disease have been identified within the past two decades. Through functional studies, genetic implications for PD pathogenesis have been linked to lysosomal, mitochondrial, and more recently synaptic dysfunction. Mutations in clathrin-mediated synaptic vesicle recycling genes leading to early-onset Parkinsonism, such as the recently identified synaptic PD gene DNAJC6 (auxilin), are rare. However, there is growing interest to study the regulation of synaptic function by more common PD genes such as LRRK2, the most commonly mutated gene in PD. In this study, we investigate the cellular consequences resulting from LRRK2 regulation of auxilin in clathrin-mediated synaptic vesicle recycling using PD patient-derived human DA induced pluripotent stem cells (iPSCs). Our results show that LRRK2 is able to interact with and phosphorylate auxilin at novel sites. As mutations in LRRK2

have been shown to increase its kinase activity, our data further suggests that misregulated phosphorylation of auxilin by LRRK2 results in deficient synaptic vesicle recycling. Taken together, our results propose a new role for LRRK2 at the synapse through modulation of auxilin and a potential mechanism by which dopaminergic neurodegeneration is mediated by synaptic dysfunction.

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C20 G-A

HIGH DENSITIES OF ACTIVATED MICROGLIA ARE PRESENT IN CORTICAL WHITE MATTER AND CORRESPOND TO REGIONS OF GREATEST ATROPHY IN PRIMARY PROGRESSIVE APHASIA

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Background: While deposition of abnormal proteins and other pathology in cortical gray matter in neurodegenerative disorders has received extensive experimental attention, little is known about the extent and nature of white matter abnormalities. Primary progressive aphasia (PPA) is a clinical dementia syndrome characterized by dissolution of language function and is associated with Alzheimer disease (AD) or frontotemporal lobar degeneration pathology. We have shown extensive activation of microglia in gray matter in PPA brains regardless of the underlying molecular pathology. Here we investigated activation of microglia in cortical white matter in PPA brains with AD or TDP-43 pathology, and its relationship with cortical atrophy.

Methods: Brains of PPA-AD (n=2) and PPA-TDP (n=2) participants were cut into whole hemisphere sections, and a 1/24 series of sections were processed with immunohistochemical or histopathological procedures to visualize plaques, tangles, TDP-43 inclusions, and HLA-DR-positive activated microglia. Atrophy was quantified using FreeSurfer software in three participants with structural MRI scans collected close to death, and assessed in one participant using clinical MRI scans. Paraffin-embedded sections from additional PPA-TDP participants with GRN mutations were also examined (n=4).

Results: Four cases with available MRI displayed pronounced asymmetric atrophy restricted to the perisylvian language network. Whole hemispheric sections displayed substantial asymmetric densities of activated microglia throughout the white matter that surpassed the densities in adjacent gray matter, and allowed demarcation of the white/gray matter junction with the naked eye. Examination of paraffin-embedded sections confirmed presence of high densities of activated microglia in cortical white matter. The highest densities of activated microglia in white matter occurred asymmetrically in cortical areas affiliated with language function, and closely matched patterns of gray matter atrophy detected by MRI scans in each case.

Conclusions: Microglia display a pattern of activation in PPA characterized by substantial accumulation in cortical white matter with highest densities at sites of greatest atrophy. While the extent of activation of microglia in white matter in other neurodegenerative disorders is incompletely understood, our findings point to the possibility that activated microglia play an active role in neurodegenerative mechanisms in the white matter, and correspond to *in vivo* cortical gray matter atrophy.

C21 UG-B

UNDERSTANDING THE NATURE OF TOXICITY OF PARKINSON'S DISEASE ASSOCIATED ALPHA-SYNUCLEIN FAMILIAL MUTANTS H50Q, G51D, AND A53E WITH YEAST MODELS

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Parkinson's disease (PD) is associated with the aggregation and misfolding of alpha-synuclein in midbrain dopaminergic neurons. The gene for alpha-synuclein has six known mutations that directly cause familial forms of PD. The pathological determinants of three of these mutants (A30P, E46K, and A53T) are well characterized in diverse model systems and they that reveal that each mutant affects cellular toxicity in distinctive ways. The three more recently discovered familial mutants (H50Q, G51D, and A53E) are not extensively studied. We expressed H50Q, G51D, and A53E mutants in budding and fission yeasts model systems and hypothesized that each would generate toxicity by altering their membrane association and aggregation properties, and by disrupting cellular pathways including nitrative stress responses and endocytosis, but each would do so in distinctive ways. First, we found that the H50Q and A53E mutants were toxic to yeast, and bound membranes and aggregated within yeast, while G51D was cytoplasmically diffuse and nontoxic. Secondly, and surprisingly, we found that G51D mutant dominated over H50Q and A53E when these mutants were combined in double/triple mutants. Thirdly, we asked whether the loss of the original amino acid or the gain of the new amino acid in each new familial mutant is responsible for disease. We created four substitution mutations for H50Q, G51D, and A53E in both yeasts models corresponding to the four functional classes of amino acids. We found that H50D was cytoplasmically diffuse and nontoxic, G51A bound membranes and aggregated like WT, G51E was cytoplasmically diffuse and nontoxic like G51D, and A53R

was cytoplasmically diffuse and nontoxic, suggesting both the loss of the original amino acid and the gain of the new amino acid are key. Finally, we are currently characterizing these familial mutants in yeast strains altered for endocytosis, nitrative stress, and sumoylation. Collectively, this work adds insight into the pathogenicity of different familial PD mutants of alpha-synuclein.

Parkinson's Disease Foundation

C22 G-A

POTENTIAL PRECLINICAL GAIT AND BALANCE MARKERS FOR DEVELOPING FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)

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BACKGROUND: Carriers of a premutation size 55-200 CGG repeat expansion in the *fragile X mental retardation 1* (*FMR1*) gene are at risk for developing FXTAS, a disorder marked by ataxia, balance deficits, and cognitive impairment. Risk factors for FXTAS are not completely understood and preclinical detection methods are needed. Therefore, we conducted gait and balance "stress" tests using dual-task (DT) cognitive interference, which we hypothesized would reveal early motor impairments in asymptomatic *FMR1* premutation (PM) carriers.

METHODS: PM carriers without FXTAS (n=14; 62.4 ± 9.4 yrs), PM carriers with FXTAS (n=9; 67.1 ± 10.1 yrs) and controls (n=22; 60.0 ± 10.8 yrs) underwent gait/balance testing using a 2 minute walk test and postural control test (i-SWAY) with an inertial sensor system (APDM; Oregon). Gait analysis was performed at a self-selected and fast pace and a DT condition. Stance, vision, surface stability, and cognitive demand were varied to modulate postural challenge on the i-SWAY. DT conditions included a verbal fluency task.

RESULTS: During fast paced gait, PM carriers without FXTAS demonstrated reduced total distance traveled ($p = 0.03$) and cadence ($p = 0.04$), and longer turn step time ($p = 0.046$). They also had slower stride velocities during DT walking ($p < 0.0001$) and their DT cost for total distance walked was higher than controls ($p < 0.05$). PM carriers with and without FXTAS exhibited worse balance on the i-SWAY than controls, with more difficult conditions yielding the most highly significant results ($p = 0.04$ to < 0.0001).

CONCLUSIONS: PM carriers demonstrate worse gait at fast speeds and under DT conditions and worse balance under challenging conditions. This suggests that these quantitative measures may be sensitive to produce at risk markers for FXTAS. Identification of preclinical motor signs in FXTAS will provide an early intervention window for preventative rehabilitation strategies and disease modifying drugs.

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C23

IDENTIFYING SMALL MOLECULES THAT ANTAGONIZE PRIONS AND ALLEVIATE AMYLOID TOXICITY

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Prions, proteinaceous infectious particles, are misfolded proteins that can self-propagate by recruiting their isomers to adopt their misfolded conformations. Prions can cause neurodegenerative disorders called transmissible spongiform encephalopathies. It is believed that a similar protein-only mechanism also underlies several other mammalian misfolding diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease. These diseases are characterized by the accumulation of aggregates with altered amyloid conformations, and they are incurable. Thus, there is an urgent need for the development of new therapeutics. *Saccharomyces cerevisiae*, budding yeast, is a good model system for this type of research as it contains several amyloid-based prion elements. In addition, several neurodegenerative disease models have been established in yeast for α-synuclein, FUS (fused in sarcoma), and Htt103Q (a mutant Huntingtin protein fragment with an expanded glutamine tract). Using these *S. cerevisiae* disease models, we tested 13 compounds, which were previously shown to eliminate the yeast prion [*SWI*$^+$] in a high-throughput screen, for their antagonistic activities in the yeast disease models, as well as other yeast prions including [*PSI*$^+$], [URE3], and [*MOT3*$^+$]. We specifically measured if these small molecule compounds could suppress the toxicity caused by aggregation of the disease-associated proteins in a cell growth assay. For yeast prions, a colony color change assay combined with fluorescence microscopy was used to determine prion curing. Preliminary results show that some compounds work to eliminate the [*PSI*$^+$] and [*MOT3*$^+$] prions, but we have not found clear results for their effect on yeast models of neurodegenerative diseases. The identification of compounds that reduce the toxicity of neurodegenerative proteins and eliminate yeast prions will aid our understanding of the mechanisms that underlie protein misfolding. These compounds may also have potential as probes for prion research or as therapeutic drugs for neurodegenerative diseases. This study is funded through a grant from the U.S. National Institutes of Health (R01GM110045), Northwestern University Interdepartmental Neuroscience, and The Graduate School at Northwestern University.

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C24 PD-A

HDAC6 INHIBITORS SHOW A CELLULAR ANTIDEPRESSANT SIGNATURE, TRANSLOCATING ACTIVATED Gαs FROM LIPID-RAFTS

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Presently available antidepressant therapies for treating major depressive disorder meet with variable therapeutic success. Histone deacetylase-6 (HDAC-6) enzymes involved in deacetylation of α-tubulin are overexpressed in mood disorders. HDAC6 knockout mice mimic traditional antidepressant treatments. Nonetheless, a possible role for HDAC6 inhibitors in the treatment of depression remains elusive. Previously we have shown that sustained treatment of rats or glioma cells with several classes of antidepressants translocates $G\alpha_s$ from lipid rafts toward increased association with adenylyl cyclase in a non-raft plasma membrane domain. Concomitant with this is a sustained increase in cAMP production. While $G\alpha_s$ interacts directly with tubulin to modify microtubule dynamics, tubulin also acts as an anchor for $G\alpha_s$ in lipid rafts. Since HDAC-6 inhibitors potentiate α-tubulin acetylation, we hypothesize that acetylation of α-tubulin disrupts tubulin-$G\alpha_s$ anchoring, rendering $G\alpha_s$ free to activate AC. To test this, C6 Glioma (C6) cells were treated with HDAC-6 inhibitor, tubastatin-A. The acetylation status of α-tubulin and localization of $G\alpha_s$ subunit in/out of lipid-raft membrane domains were studied. Chronic treatment with tubastatin-A not only increased acetylation of α-tubulin but also moved $G\alpha_s$ out of lipid-rafts, without changing total $G\alpha_s$. However, traditional antidepressants, escitalopram (SSRI) and imipramine (TCA), as shown in our previous studies only showed $G\alpha_s$ translocation out of rafts and no changes in acetylation status of α-tubulin. Fluorescence Recovery After Photobleaching (FRAP) on C6 cells stably expressing GFP-$G\alpha_s$, was conducted and cells pretreated with tubastatin-A showed an “antidepressant signature” similar to that of with escitalopram. Finally, two indicators of downstream cAMP signaling were examined. cAMP response element binding protein phosphorylation (CREB) and expression of brain derived neurotrophic factor (BDNF) were both elevated by tubastatin-A, similar to that seen following treatment with SSRI and TCA. These findings suggest HDAC6 inhibitors show a cellular profile resembling antidepressants. Therefore, compounds that decrease tubulin-$G\alpha_s$ complexes by increasing acetylation of α-tubulin may show promise for antidepressant action.

NIH, VA, American Heart Association

C25UG-B

STRIATAL TRANSCRIPTOME OF MICE SELECTIVELY BRED FOR INCREASED PHYSICAL ACTIVITY PROVIDES NOVEL INSIGHTS INTO THE MOLECULAR ETIOLOGY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Despite the prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) in our society, and our readiness to dispense pharmaceutical interventions, much of the underlying etiology remains unknown. To help untangle the genetic underpinnings of ADHD we developed a High-Active mouse line through selective breeding which recapitulates some of the core features of ADHD. Control animals were randomly bred from the same starting population. In addition to hyperactivity, the High-Active mice also display motor impulsivity, which is ameliorated by therapeutic doses of amphetamine. Previous work has implicated altered striatal function in ADHD, but the molecular mechanisms are not known. The goal of this study was to identify gene expression differences in the striatum of our High-Active line as compared to the Control line. RNA was extracted and sequenced from the entire striatum of 10 High-Active and 10 Control mice. Through statistical analysis and Weighted Gene Co-Expression Network Analysis (WGCNA), we have found many significant differences between the selected and control lines. Specifically, latrophilin 3 (LPHN3), which is associated with increased susceptibility to ADHD in human GWAS studies, is significantly downregulated, and certain genes involved in Wnt signaling, such as β-catenin interacting protein (CTNNBIP1), are upregulated in our High-Active relative to Control line. WGCNA uncovered a network of correlated genes involved in monoamine signaling that are differentially expressed between the High-Active and Control lines, including increased expression of the gene for the dopamine D5 receptor (DRD5). Future work will identify potential novel medications by their ability to reverse the gene expression changes observed in the striatum between High-Active and Control lines.

C26 UG-B

INSIGHT INTO PARKINSON’S DISEASE FROM YEASTS: *GROWING EVIDENCE FOR SUMOYLATION AS A PROTECTIVE FACTOR AGAINST A-SYNUCLEIN TOXICITY*

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Parkinson’s disease (PD) is a neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy

bodies, which are mainly composed of misfolded alpha-synuclein protein. Alpha-synuclein is a highly post-translationally modified protein. While phosphorylation and nitration of alpha-synuclein is well studied as aids to PD pathology, less is known about sumoylation, which is proposed to be neuroprotective based on limited studies. The majority of sumoylation takes place on the lysine-96 and lysine-102 sites of alpha-synuclein and it increases the protein's solubility. The goal of this research was to better understand the role of sumoylation in regulating alpha-synuclein toxicity, and we performed four studies towards it. First, we evaluated the effects of blocking sumoylation on alpha-synuclein in the well-established budding and fission yeast models for PD and found that alpha-synuclein becomes more aggregated and toxic and localized less at the plasma membrane. Second, we evaluated the effects altering sumoylation pathways by using yeast strains with reduced ($ulp1^{ts}$) or excessive sumoylation ($smt3^{ts}$), and found that alpha-synuclein aggregates more with reduced sumoylation, but becomes less toxic with increased sumoylation. Third, we asked how altering phosphorylation of alpha-synuclein would alter sumoylation's protective role and found that blocking phosphorylation reduced alpha-synuclein toxicity. Finally, we evaluated whether blocking sumoylation on familial PD mutant versions of alpha-synuclein would exacerbate its toxicity, but we have found little evidence to that effect. In the future, we will conduct further studies to understand how sumoylation affects other variants and modifications of alpha-synuclein.

C27

DELTA OPIOID RECEPTOR AS A TARGET FOR MIGRAINE – CGRP CO-EXPRESSION AND INHIBITION OF MEDICATION OVERUSE HEADACHE

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Migraine is an extraordinarily common brain disorder for which therapeutic options continue to be limited. We have previously demonstrated that in preclinical animal models, delta opioid receptor agonists may be promising targets for the treatment of migraine. Delta agonists effectively inhibit cortical spreading depression, as well as nitroglycerin-induced hyperalgesia and negative affect. A better understanding of how delta opioid receptor modulates migraine mechanisms would encourage future development of this target. The neuropeptide, calcitonin gene related peptide (CGRP) plays a pivotal role in the induction and maintenance of migraine, primarily through the peripheral afferents projecting from the trigeminal ganglia. The aim of this study was to characterize the expression of delta opioid receptor in trigeminal ganglia, and on CGRP-expressing neurons specifically. To visualize the delta opioid receptor, we used knockin mice in which the endogenous receptor was replaced by a fluorescent tagged delta opioid receptor (DOR-eGFP). We observed a significant population of trigeminal ganglia which co-expressed CGRP with DOR-eGFP. This data suggests that delta agonists may produce their anti-migraine effects by directly modulating CGRP-expressing ganglia. As a further goal of this study we also tested delta agonists in a model of sumatriptan-induced medication overuse headache (MOH). In this case, C57BL6 mice were treated chronically with sumatriptan for 11 days, which produced severe mechanical hypersensitivity. The delta agonist, SNC80, inhibited this hyperalgesia, and suggests that delta agonist could be an effective strategy for managing MOH. Together, this work provides further evidence that delta opioid receptors are promising targets for migraine treatment.

C28 PD-A

THE COMBINATION OF IMMUNE TOLERANCE AND MYELIN REPAIR THERAPY TO EFFECTIVELY TARGET DISEASE COURSE AND SEVERITY IN MULTIPLE SCLEROSIS

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The CNS autoimmune disease Multiple Sclerosis (MS) is characterized by demyelination and neurodegeneration. Available FDA-approved disease modifying therapies are global immunosuppressants and have limited efficiency. We have developed a novel method of inducing immune tolerance to selectively regulate known immune responses without compromising the entire adaptive immune system. We have demonstrated an effective means of ameliorating disease in a mouse model of MS through tolerance induction in autoreactive T cells using i.v. infusion of nanoparticles coupled with or encapsulating myelin peptides (Ag-PLG) that effectively reduces disease burden in relapsing-remitting (RR-EAE) and chronic-progressive (C-EAE) mouse models of experimental autoimmune encephalomyelitis. This works to prevent disease induction, but more importantly can stop disease progression in mice treated following the initial clinical episode resulting in antigen-specific blockade of disease relapses. At present, there are no available therapies marketed for myelin repair in MS. The objectives of the study were to prevent disease progression as well as to promote CNS repair and neuroprotection. We tested an FDA approved cardiac glycoside (Na+/K+ ATPase) and uncovered it promoted an increase in the oligodendrocyte cell lineage *in vitro* and *in vivo*, in the non-T cell-mediated Cuprizone model of demyelination/remyelination promoted a quicker restoration of myelin integrity, and improved clinical score throughout the autoreactive Th1/Th17 driven C57BL/6 Chronic EAE time course. Additionally, we tested the hypothesis that to effectively target disease course and severity in MS, regulated by autoimmunity and neurodegeneration, a combination of selective immune regulation and myelin repair therapy is required. Combination therapy using Ag-PLG

immunoregulatory therapy and the cardiac glycoside completely ameliorated clinical disease severity. Findings from these studies may not only prove a rapid and safe therapeutic strategy for EAE reversal, but will pave the way for future clinical studies in MS undertaking this combinatorial therapeutic approach.

NMSS, NIH

C29 UG-A

SPATIAL EFFECTS ON AβO AMOUNTS IN C57 5XFAD MICE

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Alzheimer's disease (AD) is a progressive, neurodegenerative disease that is characterized by the decline of memory, thinking processes, and behavior. Currently, familial AD (fAD) is caused by an amyloid precursor protein (APP) mutation, which increases Aβ42 peptide production. It has been found that transgenic mice (5xFAD) that express mutant APP overproduce Aβ42 and get fAD, which makes 5xFAD mice useful to study. AD patheogenesis is also attributed to unstable small monomers known as amyloid beta oligomers (AβOs). However due to their heterogeneous biochemical and biophysical nature, lack of stability, and low abundance in human AD brain, characterizing the oligomers is difficult.

I am studying the various AβO amounts, as well as the various amyloid beta species present in 5xFAD mice of different ages. I expect that AβOs contribute to increased neuronal loss and there will be more amyloid beta oligomers present in older mice as AβOs will have accumulated over time. I have been testing this by analyzing five groups of mouse brain tissue before, during, and after the amyloid plaques and/or cognitive impairment start to occur (~3,6,9 months old). I have been measuring amyloid beta species by using NU2 for AβOs and 6E10 for plaques and fibrils through dot blot analysis. Thus far, I have concluded that there are ~600 fmol AβOs/μg TP in the test mice and will proceed to the analysis of the first group (16 mice) after seeing that the test mice provided positive results. After analyzing the first group, I should have approximate AβO amounts for one age group of mice and will be able to conclude any trends about AβO amount correlation to age after all groups of mice have been analyzed.

C30 G-B

ROLE OF GPCRS AND GA_S IN THE ANTIDEPRESSANT ACTION OF KETAMINE

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Ketamine produces rapid and robust antidepressant effects in depressed patients within hours of administration, often when traditional antidepressant compounds have failed to alleviate symptoms even after 2 months of treatment. We hypothesized that ketamine would translocate $G\alpha_s$ from lipid rafts to non-raft microdomains, similarly to other antidepressants but with a distinct, abbreviated treatment duration. C6 glioma and C6 cells stably transfected with $G\alpha_s$-GFP were treated with 10uM ketamine for 15 minutes, which translocated $G\alpha_s$ from lipid raft domains to non-raft domains. Other NMDA antagonist did not translocate $G\alpha_s$ from lipid raft to non-raft domains. The ketamine induced $G\alpha_s$ plasma membrane redistribution allows increased functional coupling of $G\alpha_s$ and adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). Furthermore, increased intracellular cAMP increased phosphorylation of cAMP response element-binding protein (CREB), which, in turn, increased BDNF expression. These results reveal a novel antidepressant mechanism mediated by acute ketamine treatment in glial cells that may contribute to ketamine's powerful antidepressant effect.

NIH, VA

THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1

ISOLATED BULLFROG ROSTRAL BRAINSTEMS EXHIBIT A DAMGO-INSENSITIVE LUNG-LIKE EPISODIC RHYTHM IN THE PRESENCE OF BICUCULLINE

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Respiratory behavior in terrestrial animals is primarily controlled via neural circuits in the medulla. A site in the amphibian rostral medulla at the level of the abducens nerve (CN VI) is believed to be homologous to the pre-Bötzinger complex in mammals. The μ-opioid agonist DAMGO has a suppressive effect, and the $GABA_A$ receptor antagonist bicuculline has an excitatory effect on lung activity in mammals and amphibians. However, the locations of action in amphibians are unknown. Therefore, we examined the effect of DAMGO and bicuculline on isolated rostral brainstem tissue.

We isolated brainstems from bullfrog tadpoles, placed them in a recording chamber, and allowed them to recover for 1 hour perfused with artificial cerebral spinal fluid (aCSF) equilibrated with 98.5% O_2 and 1.5% CO_2 (pH 7.8). During this time, neural activity from the facial (CN VII) and hypoglossal (CN XII) cranial nerves was recorded. Following recovery, brainstems were transected just rostral to the trigeminal (CN

V) nerve, and at the level of the glossopharyngeal nerve (CN IX), removing the caudal medulla. Then activity from the trigeminal (CN V) and facial (CN VII) nerves was recorded. A cocktail containing either DAMGO (120 nM) and bicuculline methochloride (5 μM) or bicuculline alone was subsequently bath applied for 30 minutes.The transection alone resulted in a loss of discernable respiratory rhythm. However, bicuculline application caused a lung-like episodic rhythm to reappear. Contrary to the suppressive effect DAMGO has on lung activity in other preparations (including intact isolated amphibian brainstems), this rhythm was not affected by the addition of DAMGO in our transected preparation. This work informs the comparison of amphibian and mammalian respiratory oscillators and the consideration of their homology and differences.

THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1 UG-B

APOE GENOTYPE-DEPENDENT DIFFERENTIAL EXPRESSION OF GROWTH FACTORS IN BRAIN

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Innate immune responses to CNS insult conclude with anti-inflammatory cues that help return the previously inflamed parenchyma to its quiescent state. In brain, glia commonly take on this essential cellular role, synthesizing and secreting growth factors that support surrounding neuronal populations. Indeed, targeting of specific growth factors is thought to represent a valuable therapeutic approach to the treatment and prevention of various neurodegenerative disorders, including Alzheimer's and Parkinson's disease. Astrocytes are known to drive relevant anti-inflammatory and neuroprotective processes in response to the activation of toll-like receptors (TLRs) by both sterile and non-sterile agents. *APOE* is a polymorphic gene in humans that is known to differentially modulate TLR-dependent innate immune activities in brain. In addition, the ε4 allele represents a clinically relevant genetic risk factor for the initiation and outcome of many neurodegenerative diseases, although the precise mechanism remains unknown. Here we show that astrocytes display *APOE* genotype-dependent differential expression of neurotropic factors in response to TLR activation. These findings provide a possible cellular basis for *APOE* risk and support the further investigation of glial-derived growth factors as potential therapeutic targets for CNS disease. This study is funded by the DePaul University Research Council and the Louis Stoke Alliance for Minority Participation.
DePaul URC & LSAMP

F2 UG-A

IMPROVING NEURITE OUTGROWTH IN STROKE USING A CELL CULTURE MODEL

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Stroke, the fifth leading cause of death in America, results in astrocytes becoming reactive and forming a glial scar surrounding the area of dead neurons. While the glial scar acts to protect the healthy part of the brain, it also prevents healthy neurons from repairing the dead tissue by inhibiting neurite regeneration.The focus of the research was to further understand neurite outgrowth using a neuroblastoma cell culture model. To induce differentiation, N2a neuroblastoma cells were exposed to either different concentrations of retinoic acid added at various time points in the cell's life cycle, serum starvation, or a combination of both. The retinoic acid was added over a period of two days. The results suggest that serum starvation and the addition of retinoic acid increases neurite length and outgrowth. Specifically, serum starved N2a cells in Fetal Bovine Serum exposed to high concentrations of retinoic acid at plating showed the highest percentage of differentiated cells. The conditions found to best differentiate N2a cells can aid future research in developing treatments in which the brain will repair connections lost through neurite regeneration. The long term goal of the project is to improve patient recovery after stroke by improving neurite outgrowth.

F3 G-A

INDUCTION OF LYSOSOMAL BIOGENESIS BY CINNAMIC ACID: IMPLICATIONS FOR LYSOSOMAL CLEARANCE IN NEURODEGENERATIVE DISORDERS

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Lysosomes are enzyme containing membrane enclosed organelles which are primarily known as the waste management machinery of the cell. They participate in degradation of extracellular as well as cytoplasmic molecules via the process of endocytosis and autophagy. The alteration in lysosomal function has been observed in many neurodegenerative diseases. Therefore enhancing the lysosomal content along with the activity of lysosomal enzymes could be a therapeutic strategy for treating various neurodegenerative disorders. In our present study, we examined whether Cinnamic acid (CA), a metabolite of cinnamon, could induce lysosomal biogenesis and thus stimulate lysosomal clearance activity in mouse primary

astrocytes. CA was found to increase the total lysosome content in primary astrocytes indicated by the lysotracker staining. Electron microscopy further confirmed the presence of increased number of lysosomal and autophagy vesicles with CA treatment. The lysosomal membrane protein LAMP2 expression was also found to be increased which indicated enhanced lysosomal biogenesis. The functional activity of lysosomal enzyme tripeptidyl peptidase 1 (TPP1) was upregulated following CA treatment. We further checked the expression of transcription factor EB (TFEB), the master regulator of lysosomal biogenesis and found that CA increased the expression of TFEB in wild type (WT) primary astrocytes. The presence of PPRE (Peroxisome Proliferator-activated receptor or PPAR Response element) on the TFEB promoter prompted us to check the involvement of different PPARs, transcription factors involved in lipid metabolism, in CA mediated upregulation of lysosomal biogenesis. We found that CA enhances the lysosome content as well as TFEB expression in WT and PPARβ-/- astrocytes, but not in PPARα-/- astrocytes which suggested that specifically PPAR alpha might play a role in the CA induced lysosomal biogenesis. Thus stimulation of lysosomal biogenesis by CA may have therapeutic implications for neurodegenerative disorders. This study was supported by grants from the NIH (AG050431 AND NS 08354) to KP.

F4 G-A

REGULATION OF NMDAR TRAFFICKING BY PROTEIN PHOSPHATASE 1

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N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors that are responsible for the molecular basis of learning and memory through their ability to control processes such as synaptic plasticity and synaptic maturation. NMDARs are able to achieve these phenomena through their ability to activate specific intracellular cascades in response to receptor activation. The subunit composition and localization of the receptor regulate which intracellular cascades are triggered upon NMDAR activation. Thus, a key aspect of NMDAR regulation and function is tight control over trafficking of the receptor.

Posttranslational modifications are a crucial component of receptor trafficking. We have previously investigated how phosphorylation within the PDZ-binding domain of the GluN2B subunit of NMDARs results in the disruption of NMDARs from scaffolding proteins to reduce the synaptic content of the receptor. More recently, we sought to understand how the complementary reaction, dephosphorylation of this site, is controlled. Using primary cortical neurons, we have identified this dephosphorylation as dependent on calcium influx into the cell following activation of extrasynaptic GluN2B-containing NMDARs.

In an effort to better understand the mediators of this dephosphorylation, we screened protein phosphatases and have identified protein phosphatase 1 (PP1) as being responsible for dephosphorylating the GluN2B PDZ-binding domain. However, because PP1 is a constitutively active phosphatase, there exist a number of molecular modes of regulation to control its activity. These include inhibitory PP1 phosphorylation, association with endogenous inhibitor proteins, and subcellular substrate targeting. Because canonical PP1 regulation involves a mixture of these forms of regulation, we are examining how each of these mechanisms may play a role in regulating PP1 activity against GluN2B's PDZ-binding domain. Ultimately, we believe that understanding how PP1 regulates this posttranslational modification and its consequence on NMDAR trafficking and localization will help to understand how physiological NMDAR trafficking occurs and how this is altered in disease. Support for this work was provided by the NIH (R00 AG041225) and the Northwestern University CMBD Training Program (T32 GM08061).

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F5 UG-B

NG2 KNOCK-OUT IN NEU7 AND A7 ASTROCYTE CELL LINES TO PROMOTE NEURONAL REGENERATION

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Stroke is one of the leading causes of death in America and worldwide. After a stroke, neuronal regeneration is inhibited due to the astrocytes surrounding the tissue becoming reactive. Reactive astrocytes are non-permissive to axon outgrowth, and improving our understanding of astrocyte reactivity can facilitate development of more targeted therapies for neuronal regeneration. Neu7 cells are an astrocyte cell line that models this reactive phenotype due to an increased production of inhibitory chondroitin sulfate proteoglycans. Of these proteoglycans, chondroitin sulfate proteoglycan 4 (NG2) has been found to be the most inhibitory to axon regeneration. A7 cells are a model cell line for astrocytes that are permissive to axon outgrowth, having a downregulated production of NG2. In our study, the CRISPR/Cas9 system was used to produce NG2 knockout Neu7 and A7 cell lines. NG2 is a 35,046 base pair long gene with ten exons. We created guide sequences targeting exons 1, 3, 5 and 10, and bacterial cloning was used to construct plasmids containing guide sequences, Cas9 and green fluorescent protein (GFP). Sanger sequencing and alignment identified correctly constructed plasmids. Transfection efficiency was determined for select plasmids by transfection into Neu7 cells. Ongoing experiments will continue to determine optimal conditions for transfection and develop neuronal co-cultures with transfected Neu7 and A7 cells. We

believe these experiments will aid in the development of new therapies for neuronal regeneration.

F6 G-B

PAIRED RECORDINGS OF PYRAMIDAL CELLS IN THE SUBICULUM REVEAL LOCAL EXCITATORY MICROCIRCUITS

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Information exchange between neurons is accomplished using sequences of action potentials that result from the integration of local microcircuits. Unraveling the connectivity of these microcircuits and how they contribute to network activity is vital for understanding how information is relayed through the brain. Interestingly, despite its role as the main output region of the hippocampus, the microcircuity of the subiculum remains understudied. Additionally, recent evidence suggests that the subiculum is involved in generating both interictal and ictal activity in epileptic patients, providing impetus to study how these microcircuits contribute to disease. Most work involving the subiculum has focused on the excitable properties of the constituent pyramidal cells, which can be classified as either regular spiking or bursting. However, little is known about the regional synaptic connectivity. We sought to physiologically and anatomically characterize the excitatory connections of the subiculum at the individual neuron level. Using paired whole cell recordings, we have shown significant levels of connectivity between the principal cells of the subiculum. Connections were observed between bursting to bursting, regular to regular, bursting to regular, and regular to bursting neurons. These synaptic connections are excitatory and mediated by AMPA receptors at resting potential. The EPSP kinetics were similar between connection patterns, but the connection probability was highest when bursting cells were the post-synaptic target. Additionally, anatomical reconstruction of recorded cells allowed us to map the location of putative synapses. Ultimately, this work will provide insight into the population dynamics of the subiculum, which is vital for understanding the physiology of the subiculum and its role in epilepsy.

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F7 G-A

ACTIVATION OF PPAR ALPHA INCREASES NURR1 IN DOPAMINERGIC NEURONS

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Parkinson's disease (PD) is the devastating neurodegenerative disease of ventral midbrain, which is characterized by the progressive loss of dopaminergic (DA) neurons. Mutation of nurr1 genes had been shown to be involved in the loss of DA neurons and eventually the development of parkinsonian pathologies. However, the molecular mechanism to upregulate the expression of Nurr1 has been poorly understood. Our mRNA analyses followed by different immunoassays clearly indicated that PPARα agonist gemfibrozil is strongly upregulated the expression of Nurr1 in wild-type, but not in ppara-null DA neurons suggesting PPARα might be involved in the upregulation of Nurr1. Moreover, identification of conserved PPRE element in the promoter of nurr1 gene followed by chromatin immunoprecipitation analysis, PPRE luciferase assay and manipulation of nurr1 gene by viral transduction of different ppara plasmids confirmed that PPARα is indeed involved in the expression of Nurr1. Finally, we validated the effect of PPARα on the expression of nurr1 gene and subsequent protection of TH neurons in MPTP-induced mouse model of PD. Our current study identifies PPARα is a novel regulator of Nurr1 and Nurr1-mediated protection of parkinsonian pathologies.

F8 UG-B

TRANSPORT AND DEGRADATION OF THE SLO-1 BK CHANNEL IN C. ELEGANS

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Neurons and muscle cells are activated by calcium influx. However, uncontrolled calcium influx can be detrimental to these cells. One of the important feedback negative regulators is a calcium-activated potassium SLO-1 BK channel. The SLO-1 channel is conserved across species, including the nematode, *C. elegans*. Research has also shown that SLO-1 can also be activated by ethanol, leading to inhibitory effects. In *C. elegans* the protein ERG-28 has been identified as the molecule responsible for transporting SLO-1 from its synthesis in the endoplasmic reticulum to the plasma membrane. *erg-28* mutants show greatly reduced SLO-1 signaling, suggesting ER associated degradation of the potassium channel via the ubiquitin-proteasome system. In this study, using both fluorescent microscopy and behavioral studies in *C. elegans*, we show a ubiquitin ligase which when mutated results in both increased fluorescence and sensitivity to ethanol. This would suggest that it is responsible for the degradation of SLO-1. We also performed mutagenesis tests on *C. elegans* with RFP tagged ERG-28 in order to better elucidate the *erg-28* and *slo-1* pathways, resulting in the creation of multiple mutants.

F9 PD-A

COORDINATED SPIKING IN CA3 PROPAGATES TO HILAR MOSSY CELLS IN JUVENILE MICE BUT ONLY RARELY IN ADULT MICE

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Temporal lobe epilepsy is a disorder of altered hippocampal network activity associated with aberrant excitability and widespread degeneration of hilar mossy cells (HMCs), suggesting that HMCs play an important role in hippocampal network activity. A clearer delineation of excitatory input to HMCs in physiological and pathological conditions will be essential for understanding how these cells contribute to circuit dynamics in the dentate gyrus. HMCs bridge distant hippocampal areas by relaying information from granule cells (GCs) and CA3 pyramidal neurons (CA3) to dentate gyrus; however, many aspects of GC-HMC and CA3-HMC synapses remain uncharacterized. To examine these HMC excitatory inputs, we are recording both spontaneous and evoked EPSCs in HMCs in acute slices from juvenile (~P20) and adult (~P65) mice, detailing excitatory synaptic physiology, the propagation of seizure-like events to HMCs, and how these properties evolve during development.

In vivo administration of certain drugs can induce chronic seizure states, but how HMCs participate in this altered network activity is unknown. We found that acute application of bicuculline and picrotoxin, pilocarpine, or 4-aminopyridine (4-AP) in acute slices induced coordinated firing in CA3 which propagated into the hilus resulting in compound EPSCs (cEPSCs) in HMCs (amplitude: 4255 ± 245 pA). cEPSC frequency was greatly diminished with aging (juvenile: 2.19 ± 0.25 Hz; adult: 0.20 ± 0.16 Hz), suggesting that developmental changes in hippocampal circuitry diminish the strength of these coordinated bursts or their propagation to HMCs.

To examine if the decrease in cEPSCs with aging could be due to decreased connectivity of HMCs, we examined synaptic physiology at HMC synapses in juvenile and adult mice. We found that HMCs receive significant excitatory input from both CA3 and GCs. Evoked CA3-HMC EPSCs were of small amplitude and facilitated during paired stimulation (paired pulse ratio: 1.95 ± 0.15). In contrast, evoked GC-HMC EPSCs were large amplitude with modest facilitation (paired pulse ratio: 1.66 ± 0.09), which was surprising given that anatomically similar GC-CA3 synapses display much more robust facilitation during paired stimuli of mossy fibers. CA3-HMC and GC-HMC excitatory synaptic function was similar in juvenile and adult mice, suggesting that decreased HMC connectivity likely is unlikely to account for the reduction in cEPSCs with aging. These data show that HMCs receive comparatively weaker synaptic input from CA3 than from GCs, but that strong CA3 input drives the propagation of seizure-like events into the hilus in the presence of pro-epileptic agents.

F10 UG-B

MITOCHONDRIA ADJACENT TO RIBBON SYNAPSES IN VESTIBULAR HAIR CELLS ARE NOT POLARIZED TOWARD THE SYNAPSE

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Mitochondria are generally known as “the powerhouses of the cell”. In our research, 3D models of
mitochondria in vestibular hair cells were constructed from electron microscope (EM) tomograms to understand the structural role of their internal cristae in support of neuronal activity at ribbon synapses. The mitochondrial inner compartment is made up of the, the inner membrane and the cristae. Recent EM tomography studies have shown us that these two membrane domains are connected by small tubular structures known as crista junctions (CJs). CJs “have been proposed to regulate the dynamic distribution of proteins, lipids, and soluble metabolites between mitochondrial subcompartments” (Zick et al. 2009). Mitochondrial cristae are the location of most of the enzymes and is responsible for cellular respiration and ATP production, and therefore play an essential role in cellular activities. A ribbon synapse is known to be a ‘high capacity docking site’ of synaptic vesicles that provide the fusion sites for ‘active zones’ and they are known to have a large supply of “immobile synaptic vesicles rapidly available for exocytosis” (Schmitz et al. 1996). The vesicles are powered by ATP produced by mitochondria. The goal of this study was to test the hypothesis of whether the distance of a mitochondrion from a synapse would have an influence on the number of cristae junctions(CJs) on the mitochondrion. Our hypothesis is that cristae that are present in the mitochondrion, are oriented perpendicular to the ribbon and would be expected to demonstrate a higher number of CJs on the side of the mitochondrion facing the ribbon synapse. Using our reconstructions, the number of CJs present in a mitochondrion is counted. In our tomograms, we observed that the ratio of CJs towards the ribbon to the CJs away from the ribbon synapse is close to 1:1 regardless of the distance from the ribbon synapse. From this we can conclude, despite the cristae being oriented perpendicular to the ribbon synapse, distance from the synapse apparently does not affect whether CJs are more prevalent on the side adjacent to the synaptic ribbon in vestibular hair cells.

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F11 UG-A

APOE GENOTYPIC INFLUENCES ON MULTIPLE SCLEROSIS

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Multiple Sclerosis (MS) is an autoimmune disease that demyelinates the central nervous system (CNS) and leads to a loss of neuron conductivity. T helper (Th) cells promote inflammation in the CNS by responding to myelin antigens and activating microglia cells and astrocytes, the resident immune cells of the brain. Proinflammatory cytokines synthesized and secreted by Th cells have profound effects on the brain and represent a possible initiator and key mediator of MS pathogenesis. While the precise molecular and cellular mechanisms underlying CNS sensitivity to Th cells and their secreted products remain poorly understood, genetic risk factors offer important insight to the puzzle. *APOE* encodes apolipoprotein E and is uniquely polymorphic in humans. Inheritance of the ε4 allele is associated with increased disease severity and progression, as well as poorer outcomes in many neurodegenerative diseases, including MS. In addition, *APOE* genotype determines microglial and astrocyte responses to a wide range of inflammatory stimuli. Here we present data supporting *APOE* genotype-dependent differential glial response to MS-relevant stimuli. This project was funded by the DePaul University Research council.

F12 G-B

SEPARATION OF LEC LAYER III NEURONAL EXCITABILITY IN NORMAL AGING

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Aging is often associated with a decline in hippocampus-dependent learning and memory, although not all subjects exhibit learning impairments as they age. Previous research has shown that within the CA1 region of the hippocampus, there is a separation in the aging population in terms of intrinsic excitability. CA1 neurons from aged subjects that are learning impaired have decreased excitability relative to neurons from young animals, while neurons from aged subjects that retain learning ability have comparable excitability to young counterparts. The current project focuses on determining whether intrinsic excitability within the principal neurons of the entorhinal cortex also underlies learning deficits in aged subjects. The entorhinal cortex relays information from cortical regions to the hippocampus and is highly susceptible to aging-related changes. Specifically, the lateral portion of the entorhinal cortex (LEC) been suggested to support hippocampus-dependent temporal associative learning and is also the initial site of manifestation for Alzheimer's disease. Therefore, whole cell current clamp recordings were performed on the pyramidal neurons of layer III of the LEC from young adult (3-6 month old) and aged (29-32 month old) F1 F344xBN hybrid rats. These neurons project directly to CA1 of the hippocampus. Measures of intrinsic excitability include accommodation and postburst afterhyperpolarization (AHP). Our preliminary results indicate a separation in the aging population in excitability in the LEC, such that there is a population of neurons that are less excitable and another population of neurons that remain as excitable as young counterparts. The results are similar to previous data from the CA1 region of the hippocampus and suggest LEC intrinsic excitability may also be a measure and mechanism supporting learning. Identification of these changes in aging will point to a potential target for future therapeutics in alleviating aging-related learning and memory deficits.

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F13 PD-A

SPIKING AND TRANSMISSION IN CALYCEAL TERMINALS IN DIFFERENT ZONES OF THE MOUSE UTRICULAR EPITHELIUM

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Vestibular primary afferents form calyceal endings surrounding type I hair cells, bouton endings contacting type II hair cells, or both. In the utricular epithelium, functional differences between afferents are correlated with zones (striola, S, and extrastriola, ES): ES afferents have more regular spike timing and more tonic responses than S afferents. Low-voltage-activated K (K_{LV}) channels of the Kv1 and Kv7 families and HCN channels have been implicated in vestibular afferent spike regularity. Calyceal HCN channels have also recently been implicated in a novel form of non-quantal (NQ) transmission from hair cells to calyx (Contini et al. ARO Abstr. 2016). To assess the contributions of K_{LV} and HCN (h) currents to zonal variations in function, we record from calyces (postnatal days, P, 10-27, n=68) in an excised, intact preparation of the mouse utricle and map the locations.

S calyces had significantly larger K_{LV} ($p<0.001$) and HCN currents ($p<0.01$) than ES calyces. For K_{LV} current, the difference was accounted for the larger size of S calyces, more of which are complex (surround multiple type I hair cells). For I_h there may be greater current density in the striola. Spike rate was similar across zones (22.5±5.6 spikes/s, SE, 33 calyces). As *in vivo*, spiking was more irregular in S calyces than in LES calyces: CV 1.1±0.25 (4) vs. 0.6±0.09 (12), p=0.02; Fano factor, FF, 0.8 vs. 0.04, p=0.002. In 6 LES calyces, ~60% block of K_{LV} current with a Kv7 blocker (10 μM XE991) increased spike regularity (CV 0.11 ± 0.01, p = 0.007; FF 0.0007, p = 0.037), without significantly altering rate. This result supports the hypothesis that K_{LV} channels contribute to spike irregularity in the rodent afferent nerve.

Previously we demonstrated NQ transmission in S calyces from the rat saccule in the first postnatal week (Songer & Eatock 2013). We have extended these findings to include mouse utricular calyces, ES calyces, and older calyces (P13-P26). 15/17 calyces driven by deflection of an enclosed type I hair bundle had clear NQ responses. At 2 Hz, NQ currents were 10-150 pA (peak-to-peak; median 18 pA) and NQ potentials were 2-16 mV (median 4 mV). Comparison of hair cell and calyceal responses to similar stimuli shows synaptic modifications of the signal. In contrast to reports from turtle, we find that NQ responses are faster than conventional quantal responses and drive afferent spiking with high vector strength up to 100 Hz. R01DC012347

F14 PD-B

A SYNAPTIC ROLE OF FKBP5, A GENETIC RISK FACTOR FOR STRESS-RELATED PSYCHIATRIC DISORDERS

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The development of psychiatric disorders, such as depression, post-traumatic stress-disorder, and bipolar disorder has been shown to be associated with alterations in neuronal structure and function, particularly in the cerebral cortex. While recent large scale clinical genomics studies have identified genetic risk factors for psychiatric disorders, the functional analysis of these risk genes and their encoded proteins is the next major challenge. Among these, FKBP5, encoding FK506 binding protein 5, is a prominent genetic risk factor for stress-related mood and anxiety disorders, including depression and post-traumatic stress-disorder. However, the mechanisms by which FKBP5 contributes to disease pathogenesis are not well understood. While a role for FKBP5 as a glucocorticoid receptor co-chaperone have been postulated, additional mechanisms have not been investigated in the brain. We hypothesized that FKBP5 may also function at synapses, sites relevant for the pathogenesis of psychiatric disorders. By utilizing an ***in vitro*** model of stress and primary rodent cortical cultures we have found independent effects of stress and FKBP5 on neuronal morphology. Furthermore, our super-resolution microscopy and live cell imaging techniques have revealed a unique synaptic role of FKBP5. Further studies investigating the molecular pathways involved in FKBP5-mediated synaptic processes can provide insight into disease pathogenesis and lead to novel therapeutic strategies. The study is funded by NIH 5R01MH107182-02.

F15

SEX DIFFERENCES IN THE BASOLATERAL AMYGDALA: NEURONAL ACTIVITY AND THE EXPRESSION OF SMALL CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CHANNELS.

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Anxiety disorders are the most prevalent form of mental illness in the US and women are twice as likely as men to develop anxiety disorders; yet studies that examine sex differences in the neurobiology related to these disorders are limited. The basolateral amygdala (BLA) is a critical component of the neurocircuits involved in anxiety and fear responses. Furthermore, the amygdala is hyperactive in patients with anxiety disorders and is more active in females during specific affective tasks. This suggests that BLA activity may contribute to the sex differences in the pathophysiology of anxiety. We hypothesized that BLA neurons in female rats are more excitable than males. *In vivo* electrophysiological recordings were utilized to record spontaneous BLA neuronal activity in naïve male and intact cycling naïve female rats. We found that independent of cycle stage, females had a significantly higher basal firing frequency in the BLA compared to males. The activity of these neurons is regulated, in part, by after-hyperpolarization potentials (AHP) that limit neuronal firing frequency. Therefore, we measured membrane excitability *in vitro* and found that cycling females also had smaller AHP amplitudes compared to males. Since small conductance calcium-activated potassium (SK) channels contribute to components of AHP, we measured the relative expression of SK channel mRNA and protein levels in the BLA of naïve rats. Using quantitative real time PCR (qPCR), we found that relative mRNA levels of all SK channel isoforms (SK1-4) were comparable between sexes. However, Western blot analysis revealed that SK2 channel protein expression was significantly reduced in female rats, irrespective of estrous cycle stage, compared to males. Together this suggests that sex differences in SK2 protein expression are not likely due to differences in transcription, rather SK2 protein levels may be altered in females through differential post-translational modifications compared to males. These results implicate a role for SK2 channels in the sexually divergent BLA neuron activity and AHP amplitudes in naïve rats. Moreover, these studies identify a potential therapeutic target for the treatment of anxiety related disorders, and enhance our understanding of sex differences in anxiety. This study is funded by a research grant from the National Institute of Health (R01MH100536).

F16 G-B

ESTROGEN RECEPTORS IN THE VENTRAL TEGMENTAL AREA AFFECT NEURONAL RESPONSES TO ETHANOL AND DOPAMINE

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Gender Differences in alcohol use disorder may be modulated by sex hormones, such as estrogen. 17β-estradiol (E2), the predominant form of circulating estrogen in pre-menopausal females, increases binge-like drinking and enhances ethanol conditioned place preference in mice, suggesting that E2 affects the rewarding properties of ethanol. The ventral tegmental area (VTA) is critically involved in the rewarding and reinforcing effects of ethanol. In order to determine the role of estrogen receptors in VTA physiology, gonadally-intact female mice were sacrificed during diestrus (high E2) or estrus (low E2) for electrophysiology recordings. Consistent with our previous findings, the excitatory response to ethanol and inhibitory response to dopamine were greater in diestrus compared with estrus. A 90-minuute treatment of VTA slices with an estrogen receptor antagonist (ICI 182,780) from diestrus females reduced ethanol-stimulated neuronal firing by 55.6%, but had no effect on ethanol-stimulated firing of neurons in slices from estrus females. Surprisingly, ICI 182,780 did not affect inhibition by dopamine, suggesting different mechanisms of action of estrogen receptors in altering ethanol and dopamine responses. The response of VTA slices to dopamine and ethanol in ovariectomized (OVX) female mice treated with E2 compared with vehicle are consistent with the high estradiol state of diestrus compared with estrus. We are currently measuring gene expression of dopamine and other types of receptors in the VTA to determine the molecular changes induced by E2. Our data indicate that E2 modulates VTA neuron physiology and may contribute to the reinforcing and rewarding effects of alcohol in females.

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F17 PD-B

CYTOKINE REGULATION AND FUNCTION OF MICROGLIA-DERIVED MEMBRANE NANOTUBES AT THE NEURO-IMMUNE INTERFACE

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Microglia are brain-resident innate immune cells that continually survey their surroundings with dynamic membrane processes and shape neural circuits by complement-dependent elimination of extranumerary synapses. Their morphology and function are highly related and dependent on complex environmental signals, including pro- and anti-inflammatory cytokines. Acutely activated microglia mediate innate responses to immunologic stimuli, but chronic activation contributes to neurodevelopmental and neurodegenerative disorders via partially unknown mechanisms. Membrane nanotubes (MNTs) are long, ultrafine conduits that can support rapid intercellular communication and be regulated by pro-inflammatory cytokines in other innate immune cells. Here we investigate for the first time how MNTs facilitate microglia-neuron cross-talk using a murine co-culture system of microglia and primary cortical neurons. We used live-cell confocal microscopy to show that isolated microglia can develop dynamic MNT networks, which were not attached to the substrate. MNTs formed by filopodia extension or withdrawal of primary processes from target cell contact and supported surface molecule exchange. Migrating microglia also frequently left behind long trails of static, substratum-attached retraction fibers. MNTs were notably $CD11b^+$ and originated from the tips of CD11b-enriched primary processes. We used super-resolution structured illumination and lattice light sheet microscopy to resolve synaptic and MNT nano-domains and to improve spatio-temporal resolution of cell-cell interactions, respectively. Co-cultures were treated with a pleiotropic cytokine essential for steady-state microglia maintenance in vivo and in vitro, TGF-β, which substantially increased $CD11b^+$ MNT and retraction fiber formation in microglia. These processes contacted other microglia or synaptic elements, including dendritic spines and axon terminals, and often formed along the length of axons. Pro-inflammatory cytokine (IFN-γ + TNF-α) treatment of co-cultures enhanced MNT formation in amoeboid microglia. These data show that MNTs can be induced by TGF-β in steady-state or pro-inflammatory cytokines in activated microglia. The conduits can prolong contact with neurons or microglia and likely function in CD11b-dependent processes, i.e. adhesion and/or complement-dependent synapse elimination. An improved understanding of MNT-mediated microglia-neuron communication may identify novel therapeutic targets for neurological disorders in which aberrant cytokine production contributes to pathology.

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THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1

A HIGH THROUGHPUT, HUMAN, IN VITRO MODEL FOR DRUG DISCOVERY IN TRAUMATIC AXONAL INJURY

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Traumatic brain injury (TBI) causes 52,000 deaths, 275,000 hospitalizations and $76 billion in medical costs in the United

States every year. More than 30 clinical trials have failed in this condition without a single success. Clinical trials are difficult in TBI because therapeutic responses in rodent models do not necessarily predict therapeutic responses in humans. Also, the pathology of TBI is highly heterogeneous, encompassing any combination of hematoma, edema, contusion and traumatic axonal injury (TAI). In effect, a conventional TBI trial challenges a candidate therapy to treat several diseases simultaneously. The current consensus in the field is that future trials should target these pathologies in isolation as much as possible. In this work, candidate compounds are sought for future clinical trials using a human in vitro model of TAI. This model employs human induced pluripotent stem cell (hiPSC)-derived neurons. These cells are cultured in a 96 well plate with a flexible growth substrate and subjected to a repeatable, quantifiable stretch insult to simulate trauma. They are then imaged fluorescently to visualize and quantify neurite morphology and cell viability. Increasing stretch leads to an increasing injury phenotype, as measured by these parameters. Dozens of phenotypes are quantified in these images and reduced to a single, maximally sensitive, injury parameter using multi-variate statistical methods. This assay is currently being refined to prepare the first high throughput screen for agents to treat TAI. It is also being adapted to create a model that produces co-cultures of injured and uninjured cells.

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G2 UG-B

DIFFUSION TENSOR IMAGING DETECTS ACUTE AND CHRONIC CHANGES DUE TO TRAUMATIC BRAIN INJURY IN A BLAST INJURED RAT MODEL

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Introduction Traumatic Brain Injury (TBI) is a leading cause of mortality and morbidity but remains difficult to diagnose due to lack of specificity and sensitivity in common imaging techniques. Diffusion tensor imaging (DTI) enables measurement of the diffusion of water in tissue and has been successful in studying white matter tracts in vivo, the most common location for pathology in TBI. The purpose of this study is to characterize the temporal evolution of TBI due to blast injury in a rat model. Using DTI we have detected acute and chronic changes in the corpus callosum (CC) that suggest axonal damage.

Methods Blast injury was administered to Sprague-Dawley rats to the right side of the head at an average pressure of 58.6 psi via blast tube. These blast-injury rats, along with a control group that did not undergo any injury, were imaged in vivo using EPI-DTI one day (D1) and 14 days (D14) post injury (n=5). Diffusion images were analyzed to calculate four metrics of DTI for each pixel: fractional anisotropy (FA), trace, and axial and radial diffusivity. DTI parameters were measured in six regions of interest. The medial right and left CC, the lateral right and left CC and the right and left cingulum. Furthermore, these regions were analyzed in six coronal slices of the brain comprising the splenium, body and genu of the CC. Regions of interest were manually drawn onto each image using visual anatomical landmarks to better accommodate the variations in anatomy between each rat. The blast injury rats were compared to the control group at the two timepoints for all four DTI parameters using standard one-tailed, unequal variance t-tests.

Results At D1, injured rats showed lower FA, higher trace, and higher axial and radial diffusivity in many regions of the CC and cingulum when compared to the control group. Notably, in the medial CC there was a 7.4% decrease in FA ipsilateral to blast injury, but only a 1.8% decrease contralaterally. At D14, the injured rats showed higher FA in the CC splenium, and lower trace in all regions of the CC and cingulum, with no significant differences between the left and right sides. Furthermore, injured rats showed higher radial diffusivity and lower axial diffusivity in the CC, and lower radial and axial diffusivity in the cingulum. The decreased FA in TBI rats at D1 indicates demyelination and disruption of white matter structure due to axonal injury from the blast. The subsequent increase in FA at D14 shows evidence of white matter tract recovery through excessive remyelination.

Conclusion

The results from this study support the potential of DTI to differentiate brain changes associated with acute and chronic phases of blast injury.

G3 G-A

THE DELTA OPIOID RECEPTOR AS AN EMERGING THERAPY FOR MTBI-INDUCED HEADACHES

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Mild traumatic brain injury (mTBI) impacts approximately 1.3 million Americans per year, causing behavioral, cognitive, and emotional deficits. Of the many disabilities resulting from mTBI, post-traumatic headache (PTH) is the most common and long-lasting impairment. Often persisting for up to a year, PTH is most commonly associated with a migraine phenotype. To date, the mechanisms underlying the progression of mTBI to PTH have not been fully elucidated. We aim to develop a novel mouse model that reflects the relationship between mTBI and PTH by combining the closed head weight drop method and the nitroglycerin (NTG) chronic migraine model. NTG is a known human migraine trigger that also produces

migraine-associated hyperalgesia in mice. In the mTBI groups, a 30 gram weight impacts the intact crania of anesthetized C57Bl6/J adult male mice. Sham groups undergo anesthesia, but are not impacted. After 2 weeks of recovery, mice are chronically treated with saline, 0.1 mg/kg NTG, or 10 mg/kg NTG over 5 test days. Basal and post-treatment mechanical thresholds are assessed using von Frey hair stimulation. Only the mTBI group developed a progressive and sustained basal hypersensitivity to the low dose of NTG, while the high dose of NTG produced hypersensitivity in both sham and mTBI groups. Both doses of NTG induced comparable acute (post-treatment) hyperalgesia in both groups, 2 hours after injection. Additionally, mTBI groups treated with a low dose of NTG were sensitive to sumatriptan, an abortive migraine therapy. Furthermore, mTBI groups treated with a low dose of NTG were also sensitive to SNC80, a delta opioid receptor agonist. mTBI appears to produce an increased sensitivity to migraine-associated pain within the NTG model of chronic migraine, which is alleviated by sumatriptan and SNC80. Future gene and protein expression studies will explore the role of neuropeptides associated with migraine in this mouse model.

THEME H. SENSORY AND MOTOR SYSTEMS

H1 UG-A

MARBLED CRAYFISH: A NEW GENETIC MODEL ORGANISM FOR STUDYING THE INFLUENCE OF NEUROMODULATORS ON NETWORK DYNAMICS

Casey Gährs, Carola Städele, Abigail Benson, Wolfgang Stein, and Andrés Vidal-Gadea

ALL authors have affiliation with School of Biological Sciences, Illinois State University. Carola Staedele also is affiliated with Department of Integrative Biology and Physiology, UCLA.

The coordinated activity of the nervous system and its many interconnected neurons allows animals to rapidly adapt to changing environmental and endogenous conditions. This neural flexibility can be attributed in part to the modulatory effects of transmitters, small chemical molecules that alter neuronal activity. To understand the mechanisms underlying neuromodulation and its influence on neural network dynamics, it is essential to conduct a thorough examination of modulator origins, targets, molecular pathways, and resulting physiological responses. This has been challenging using existing animal model organisms due to lack of identified neurons and circuits, access to cellular and circuit dynamics, or availability of genetic tools.

Our group is working to overcome these limitations by establishing the marbled crayfish, *Procambarus virginalis,* as a new genetic model organism that combines direct access to neuronal dynamics with novel molecular tools. This will lay the foundation for investigating the causal relationships between genes, physiology, and behavior at the single-neuron level. The marbled crayfish's parthenogenetic reproductive strategy, ex-utero breeding, and short life cycle are advantageous traits in this endeavor.

We previously demonstrated that oocytes are readily accessible, can be cultured *in vitro*, and can sustain delivery of genetic constructs. An initial annotation of our recently sequenced *de novo* whole-genome is being utilized to design genetic constructs for 1) fluorescence-labeling of neurons that express genes of interest (eg. modulatory transmitters and their receptors) and 2) evaluating the consequences of RNAi-mediated gene silencing on neuronal physiology and animal behavior. Our preliminary data suggest that amplified promoter regions of neuronal genes of interest can be cloned into plasmids containing green fluorescent protein and a viral enhancer. These chimeric vectors will be injected into crayfish oocytes to specifically label neurons expressing genes of interest.

H2 UG-A

CRISTAE IN INNER HAIR CELL MITOCHONDRIA ARE POLARIZED TOWARD CUTICULAR PLATE

Kevin Arias

University of Illinois at Chicago

The main purpose of this research is to study the structure and the functionality of mitochondria located in inner ear hair cells. According to size, mitochondria can be divided into three different sub-types: large, medium, and small. In this particular scenario, our focus rest upon a large mitochondria located in very close proximity to the Cuticular Plate (CP) in a vestibular type-1 hair cell. A criterion we have been taking into great analysis is the identification of the amount of Cristae Junctions (CJs) facing the CP in comparison with the amount of CJs located on the other side facing away from the CP. Cjs are tubular connections promoting a direct interaction between the mitochondria cristae and the mitochondria inner membrane. (Rabl et al. 2009) We have speculated that the amount of CJs facing the CP will be considerably higher in contrast to the opposite side facing away from it. This suggests a polarization of CJs on one side, so that can transport ATP and Ca^{2+} to points of interest, such as stereociliar rootlets and the CP (Perkins et al. 2010). In order to identify the desired structures, we have been using IMOD, a model editing and image display program developed by the University of Colorado. First, we examine the mitochondria tomogram section by section and with the help of the software, we can trace individual crista very accurately. We follow this process for every observable cristae along with the mitochondria membranes; when all the tracing is done, we mesh it and we will get a 3D representation of the mitochondria in the tomogram. In addition, IMOD serves as a tool to obtain accurate data about the mitochondria such as surface area. After the large mitochondria was reconstructed, we proceeded to analyze the get data in the amount of CJs.

We observed a higher amount of CJs facing the CP. In conclusion, the data obtained supported our hypothesis that CJs are observed in greater amount in sites requiring more ATP.

H3 G-A

STIMULUS-DEPENDENT RECRUITMENT OF LATERAL INHIBITION UNDERLIES RETINAL MOTION COMPUTATION

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QC: Committee on Computation Neuroscience, Univ. of Chicago QC, ZP,DK,WW: Department of Neurobiology, Univ. of Chicago

A critical function of neural circuitry in the brain is detecting relevant features in the environment. Direction selective circuit of the retina is a classic model to study feature detection. Retinal direction selectivity first arises in the dendrites of starburst amacrine cells (SACs), a class of interneurons that provide directionally tuned inhibitory inputs onto direction selective ganglion cells (DSGCs. The neural mechanisms underlying the direction selectivity of SACs and DSGCs have been intensely studied for decades. However, an important piece missing from the current circuit model is how lateral inhibition onto SACs participates in motion detection. This gap in understanding primarily stems from a lack of synapse-specific manipulations. This gap in understanding is also due to another pressing problem. Since all published studies have focused on synaptic interactions in the On sublamina of the retina due to greater accessibility of On SACs for functional analysis, the synaptic mechanisms underlying direction selectivity in the Off pathway have been completely ignored.

We have dissected the inhibitory inputs onto both On and Off SACs using a combination of synapse-specific genetic manipulations, two-photon calcium imaging, electrophysiology and pharmacology. These techniques have enabled us to elucidate novel functions of the distinct inhibitory circuit components in direction selectivity.

Lateral inhibition is an evolutionarily-conserved circuit motif found throughout the nervous system. Our study delineates the precise functional roles of this motif in a well-defined neural computation. It also demonstrates that comprehensive understanding of sensory coding requires carefully selecting sensory stimuli that reflect the challenges posed by the natural environment. Therefore, we believe that our study will be of broad interest to neuroscientists working on neural circuit function in both experimental and computational regimes. Our findings provide important mechanistic insights into the direction selective circuit, and highlight the importance of using both simple and complex stimuli when studying multiple levels of neural mechanisms underlying visual processing

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H4 PD-A

ELECTROPHYSIOLOGY OF REGENERATED HAIR CELLS IN THE MOUSE UTRICLE

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Balance disorders can severely affect quality of life. The most common cause for balance disorders is the lost of hair cells of the sensory epithelia in the inner ear. The sensory epithelia of the vestibular system in mammals have two types of hair cells, type I and type II. Each type is well defined by its shape, its afferent innervation and its conductances. Vestibular sensory epithelia spontaneously regenerate after damage and anatomical evidence suggests that the regenerated hair cells are type II (Golub et al., J Neurosci 32:15093, 2012).

Using whole-cell patch clamp technique in a semi-intact preparation of the mouse utricle we have characterized the electrophysiological properties of regenerated hair cells in the mouse utricle, in order to determine the corresponding cell subtype. To stimulate hair cell regeneration, we treated *Pouf4f3*$^{-/DTR}$ mice with diphtheria toxin, which kills many hair cells (Golub et al., *ibid*.). We have recorded from regenerating hair cells, recognized by their small hair bundles, at various stages (from 14 to 140 days post-treatment). All resembled type II or immature hair cells in the expression of delayed rectifier K channels that activate positive to resting potential, and all lacked the type I-specific low-voltage activated conductance, g_{KL}, and afferent calyceal terminals (Rüsch et al., J Neurosci 18: 7487, 1998). Moreover, several regenerated hair cells (20/53) had voltage-gated Na^+ (Na_V) conductances, consistent with an immature state (Wooltorton et al., J Neurophysiol 97: 1684, 2007). Such channels may enhance rapid depolarizations and therefore calcium channel activation, facilitating the release of neurotransmitter (Masetto et al., J Neurophysiol 90: 1266, 2003). Many of these regenerated hair cells (23/53) bore basolateral extensions; this was the only feature that denoted some degree of maturity, since basolateral extensions were described only for mature type II hair cells (Pujol et al., J Comp Neurol 522:3141, 2014).

The immature state and small number (Golub et al., *ibid.*) of regenerated hair cells and the lack of differentiation into mature type I cells suggests that in mammalian vestibular epithelia there are barriers to full recovery of function following widespread hair cell death.

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H5 PD-B

DIVERSITY OF M1 INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS

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M1, one subtype of melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs), is subdivided into two different molecular subpopulations based on whether they express the transcription factor Brn3b (Brn3b-positive or Brn3b-negative cells). These two populations show divergent brain targeting and functions in non-image-forming behaviors. M1 cells have previously been reported to be morphologically and physiologically homogeneous populations. However, whether these subpopulations have distinct physiological and morphological properties has not been directly tested.

To compare physiological properties, *in vitro* single cell recording was performed in a whole cell configuration. M1 cells were fluorescently identified by green fluorescent protein expression in Opn4 (melanopsin gene) locus. Light responses were examined with dim (9.2 log photons/cm^2·s; 480 nm-wavelength) and bright light (13.2 log photons/cm^2·s) in a current–clamp mode. The recorded cells were filled with neurobiotin during recording and then incubated with streptavidin to analyze morphological properties. Cells were subsequently immunostained for Brn3b.

M1 cells showed distinct light responses under dim light: some responded as strong as with bright light and others did not respond. These dim light responses were abolished by a blockade of synaptic inputs. We also found that the two different M1 subpopulations exhibited physiological differences in resting membrane potential and intrinsic membrane properties as well as morphological differences in a total dendritic length and dendritic field. Unexpectedly, we found that these distinct properties did not correlate with whether M1 cells expressed Brn3b.

Our data indicate that there are two functional populations of M1 cells: those specialized for signaling under very dim light conditions, and those that signal primarily under bright light conditions. These M1 cells also show distinct morphological and resting physiological properties, further indicating that they likely relay distinct streams of light information to the brain and have differential influences on behavior. Thus, these findings directly contradict the prevailing view that M1 ipRGCs are a relatively homogenous population of cells with similar morphological and functional properties.The Kirchgessner

H6 UG-A

STRUCTURAL ANALYSIS OF INNER EAR HAIR CELL MITOCHONDRIA NEAR THE STRIATED ORGANELLE

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Mitochondria are important organelles found in every cell of the body. The current depiction of a mitochondrion, containing an inner membrane (IM), outer membrane and cristae that increase the surface area of the IM, has been the universally accepted model for decades. Although the basic function and structure of mitochondria have been studied, careful analysis of recent data gathered from electron microscopy has led to the identification of structurally and functionally different subpopulations of mitochondria in the inner ear (Lysakowski and Goldberg, 1997). There are currently several known mitochondrial-related deafness and vestibular disorders, such as dizziness, vertigo and nystagmus (Iwasaki et al., 2011). In order to further characterize the mitochondrial subpopulations and relate them to these associated diseases, we used IMOD software to create 3D models of mitochondria located near different energy-demanding cellular components. From these models, we can collect quantitative data such as crista surface area and volume and whole mitochondrion values. With these data, we can approximate a mitochondrion's energy output. The main structure of interest was the striated organelle (SO), a cytoskeletal structure found in the apicolateral region of hair cells. It was expected that mitochondria near the SO would have a fairly large energy output. It was hypothesized that there would be more points on the IM that joined with cristae membranes, the so-called "crista junctions" (Rabl et al., 2009; Zick et al., 2009) on the side facing the striated organelle (Perkins et al. 2010). In the future, models of the different subpopulations can be compared structurally, which can lead to an explanation of physiological differences. Exploring these differences could lead to finding the population of mitochondria affected in mitochondrial-related deafness or vestibular disorders.

H7

STIMULATION OF THE INTERNAL NASAL PASSAGES PROVIDES THE AFFERENT SIGNAL THAT INITIATES THE DIVING RESPONSE IN VOLUNTARILY DIVING RATS

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Underwater diving initiates the diving response, an autonomic cardiorespiratory reflex that includes parasympathetically-mediated bradycardia, a sympathetically-mediated increase in total peripheral resistance, and apnea. The Anterior Ethmoidal Nerve (AEN) is thought to provide the primary afferent signal that initiates this response. Central terminal AEN projections

are found with the ventral tip of the medullary dorsal horn (MDH). This region is also the location of secondary neurons that become activated during underwater diving. The AEN separates into the external nasal and internal nasal branches that innervate the external nasal region and internal nasal passages, respectively. Therefore our objective was to determine which nasal region provides the anatomic pathway for the afferent signal responsible for initiation of the diving response. The pattern of neuronal activation of secondary neurons activated by voluntary diving, as determined by neuronal Fos production, was compared with the central projections of the transganglionic tracer Wheat Germ Agglutinin (WGA) after WGA had been injected subdermally into the glabrous or hairy skin of the nose, or internal nasal passages. Sprague-Dawley rats (N=6) were trained to voluntarily dive through a 5 m underwater maze. Nine days post-surgery all rats had 24 dive trials over 2 hours to activate brainstem neurons to produce Fos. Other rats had WGA injected into the 1) hairy skin of the nose immediately superior to the left nasal vestibule (10 µl of 100% WGA; N=6); 2) glabrous skin of the nose immediately inferior to the left nasal vestibule (10 µl of 100% WGA; N=7); 3) left nasal vestibule and brushed on the glabrous skin of the left nostril immediately distal to the nasal vestibule (20 µl total of 50% WGA; N=7); and 4) left nasal passages (30 µl each at depths of 5 and 10 mm; 60 µl total of 50% WGA; N=8). Results indicate Fos was primarily located within the ventral tip of the superficial MDH and adjacent paratrigeminal nucleus, between the pyramidal decussation caudally and the obex rostrally. WGA labeling from the internal nasal passages had a very similar pattern to that of the Fos-positive neurons. Conversely WGA labeling from the hairy skin of the nose was located caudal to the pyramidal decussation, while WGA labeling from the glabrous skin of the nose was located primarily within the lateral and dorsolateral MDH. Therefore central projections from the external nasal region showed poor overlap with the Fos MDH labeling. We conclude that activation of secondary neurons during diving results from stimulation of the internal nasal passages, primarily through innervation provided by the internal nasal branch of the AEN.

H8 UG-B

CRISTAE ALIGN ACROSS MITOCHONDRIAL MEMBRANES IN VESTIBULAR HAIR CELLS TO POSSIBLY INCREASE ATP OUTPUT

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The main objective of this research is to study mitochondria in inner ear hair cells from a functional and structural perspective. Mitochondria are divided into three different sub-types, according to size: large, medium, and small. Our focus is mitochondria near the cuticular plate (CP) in vestibular Type 1 hair cells. Since these mitochondria are adjacent to the CP, we also see stereociliar rootlets (SRs) in close proximity. In addition, we hypothesized that the side facing the CP has a significantly larger amount of cristae junctions (CJs) compared to the opposite side in order to satisfy energy demand of rapidly regenerating SRs. This suggests a polarization of CJs towards one side, so that they can transport ATP and Ca^{2+} to points of interest, such as SRs and the CP (Perkins et al. 2010). Using IMOD software created by Univ. of Colorado, we examined and accurately traced individual contours that, when meshed, gave a very detailed structure of the mitochondria. By counting CJs on either side of the mitochondria, we can determine their density relative to the CP. Using “Get info” feature of IMOD we obtained accurate surface area measurements. Interestingly, lamellar cristae in one mitochondrion were seen to curve in the direction of the stereociliar rootlets and three mitochondria were observed to form a type of “super-mitochondrion” by alignment of their CJs and tethering of the outer mitochondrial membranes. Stereocilia are known to construct their actin from tip to base using myosin and rate-regulating proteins (Naoz et al. 2008). We hypothesize that mitochondria provide ATP for reconstitution of actin filaments and for maintaining the structure of the cuticular plate. The alignment of cristae between mitochondria may be able to increase ATP production. In conclusion, our results support the hypothesis that CJs are asymmetrically distributed in favor of structures of interest that require more ATP.

Naoz et al. (2008) Biophys J. 95: 5706–5718.
Perkins et al. (2010) J. Neurosci. 30: 1015-1026.
Rabl et al. (2009) J. Cell Biol. 185: 1047-1063.
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H9 UG-B

FUNCTIONAL AND MORPHOLOGICAL CHARACTERISTICS OF EFFERENT BOUTON MITOCHONDRIA OF THE INNER EAR

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Mitochondria are important organelles found in every cell of the body. The accepted structure of a mitochondrion consists of an outer and inner membrane (IM), the later folding in on itself forming structures known as cristae. The structure of the crista maximizes the membrane surface area over which cellular respiration occurs. Careful analysis of recent data gathered from electron microscopy has led to further investigation of structurally and functionally different subpopulations of mitochondria in the inner ear (Rabl et al.,

2009; Zick et al., 2009). Further investigation suggests the presence of three different mitochondrial subpopulations: large mitochondria, medium-sized mitochondria and small mitochondria, which are found in efferent boutons. The main focus of this study was the subpopulation in the efferent boutons, which are found contacting Type I and Type II hair cells of the inner ear. Utilizing IMOD software to obtain three-dimensional (3D) reconstructions of efferent mitochondria in close proximity to high energy-demanding structures, the morphological and functional characteristics of this subpopulation were studied. In a recent study (Perkins et al. 2010), it was discovered that cristae interact with the IM at specific points, termed cristae junctions (CJs). They also found that there were more CJs on the sides of mitochondria adjacent to synapses than on the opposite side, thus mitochondria appeared to be polarized. This suggests that Ca^{2+} and ATP are directed towards the synapse. Qualitative information gathered from our 3D reconstructions suggests that cristae are polarized towards similar high-energy-demanding structures such as the dense-core vesicles, synapses and adjacent mitochondria found in efferent boutons contacting afferent calyces. In addition, the tubular form of cristae observed in efferent mitochondria are a lower-energy form due to a lower capacity for dense ATP synthase molecule packing. Quantitative data included crista and IM surface areas, their respective volumes, and cristae junction counts. Key differences between efferent mitochondria and other subpopulations include the presence of tubular lower-energy form of cristae, smaller average surface area and volume, and smaller quantities of ATP synthase molecular packing. The exact correlation between CJ count and the high-energy-demanding structures remains to be determined. Nonetheless, our 3D reconstructions suggest a unique relationship between such structures, as well as the CJs between neighboring mitochondria.

Rabl et al. (2009) J. Cell Biol. 185: 1047-1063.
Zick et al. (2009) Biochim. Biophys. Acta. 1793: 5-19.
Perkins et al. (2010) J. Neurosci. 30: 1015-1026

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H10 G-B

MELANOPSIN SETS THE CONTRAST DETECTION THRESHOLD OF ON-ALPHA RETINAL GANGLION CELLS IN THE MOUSE RETINA

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) were initially thought to only mediate non-image forming visual behaviors such as circadian photoentrainment and pupil constriction. However, recent evidence suggests that melanopsin phototransduction in ipRGCs is required for behavioral contrast sensitivity. Here, we tested the hypothesis that melanopsin is required for normal contrast sensitivity at the cellular level. We specifically focused on the M4 subtype of ipRGCs, which are more commonly known as ON-alpha RGCs, because they are known to be highly sensitive to contrast.

We found that M4 ipRGCs lacking melanopsin exhibit significant deficits in contrast sensitivity across a wide range of light intensities. This effect is cell-autonomous and not due to abnormal retinal development because when we reintroduced the Gq-cascade in ipRGCs of Opn4 KO mice with Gq-DREADDS, we found that the contrast sensitivity of M4 ipRGCs could be rescued with application of clozapine N-oxide (CNO).

We have identified two possible mechanisms by which melanopsin could influence the contrast sensitivity of M4 ipRGCs. First, we found that WT M4 ipRGCs are significantly more depolarized compared to M4 cells lacking melanopsin in the presence of background light at all light intensities measured. Second, we found that melanopsin phototransduction increases the excitability of M4 cells in the presence of background light, which would allow them to respond more robustly to small synaptic currents.

These results demonstrate that the behavioral deficits in contrast sensitivity we observe in Opn4 KO animals begin at the cellular level in M4 ipRGCs, allowing us to link the signaling properties of a defined RGC population to a specific behavioral output. Melanopsin phototransduction primes M4 cells, through multiple mechanisms, to respond robustly to low contrast stimuli across a surprisingly wide range of light intensities.

Northwestern University Interdepartmental Neuroscience (NUIN)

H11 UG-A

ASSESSING THE ASYMMETRICAL DISTRIBUTION OF CRISTA JUNCTIONS IN TUBULAR MITOCHONDRIA LOCATED ADJACENT TO A POST-SYNAPTIC DENSITY OF A VESTIBULAR HAIR CELL RIBBON SYNAPSE

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Electron microscopic tomography (EMT) reveal that two inner portions of mitochondria articulate with each other via narrow tubular-shaped openings known as crista junctions (CJs) (Song et al., 2013). For our study, we predicted an asymmetrical distribution of crista junctions in mitochondria with tubular cristae located in the calyxplasm of a vestibular calyx ending adjacent to a post-synaptic density at a ribbon synapse in a vestibular hair cell. Synaptic ribbons are the form that synapses take in retinal photoreceptors and inner ear hair cells, consisting of synaptic vesicles and an electron-dense “ribbon” or docking site, and they are the location of vesicle fusion during active neurotransmitter release (Schmitz

et al., 1996). Using the EM tomograms and 3-D imaging software called IMOD, qualitative and computational data can be obtained on for tubular cristae, CJ numbers, shape, distribution and even the density of the matrix (Tasel et al., 2016). With these tools, we hypothesized that a statistically significantly larger number of CJs will appear on the sides of mitochondria near the ribbon synapse, as opposed to away from it. Furthermore, we expect metabolic activity at the synapse to also be higher, as ATP is required for signaling activity of the ribbon synapse provided by the tubular cristae (Perkins and Ellisman, 2007). Calculations, with the help of the IMOD software has helped us bear out these assumptions, using information on the number, total volume and other details on CJs of vestibular hair cells (Tasel et al., 2016) (Song et al., 2013)

Tasel et al. (2016) *J Struc Biol* 3: 253-271.
Schmitz et al. (1996) *J Neurosci* 16: 7109-16.
Perkins and Ellisman (2007) *Hdbk NChem Mol NBiol*, Springer, pp. 262 – 288.
Song et al. (2013) *Phys Rev* E6: 1-10.

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Eileen Foecking, Ph.D. — Loyola University

Third Year Councilors (2014-2017)
Irina Calin-Jageman, Ph.D. — Dominican University
Janis Eells, Ph.D. — University of Wisconsin, Milwaukee
Cindy Voisine, Ph.D. — Northeastern Illinois University

Second Year Councilors (2015-2017)
Stephanie Cacioppo, Ph.D. — University of Chicago
Emma Childs, Ph.D. — University of Illinois, Chicago
Lise Eliot, Ph.D. — Rosalind Franklin University
Michele Fornaro, Ph.D. — Midwestern University
Virgine Mansuy-Aubert, Ph.D. — Loyola University
Travis Stroub, Ph.D. — Rush University

First Year Councilors (2016-2018)
Marc Berman, Ph.D. — University of Chicago
Brinda Bradaric, Ph.D. — Rush University
Joanna Dabrowska — Rosalind Franklin University
Janis Eells, Ph.D. — University of Wisconsin, Milwaukee
Simon Kaja, Ph.D. — Loyola University
P. Hande Ozdlinler, Ph.D. — Northwestern University
Antonio Sanz-Clemente, Ph.D. — Northwestern University
Jim Wang, Ph.D. — University of Illinois Chicago

Undergraduate Program Liaison (2011-2017)
Naomi Wentworth, Ph.D. — Lake Forest College

Postdoctoral Councilors (2014-2017)
Shreaya Chakroborty, Ph.D. — Rosalind Franklin University
Haley Titus, Ph.D. — Northwestern University

Website Administrator (2014-2017)
Jennifer Yuan-Shih Hu, Ph.D. — Northwestern University

Social Media Coordinators (2016-2017)
Neemah BassiriRad — University of Illinois Chicago
Natalia Marangoni — University of Illinois Chicago

Brain Bee Coordinators (2016-2017)
Michael Calik, Ph.D. — University of Illinois Chicago
ShubhikDebBurmann, Ph.D. — Lake Forest College

Guest Councilors (2016-2017)
Andrea Poet, Ph.D. — Chicago Council on Science and Technology
Thomas Macek, Pharm.D., Ph.D. — Takeda
Eric Mohler, Ph.D. — AbbVie
Aaron Freeman — Artist in Residence

Notes