

51<sup>ST</sup> ANNUAL WCBR

JANUARY 14-19, 2018

WHISTLER, B.C.

# WINTER CONFERENCE ON BRAIN RESEARCH



# **WELCOME TO THE 2018 WINTER CONFERENCE ON BRAIN RESEARCH (WCBR)!**

Welcome to the 2018 Winter Conference on Brain Research (WCBR). This year is our 51<sup>st</sup> meeting, and only the second time the conference has been held outside the United States. The first time was 25 years ago for the 26<sup>th</sup> meeting which was also in Whistler. We are excited about the lineup of scientific and networking activities that will be offered during the conference.

The opening scientific presentation of the conference will be a plenary lecture during breakfast on Monday. Our speaker is Daphna Shohamy, Ph.D. from the Department of Psychology and Zuckerman Institute at Columbia University. Her research investigates the intersection between memory systems and decision making. Through innovative experimental design, this work has been transformative to our understanding of the cognitive processes used for human decision making. The lecture will be accessible and engaging to neuroscientists from all backgrounds and so should make a memorable start to the conference.

Throughout the conference, parallel panel presentations and daily poster sessions will span the breadth of neuroscience. There will be workshops on scientific-career pathways and on rigor and reproducibility in research. On Thursday evening, a special poster session will showcase the highest ranked posters from junior investigators. WCBR “Pioneer” panels will take place on Monday and Wednesday mornings. These sessions will each feature one speaker who has regularly attended the conference for decades and whose research has had major impact in neuroscience, followed by two earlier-career speakers from the same field. The 2018 Pioneer Awardees are Lakshmi Devi, Ph.D. for her body of work on G-protein-coupled-receptor signaling, and Daniel Weinberger, M.D. for his work on the genetic risk factors for schizophrenia and related disorders.

The conference will also host outreach events for the local community including school visits and a “brain talk” town meeting open to the general public. This year’s brain talk speaker is Susana Martinez-Conde, Ph.D. from SUNY Downstate Medical Center. She will use her research on visual perception as a

platform to describe the neural basis of magical illusions. The talk will be held on Tuesday evening, and will be followed by a book signing for Dr. Martinez-Conde's new release "Champions of Illusion", and her international bestseller "Sleights of Mind".

An important aspect of WCBR is the liberal opportunity for networking, from the opening reception on Sunday night through the banquet on Friday night. Whistler is a family-friendly resort which was ranked number one in the World by Ski Magazine in 2017. It has extensive slopes for all levels and plenty of activities for non-skiers. We hope you enjoy it.

*Paul E. M. Phillips, Conference Chair*  
*51<sup>st</sup> Winter Conference on Brain Research*  
*Whistler, B.C., January 14–19, 2018*

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# General Information

**WCBR INFORMATION DESK** is at the Whistler Conference Centre, Grand Foyer.

The Information Desk hours are as follows:

Sunday, January 14, 2018	12:00 p.m. – 7:00 p.m.
Monday, January 15, 2018	7:00 a.m. – 7:30 p.m.
Tuesday, January 16, 2018	7:00 a.m. – 7:30 p.m.
Wednesday, January 17, 2018	7:00 a.m. – 7:30 p.m.
Thursday, January 18, 2018	7:00 a.m. – 6:00 p.m.
Friday, January 19, 2018	7:00 a.m. – 6:00 p.m.

Pick up your badge at the WCBR Information Desk at the Whistler Conference Centre, Grand Foyer. If you have purchased guest meal tickets and/or a program book, these will also be available at registration.

**EXHIBITS AND POSTER SESSIONS** are in Sea to Sky Ballroom B.

**Poster presenters must set up their poster between 8:00 a.m. and 11:30 a.m. on the day of their session, except for Monday. Posters can be set up after 10:00 a.m. on Monday, January 15<sup>th</sup>. Photographing or recording material presented on a poster is not allowed unless explicitly given permission by the presenter.**

Poster Sessions are Monday, January 15 – Thursday, January 18 from 3:30 p.m. – 4:30 p.m. Presenters will be at their posters during that time. In addition, there is an optional poster viewing session Monday, January 15 – Wednesday, January 17, 12:00 p.m. - 12:30 p.m. Presenters are not required to be present during this time but are encouraged to stop by if available. Posters presented in sessions 1-3 should be removed by 8:30 p.m. on the day of their presentation.

On Thursday, January 18<sup>th</sup> there will be an additional poster session from 7:30 p.m. – 9:30 p.m. Posters presented on Thursday received high scores during the review process and will be judged onsite. Outstanding posters will be awarded at the banquet on Friday, January 19<sup>th</sup>.

**Please refer to pages 25–33 for a listing of poster sessions.**

**BREAKFAST** is served to all conference delegates during the keynote presentation on Monday, January 15<sup>th</sup> from 7:00 a.m. – 8:30 a.m. in the Sea to Sky Ballroom A.

Tuesday through Friday breakfast will be available from 6:30 a.m. – 8:30 a.m., in Whistler Conference Centre's Grand Foyer.

**LIFT TICKETS AND EQUIPMENT RENTALS:** Discounted lift tickets and equipment rentals for WCBR attendees are available **only** if reserved before January 10, 2018. Reserved tickets and/or vouchers can be picked up at any Whistler Blackcomb Guest Relations desk, Snow School Sales desk or Whistler Ticket window. Whistler ticket windows will have lift tickets available at regular price.

**BANQUET** table sign-up sheets will be posted next to the WCBR Information Desk. Please sign up in advance to reserve your table or seats. Special meals should have been requested during the registration process. If you have a specific request, please inquire at the WCBR Information Desk before Friday, January 19<sup>th</sup>.

**THE WCBR BUSINESS MEETING** will be Thursday, January 18<sup>th</sup> from 6:30 p.m. – 7:30 p.m. WCBR attendees are encouraged to attend and elect new members to the Board of Directors and the Executive Committee. Those wishing to serve can self-nominate; a nomination sign-up will be posted on the bulletin board near the WCBR Information Desk. Requirements for the positions will be posted. Please read them and make sure that you are eligible before signing up.

**ACTIVITIES FOR NON-SKIER/SNON-SNOWBOARDERS** will be posted on the bulletin board near the WCBR Information Desk and on the WCBR website/Facebook page. Non-skiers are encouraged to participate in group activities and network with other scientists during the free periods throughout the day. In addition to the group activities, non-skiers are encouraged to stop by the posters between 12:00 p.m. – 12:30 p.m., Monday, January 15 – Wednesday, January 17. Presenters are not required to attend, but are welcome. This informal poster-viewing session is an opportunity for non-skiers to network and meet colleagues for lunch.

# *Continuing Medical Education (CME)*

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Amedco and Winter Conference on Brain Research (WCBR). Amedco is accredited by the ACCME to provide continuing medical education for physicians.

Amedco designates this live activity for a maximum of 27 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.



*Don't forget to  
visit the posters  
& exhibits*

# *Committees*

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# Conference Support

## EDUCATIONAL GRANTS

The Winter Conference on Brain Research and Amedco would like to acknowledge the generosity of the companies and institutions listed below whose unrestricted educational grants have contributed to the overall quality of this meeting.

The National Institute On Drug Abuse of the National Institutes of Health under Award Number R13DA01234.

*The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.*

## CORPORATE SPONSORS

The Winter Conference on Brain Research appreciates the generous contribution of our Corporate Supporters.



## INDIVIDUAL SPONSORS AND ORGANIZATIONS

Thank you to the individuals and organizations that generously support the Travel Fellowship Program. The gift you make is used exclusively to introduce young neuroscientists to the WCBR meeting.

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*Save the Date!*

## **WINTER CONFERENCE ON BRAIN RESEARCH**

**JANUARY 28 - FEBRUARY 2, 2019  
WESTIN SNOWMASS RESORT**

# *Pioneer Awardees*

For the 51<sup>st</sup> WCBR meeting, we are honoring two scientists who have greatly contributed to the field of neuroscience, as well as to WCBR. These Pioneers will present their work during the special Pioneer Sessions on Monday, January 15<sup>th</sup> and Wednesday, January 17<sup>th</sup>.



## **LAKSHMI DEVI**

As a Professor of Pharmacology, Neuroscience, and Psychiatry at Icahn School of Medicine at Mount Sinai in New York, Dr. Lakshmi A. Devi is a leader in research on opioid and cannabinoid signaling in analgesia and addiction. She is also Dean for Academic Development and Enrichment at the Icahn School of Medicine at Mount Sinai. Among her ground-breaking scientific discoveries,

she and her team have demonstrated that G protein-coupled receptors can function as heterodimers, with unique pharmacology and selective upregulation associated with various disease states. With WCBR, Dr. Devi has attended for over 30 years, organized numerous panels and workshops, currently serves on the Board of Directors, and is taking an active role in mentoring and career development.



## **DANIEL WEINBERGER**

Dr. Daniel R. Weinberger is Director and CEO of the Lieber Institute for Brain Development at the Johns Hopkins Medical Center, and Professor of Psychiatry, Neurology, Neuroscience, and Human Genetics at the Johns Hopkins School of Medicine. His foundational work was the first to describe schizophrenia as a neurodevelopmental disorder and to identify genetic mechanisms

for disruptions in human cognition and emotional processing, research areas that have since evolved into new fields such as imaging genetics. Attending WCBR for almost 40 years, Dr. Weinberger is a long-standing and avid supporter of the meeting, its science, and its ski competitions. He has served on the Board of Directors and mentored many attendees.

# Program

## SUNDAY, JANUARY 14, 2018

**6:00 P.M. - 6:30 P.M.**

Welcome Reception for Newcomers,  
Travel Fellows, and Mentors •  
Garibaldi A

**6:30 P.M. - 7:30 P.M.**

Welcome Reception • Grand Foyer



## MONDAY, JANUARY 15, 2018

**7:00 A.M. - 8:30 A.M.**

Breakfast • Sea to Sky Ballroom A

**8:30 A.M. - 9:30 A.M.**

Plenary Address • Sea to Sky  
Ballroom A

**1. Using Memory to Guide Decisions**

*Presenter: Daphna Shohamy*

**9:45 A.M. - 10:45 A.M.**

Monday Pioneer Session # 1: Lakshmi  
Devi • Fitzsimmons

**2. Exploring the Mysteries of the  
Endogenous Opioid System**

*Pioneer: Lakshmi Devi*

*Chair: James Zadina*

*Investigators: Wakako Fujita, Elyssa  
Margolis*

**2:00 P.M. - 3:30 P.M.**

Career Development Workshop •  
Harmony A

**3. Being a Research Scientist in  
Academic and Non-Academic  
Settings: What Are the Challenges  
and Rewards?**

*Gretchen Snyder (Chair), Carrie  
Ferrario, Warren Hirst, Joel Kleinman,  
Amy Newman, Kyle Smith*

Career Development Workshop •  
Harmony B

**4. Enhancing Scientific Rigor and  
Reproducibility: Are We Doing  
Better?**

*Lique Coolen (Chair), Molly Lucas,  
Yavin Shaham, Lori Isom*

**3:30 P.M. - 4:30 P.M.**

Exhibits and Poster Session I • Sea to  
Sky Ballroom B

**MONDAY, JANUARY 15, CONTINUED**

**4:30 P.M. - 6:30 P.M.**

**Panel • Fitzsimmons**

**5. A Slippery Slope to Addiction: A Role for Neuroinflammation**

*Christopher Evans (Chair), Anna Taylor, Sandra Comer, Spencer Bujarski, Catherine Cahill*

**Short Course • Garibaldi A**

**6. Non-Mammalian Animal Models for Neuroscience Research**

*Lloyd Fricker (Chair), Monte Westerfield, Sean McBride, Michael Aschner, Catharine Rankin*

**Panel • Garibaldi B**

**7. What About Me? The Paraventricular Thalamic Nucleus in Reward Circuitry**

*Jacqueline McGinty (Chair), Morgan James, Paolo Campus, James Otis, Xiaoke Chen*

**Panel • Harmony A**

**8. Harnessing Metabolic Systems to Treat Epilepsy**

*Chris Dulla (Chair), Mark Beenhakker, John Huguenard, Susan Masino, Jong Rho*

**Panel • Harmony B**

**9. A Novel Role for Mitochondrial Metabolism in Fragile X Autism Spectrum Disorder**

*George Porter, Richard Levy, Elizabeth Jonas (Chair), Thomas Jongsens*

**Panel • Rainbow Theater**

**10. High Excitability: Cannabinoids, Neural Excitability and Implications for Neurological Disorders**

*Matthew Hill (Chair), Lynn Raymond (Co-chair), Gordon Teskey, Istvan Katona, Marja Sepers, Roger Thompson*

**Panel • Spearhead**

**11. Targeting Cyclic Nucleotides for Improving CNS Function: A Black Diamond Descent?**

*Jos Prickaerts (Chair), Lawrence Wennogle, Michy Kelly, Arjan Blokland (Co-chair)*

**Panel • Wedgemount**

**12. Dissecting the Heterogeneity of Clinical Outcomes Associated With Mood-Altering Treatments: From Drugs to Neurostimulation**

*Melanie Blair, Daphne Voineskos, Miklos Argyelan, Anil Malhotra (Chair)*

**6:30 P.M. - 7:00 P.M.**

**Refreshment Break • Valley Foyer**

**7:00 P.M. - 8:30 P.M.**

**Panel • Fitzsimmons**

**13. Selective Hypothalamic Inputs to the Lateral Habenula Underline Differential Motivated Behaviors**

*Marisela Morales (Chair), David Barker (Co-chair), Meghan Flanigan, Salvatore Lecca, Richard O'Connor*

**Panel • Garibaldi A**

**14. Assessment of the Health Impacts of Circadian and Sleep-Wake Disruption in Human**

*Diane Boivin (Chair), Philippe Boudreau, Guy Dumont*

**Panel • Garibaldi B**

**15. What's Down That Slope? Orbitofrontal Cortex and Amygdala Contributions to Outcome Anticipation**

*Nicolas Schuck, Peter Rudebeck, Alicia Izquierdo, Kate Wassum (Chair)*

**Panel • Harmony A**

**16. New Approaches for Finding Novel Anti-Seizure Drugs for Pharmacoresistant Epilepsy**

*Yevgeny Berdichevsky, Francis Dudek (Chair), Chris Dulla*

**Panel • Harmony B**

**17. Let's Make This Clear: 3D Analysis of Neural Circuits**

*Lique Coolen (Chair), Aleisha Moore, Jonathan Epp*

**Panel • Rainbow Theater**

**18. Simplifying Big Data in Neuroscience and Brain Research**

*Jeff Leek, Barbara Engelhardt, John Muschelli, Andrew Jaffe (Chair)*

**Panel • Spearhead**

**19. Neuroleptics for ALS: From Chemical Genetics to Clinical Trial**

*Pierre Drapeau (Chair), Alex Parker, Kessen Patten, Elsa Tremblay, Lawrence Korngut*

**Panel • Wedgemount**

**20. Remembering the Brain in Orthopedic Rehabilitation: Translational Neuroscience to Understand Musculoskeletal Injury**

*Alan Needle, Adam Lepley, Dustin Grooms (Chair)*

*Save the Date!*

**WINTER CONFERENCE  
ON BRAIN RESEARCH**

**JANUARY 28 - FEBRUARY 2, 2019  
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## TUESDAY, JANUARY 16, 2018

**6:30 A.M. - 8:30 A.M.**

**Breakfast • Grand Foyer**

**7:30 A.M. - 9:30 A.M.**

**Panel • Fitzsimmons**

**21. Instructive Signals for Aversive Learning and Memory**

*Sung Han, Bo Li, Joshua Johansen (Chair), Sabine Krabbe*

**Panel • Garibaldi A**

**22. One Size Does Not Fit All: Individual Differences in Substance Abuse**

*Jessica Barson (Chair), Donna Calu, Anushree Karkhanis, Sarah Leibowitz*

**Panel • Garibaldi B**

**23. Associative Thalamic Control of Reward Seeking**

*Bernard Balleine, Brian Mathur (Co-chair), Gavan McNally, Xuan Li (Chair)*

**Panel • Harmony A**

**24. Post-Traumatic Stress Disorder in the 21st Century: Genes, Environment, and Treatment**

*Joel Kleinman (Co-chair), Rachel Yehuda, Thomas Hyde (Chair), Felicia Gould, Allison Feduccia*

**Panel • Harmony B**

**25. Neuronal Circuit Basis for Auditory Cortical Function**

*Li Zhang (Chair), Daniel Polley (Co-chair), Alfonso Junior Apicella, Hysell Oviedo, Patrick Kanold, Robert Liu*

**Panel • Rainbow Theater**

**26. Frontiers in Aging Brain Research: Determining Neurobiological Substrates of Age-Related Cognitive Decline Towards Enhancing Cognitive Resilience**

*Jennifer Bizon, Mara Mather, Peter Rapp, Natalie Ebner (Chair)*

**Panel • Spearhead**

**27. Circuit Trails of Kappa Opioid Involvement in Affect and Pain**

*Jose Moron-Concepcion, Daniel Bloodgood, Jordan McCall, Catherine Cahill (Chair)*

**Panel • Wedgemount**

**28. The Synapse and Neuropsychiatric Disorders**

*Amelia Gallitano (Chair), Shenfeng Qiu, Yi Zuo, Kuan Hong Wang*

**3:30 P.M. - 4:30 P.M.**

**Exhibits and Poster Session II • Sea to Sky Ballroom B**

**4:30 P.M. - 6:30 P.M.**

**Panel • Fitzsimmons**

**29. Mechanisms by Which Viruses Impact the Brain & Behavior**

*Gretchen Neigh (Chair), Jason Paris, Jaclyn Schwarz, Javier Gonzalez-Maeso*

**Panel • Garibaldi A**

**30. Metabolic Dysregulation in Animal Models of Autism Spectrum Disorders**

*Sean McBride (Chair), Ilse Gantois, Jelena Popic, Thomas Jongens (Co-chair)*

**Panel • Garibaldi B**

**31. It's All in Your Head:  
Neurobiological Mechanisms of  
Anxiety**

*Zoe McElligott (Co-chair), Matthew Hill (Chair), Bitá Moghaddam, Michael Bruchas*

**Panel • Harmony A**

**32. Pathway-Specific Modulation of  
Neuronal Activity in Relapse to  
Drug-Seeking**

*Stephen Mahler, Giuseppe Giannotti (Chair), Aaron Garcia, Marco Venniro*

**Panel • Harmony B**

**33. Neuroimaging Psychiatric  
Biotypes**

*Marco Leyton (Chair), Hugh Garavan, Yuliya Nikolova, Patricia Conrod*

**Panel • Rainbow Theater**

**34. Recent Progress From  
Human Stem Cell Models of  
Neuropsychiatric Disease**

*Sergiu Pasca, Karun Singh, Tracy Young-Pearse, Kristen Brennand (Chair)*

**Panel • Spearhead**

**35. Does Phasic Dopamine = Excess  
Value or Might It Serve a Broader  
Role in Error-Based Learning?**

*Thorsten Kahnt, Geoffrey Schoenbaum (Chair), Ronald Keiflin, Paul Phillips*

**Panel • Wedgemount**

**36. The Role of Oxidative Stress in  
Parkinson's Disease: From Origins  
to Outcomes**

*Eugene Mosharov, Louis-Eric Trudeau, Kristen Stout, Leslie Sombers (Chair)*

**7:00 P.M. - 8:30 P.M.**

**Brain Talk Town Meeting • Sea to Sky  
Ballroom A**

**37. Champions of Illusion**

*Susana Martinez-Conde*

*Save the Date!*

**WINTER CONFERENCE  
ON BRAIN RESEARCH**

**JANUARY 28 - FEBRUARY 2, 2019  
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## WEDNESDAY, JANUARY 17, 2018

**6:30 A.M. - 8:30 A.M.**

**Breakfast •** Grand Foyer

**7:30 A.M. - 9:30 A.M.**

**Panel •** Fitzsimmons

38. **The Neglected Nuclei of Addiction: Putting Understudied Brain Regions in the Limelight**

*Christopher Chen, Elizabeth Glover (Chair), Candice Contet (Co-chair), Christelle Baunez*

**Panel •** Garibaldi A

39. **Treatments for Intellectual Disability and Autism Targeting Protein Synthesis: The Prospects for Individualized Treatments**

*Francois Bolduc (Chair), Eric Klann, Carolyn Beebe Smith, Sebastien Jacquemont*

**Panel •** Garibaldi B

40. **Rodent Models of Cannabinoid Administration: Novel Approaches and Surprising Findings**

*Barry Setlow (Chair), Ryan McLaughlin, Michael Taffe, Mary Torregrossa (Co-chair)*

**Panel •** Harmony A

41. **Chronic Behavioral Effects of Neurological and Psychological Trauma**

*Christopher Olsen (Chair), Cole Vonder Haar, Alana Conti, Carrie Jones*

**Panel •** Harmony B

42. **When Roads Converge: What Integrative Homeostatic Circuits Teach Us About Brain Plasticity in Health and Disease**

*Carie Boychuk (Chair), Javier Stern, David Mendelowitz, Jeffrey Tasker, Jasenka Zubcevic*

**Panel •** Rainbow Theater

43. **GPCR Functional Selectivity: When Bias is a Good Thing**

*Amy Newman (Chair), Laura Bohn, Marc Caron, David Sibley, J. Robert Lane*

**Panel •** Spearhead

44. **Alzheimer's Disease and Comorbidities: Modelling and Treatment Strategies**

*JoAnne McLaurin, Jerome Robert, Cheryl Wellington, Isabelle Aubert (Chair)*

**Panel •** Wedgemount

45. **Organization and Plasticity of Excitatory and Inhibitory Synapses**

*Elva Diaz, Susumu Tomita, David Bredt (Chair), Andres Maricq*

**9:45 A.M. - 10:45 A.M.**

**Wednesday Pioneer Session #2:**

**Daniel Weinberger •** Fitzsimmons

46. **Sex, Signaling and Human Brain Development**

*Pioneer: Daniel Weinberger  
Chair: Thomas Hyde  
Investigators: Elizabeth Tunbridge, Alexandra Ycaza Herrera*

### **3:30 P.M. - 4:30 P.M.**

**Exhibits and Poster Session III •** Sea to Sky Ballroom B

### **4:30 P.M. - 6:30 P.M.**

**Panel •** Fitzsimmons

**47. Net Gain and Loss: Perineuronal Nets, Plasticity, and Drugs of Abuse**

*Barbara Sorg (Chair), John Harkness (Co-Chair), Carolyn Johnson, Amy Lasek, Jordan Blacktop, Travis Brown*

**Panel •** Garibaldi A

**48. Two Sides of the Same Slope: Dissecting Separate and Shared Neural Substrates of Reward and Aversion**

*Rachel Smith, Sade Spencer (Chair), Stan Floresco, Peter Vento*

**Panel •** Garibaldi B

**49. Novel Brain Stimulation Techniques to Optimize Plasticity Induction in Humans**

*Faranak Farzan, Corey Keller (Chair), Cammie Rolle, Molly Lucas*

**Panel •** Harmony A

**50. New Therapeutic Approaches to Epilepsies Caused by Sodium Channelopathies**

*Peter Ruben (Chair), William Catterall, Lori Isom, Steven Petrou, Charles Cohen*

**Panel •** Harmony B

**51. Dissecting the Hypothalamic Arcuate Nucleus – Epicenter of Steroid Action in the Brain**

*Paul Micevych (Chair), Kevin Sinchak, Oline Ronnekleiv, Stephanie Correa*

**Panel •** Rainbow Theater

**52. Examining the Role of Autophagy in Animal Models of Intellectual Disability and Autism Spectrum**

*Suzanne Zukin (Chair), Leonard Kaczmarek, Elizabeth Jonas, Sean McBride (Co-chair)*

**Panel •** Spearhead

**53. Cues for Bad Behaviour: The Role of Aberrant Motivation Elicited by Conditioned Stimuli in Addictive and Compulsive Disorders**

*Kathryn Cunningham (Co-chair), Catharine Winstanley (Chair), Roshan Cools, Valerie Voon*

**Panel •** Wedgemount

**54. Circuit and Synaptic Mechanisms of Stress Responses: Towards an Integration of Neuroendocrine and Behavioral Responses**

*Victor Viau, Jaideep Bains, Jamie Maguire, Jason Radley (Chair)*

### **6:30 P.M. - 7:00 P.M.**

**Refreshment Break •** Valley Foyer

### **7:00 P.M. - 8:30 P.M.**

**Panel •** Fitzsimmons

**55. Dexterity: A Problem for Robotics and Biology**

*Andrew Schwartz (Chair), Neville Hogan, Gerald Loeb, Marco Santello, Francisco Valero-Cuevas*

**Panel •** Garibaldi A

**56. Secreted Axon Guidance Cues, Proteoglycans, and Perineuronal Nets in the Developing and Adult CNS**

*Jessica Kwok, Timothy Kennedy (Chair), Stephanie Harris*

## WEDNESDAY, JANUARY 17, CONTINUED

### Panel • Garibaldi B

#### 57. Ketamine and Depression

*Chadi Abdallah, Christine Ann Denny,  
Mohamed Kabbaj (Chair)*

### Panel • Harmony A

#### 58. Novel Neuroprosthetic Technologies for Diagnosis, Monitoring, and Treatment of Psychiatric Illness

*Darin Dougherty (Chair), Thilo Deckersbach, Alik Widge (Co-chair),  
Todd Herrington, Christopher Salthouse*

### Panel • Harmony B

#### 59. The Role of Activity-Dependent Neuronal Ensembles in Learning

*Leslie Whitaker (Chair), Zoe Donaldson, Rajtarun Madangopal,  
Joseph Ziminski*

### Panel • Rainbow Theater

#### 60. Microglial Targets to Treat Neuroinflammation in Neurological Disorders

*Tsuneya Ikezu, Roland Staal, Zoe Hughes (Chair)*

### Panel • Spearhead

#### 61. Circadian Clocks in Biology and Medicine: Central Control of Peripheral Oscillator Function

*Joseph Takahashi (Chair), Carla Green (Co-chair), Joseph Bass,  
Gianluca Tosini, P. Michael Iuvone*

### Panel • Wedgemount

#### 62. The Cognitive Hypothalamus

*Geoffrey Schoenbaum (Chair), Mark Rossi, Yoav Livneh, Joey Burnett,  
Melissa Sharpe (Co-chair)*



*Save the Date!*

## WINTER CONFERENCE ON BRAIN RESEARCH

**JANUARY 28 - FEBRUARY 2, 2019  
WESTIN SNOWMASS RESORT**

# THURSDAY, JANUARY 18, 2018

**6:30 A.M. - 8:30 A.M.**

**Breakfast • Grand Foyer**

**7:30 A.M. - 9:30 A.M.**

**Panel • Fitzsimmons**

63. **The NMDA Receptor/CaMKII Complex is the Center of the PSD Universe**

*Andres Barria, Lonnie Wollmuth, Katherine Roche, Roger Nicoll (Chair)*

**Panel • Garibaldi A**

64. **Stress-Induced Alterations in Limbic Neurochemistry**

*Rodrigo España (Chair), Matthew Wanat, Zachary Brodник, Lori Knackstedt, Brian Baldo*

**Panel • Garibaldi B**

65. **Mesoscopic Circuit Architecture at the Whole-Brain Level: How Structural Connectome can be Used for Functional Studies and for Disease Mechanisms**

*Hongwei Dong, Tianyi Mao (Chair), Lindsay Schwarz, Bingxing Huo*

**Panel • Harmony A**

66. **The Apple Never Falls Far: Parental Exposure to Alcohol and Other Drugs of Abuse has Deleterious Consequences on Progeny**

*Fair Vassoler, Chris Pierce, Gregg Homanics, Mathieu Wimmer (Chair)*

**Panel • Harmony B**

67. **Bench to Bedside Drug Development for the Brain: Learning From Failures**

*Nigel Greig (Chair), Howard Feldman, Nick Brandon, Thomas Swanson*

**Panel • Rainbow Theater**

68. **Cannabinoid Signaling in Health and Disease**

*Daniel Morgan, Josée Guindon (Chair), Lakshmi Devi, Alex Straker*

**Panel • Spearhead**

69. **Opioids in the Thalamo-Cortical-Striatal Pathway**

*John Williams (Chair), William Birdsong, Matthew Banghart, Aya Matsui, Ream Al-Hasani*

**Panel • Wedgemount**

70. **Individual Differences and Biomarkers in Decision Making and Addiction Vulnerability**

*Alicia Izquierdo, Melanie Tremblay, Nicola Grissom (Chair), Stephanie Groman*

**10:00 A.M. - 12:00 P.M.**

**Smitty Stevens Ski Race • GMC Race Course**

**12:00 P.M. - 2:30 P.M.**

**Mountain Lunch • Garibaldi Lift Company**

**3:30 P.M. - 4:30 P.M.**

**Exhibits and Poster Session IV • Sea to Sky Ballroom B**

## THURSDAY, JANUARY 18, CONTINUED

### 4:30 P.M. - 6:30 P.M.

#### Panel • Fitzsimmons

71. **Opioid Alternatives to Opiates: New Approaches for Separating Analgesic From Adverse Effects Mediated by Opioid Receptors**

*Elyssa Margolis, James Zadina (Chair), Wakako Fujita, Susruta Majumdar*

#### Panel • Garibaldi A

72. **Riding High With Buds in BC: Recent Advances in Cannabis/ Cannabinoid Science**

*Alan Budney (Chair), Brian Thomas, Ryan Vandrey, Evan Herrmann, Marcel Bonn-Miller*

#### Panel • Garibaldi B

73. **Decision-Making and the Amygdala: Implications for Drug Addiction**

*Caitlin Orsini (Co-chair), Mike Robinson (Chair), Yavin Shaham, Zoe McElligott*

#### Panel • Harmony A

74. **Hitting the Brakes: Mechanisms of Inhibitory Control of Dopaminergic Signaling in the VTA**

*Larry Zweifel, Abigail Polter (Chair), Alexey Ostroumov, Robyn St. Laurent (Co-chair)*

#### Panel • Harmony B

75. **Postsynaptic Mechanisms Regulating the Assembly and Stability of Neural Circuits Relevant to Neuropsychiatric Disorders**

*Shernaz Bamji, Peter Penzes, Gavin Rumbaugh (Chair), Courtney Miller*

#### Panel • Rainbow Theater

76. **Inflammation and Alpha-Synuclein Aggregation Along the Gut-Brain Axis in Parkinson's Disease**

*Anurag Tandon (Chair), Michel Desjardins, Kelvin Luk, Alain Dagher, Warren Hirst*

#### Panel • Spearhead

77. **The Pros and Cons of Modulating Prefrontal Cortical Function**

*Robert Spencer, David Devilbiss (Chair), Craig Berridge, Brian Baldo*

#### Panel • Wedgemount

78. **A Tectonic Shift in Our Thinking: Understanding the Contribution of Glia to Neural Plasticity and Behavior**

*Sade Spencer (Chair), Michael Scofield, Kyle Brown, Alfonso Araque, Heather Boger*

### 6:30 P.M. - 7:30 P.M.

#### WCBR Business Meeting • Sea to Sky Ballroom A

All are invited and encouraged to attend.

### 7:30 P.M. - 9:30 P.M.

#### Special Poster Session and Reception • Sea to Sky Ballroom B

# FRIDAY, JANUARY 19, 2018

**6:30 A.M. - 8:30 A.M.**

**Breakfast • Grand Foyer**

**7:30 A.M. - 9:30 A.M.**

**Panel • Fitzsimmons**

79. **Mixed Drinks: Alcohol Comorbidities**

*Alana Conti (Chair), Anna Lee, Bryan Yamamoto, Nick Gilpin*

**Panel • Garibaldi A**

80. **Striatum Subregions and Motivated Behavior**

*Kyle Smith (Chair), Stephan Lammel, Matthew Wanat, Stephanie Borgland*

**Panel • Garibaldi B**

81. **Crosstalk Between the Epigenome and Neural Circuits in Drug Addiction**

*Chris Pierce, Erin Calipari (Chair), Philipp Mews (Co-chair), Marcelo Wood*

**Panel • Harmony A**

82. **Biomarkers for Huntington's Disease: Why do We Need Them and What can They Tell Us?**

*Elizabeth Thomas (Chair), Amit Joshi, Blair Leavitt, Steven Potkin (Co-chair)*

**Panel • Harmony B**

83. **Mechanisms for Visual Cortical Plasticity and Reactivation of Plasticity**

*Huizhong Tao (Chair), Weifeng Xu, Aaron McGee (Co-chair), Joshua Trachtenberg, Hey-Kyoung Lee*

**Panel • Spearhead**

84. **Cerebellar Modulation of Non-Motor Brain Functions**

*Hirofumi Fujita, Erik Carlson (Chair), Krystal Parker (Co-chair), Peter Tsai*

**Short Course • Wedgemount**

85. **From Mapping to Modulation: Using Intrinsic Neural Architecture to Develop Clinically Useful Neuromodulation Tools for Psychiatry**

*Katharine Dunlop, Jonathan Downar, Colleen Hanlon (Chair)*

**4:15 P.M. - 4:30 P.M.**

**Refreshment Break • Valley Foyer**

**4:30 P.M. - 6:30 P.M.**

**Panel • Fitzsimmons**

86. **Neuroinflammation in Parkinson's Disease-The Chicken and the Egg**

*Caryl Sortwell, Ashley Harms, Malu Tansey (Co-chair), Fredric Manfredsson (Chair)*

**Panel • Garibaldi A**

87. **Rapid Trafficking in the Moguls: State Dependent Synaptic Plasticity**

*Graham Knott, Victoria Luine (Chair), Kristen Harris, Lique Coolen*

**Panel • Harmony A**

88. **There's Always Room for Dessert: Neural and Behavioral Alterations Contributing to Obesity**

*Carrie Ferrario (Chair), Stephanie Borgland, Catharine Winstanley, Rifka Derman, Uku Vainik*



## FRIDAY, JANUARY 19, CONTINUED

### Panel • Harmony B

89. **Neural Circuit Disruption in Traumatic Brain Injury: Looking Beyond Pathology to Network Alterations Across Different Severities and Modalities**

*Cole Vonder Haar, Matthew Hemphill, Akiva Cohen (Chair), Kaitlin Folweiler*

### Panel • Spearhead

90. **Enzymatic Control of Endocannabinoids: Budding Targets to Regulate Brain Function and Behavior**

*Andrea Hohmann, Aron Lichtman, Daniel Covey, Carl Lupica (Chair)*

### Panel • Wedgemount

91. **mGlu5 Receptors at the Intersection of Stress, Sex and Addiction: Tales of Rats and Humans**

*Irina Esterlis, Marek Schwendt (Chair), Erin Larson, M. Foster Olive*

**6:45 P.M. - 7:30 P.M.**

**Closing Reception • Grand Foyer**

**7:30 P.M. - 11:45 P.M.**

**Awards Banquet and Dance • Sea to Sky Ballroom**

*Save the Date!*

## WINTER CONFERENCE ON BRAIN RESEARCH

**JANUARY 28 - FEBRUARY 2, 2019  
WESTIN SNOWMASS RESORT**

# POSTER SESSION I

## MONDAY, JANUARY 15, 2018 • SEA TO SKY BALLROOM B

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Monday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters should be set up by 11:30 a.m. on Monday and must be removed by 8:30 p.m. on Monday.

- |   |   |
|---|---|
| <p><b>M1. Assessment of “Stress-Responsivity” in Sign-Trackers and Goal-Trackers</b><br/><i>Sofia Lopez</i></p> <p><b>M2. Decoding Ventral Striatal Oscillations Related to Feeding Behavior: Toward Real-Time Models That Generalize Across Individual Animals and Brain States</b><br/><i>Lucas Dwiell</i></p> <p><b>M3. Dissecting Gene-Early Life Stress Interactions in Cocaine Responsiveness and Sensorimotor Gating</b><br/><i>Tod Kippin</i></p> <p><b>M4. Endocannabinoids on Cortical Terminals Orchestrate Local Modulation of Dopamine Release in the Nucleus Accumbens</b><br/><i>Yolanda Mateo</i></p> <p><b>M5. The Effect of Inhibited Dopamine Release in the Nigrostriatal Pathway on Risky Decision Making in Rats</b><br/><i>Brett Hathaway</i></p> <p><b>M6. Cerebellar Activation During a Multisensory Stroop Task is Associated With Mood, Anxiety and Alcohol Use Disorder (AUD) Severity in AUD</b><br/><i>Claire Wilcox</i></p> | <p><b>M7. Auditory Processing of Mate Choice Cues in the Female Songbird</b><br/><i>Koedi Lawley</i></p> <p><b>M8. CB1 Receptor Signaling Enhances Associative Strength in Pavlovian and Instrumental Settings</b><br/><i>Donna Calu</i></p> <p><b>M9. Characterization of Behavioral and EEG Phenotypes in a Novel Rat Model of Angelman Syndrome</b><br/><i>Anne Anderson</i></p> <p><b>M10. Comparison of Device Assisted Therapies for Parkinson’s Disease</b><br/><i>Neil Mahant</i></p> <p><b>M11. Progranulin Loss Dysregulates Splenic and Peripheral Blood Immune Cells Populations and may Contribute to Neuroinflammation and Neurodegeneration in Early-Onset Dementia</b><br/><i>Thomas Kukar</i></p> <p><b>M12. Three-Dimensional Imaging of Kisspeptin Neurons in the Mammalian Brain Using Optical Tissue Clearing and Immunocytochemistry</b><br/><i>Aleisha Moore</i></p> |
|---|---|

**M13. Activation of Hypothalamic Oxytocin Neurons Restores Oxytocin Release to Parasympathetic Cardiac Vagal Neurons of the Brainstem in Left Ventricular Hypertrophy Induced Heart Failure**

*David Mendelowitz*

**M14. Cue-Triggered Food-Seeking is Modulated by the Ovarian Cycle in Obesity-Prone, but not in Obesity-Resistant Female Rats**

*Yanaira Alonso-Caraballo*

**M15. GABAA Agonist Drugs Increase Neonatal Seizure-Associated Neuronal Injury**

*Claude Wasterlain*

**M16. Spreading Depolarization-Induced Disruption of Dendrites and Dendritic Spines in the Murine Neocortex Revealed by Two-Photon Imaging and Quantitative Serial Section Electron Microscopy**

*Sergei Kirov*

**M17. Lipid Peroxidative Damage is Higher in Traumatic Brain Injuries Complicated by Parenchymal Hemorrhages: Rationale for the Selective Benefit of Tirilazad in Traumatic Subarachnoid Hemorrhage Patients**

*Edward Hall*

**M18. Repeat Concussion Causes Impairments in Attention and Motor Impulsivity**

*Kris Martens*

**M19.  $\mu$ -Opioid Receptors in Nociceptive Afferents Produce a Sustained Suppression of Hyperalgesia During Chronic Pain**

*Juan Carlos Marvizon*

**M20. The Parabrachial Complex: A Nexus of Ascending and Descending Pain Systems**

*Asaf Keller*

**M21. DLPFC Transcriptome Defines Two Molecular Subtypes of Schizophrenia**

*C. Harker Rhodes*

**M22. Increased GABA-Mediated Phasic Inhibition in the Contralateral Hippocampus 7 Days Following Middle Cerebral Artery Stroke**

*Nicole McKinnon*

**M23. mTORC1-Mediated Late LTP in Somatostatin Interneurons Regulates Hippocampal Network Plasticity and Memory**

*Jean-Claude Lacaille*

# POSTER SESSION II

**TUESDAY, JANUARY 16, 2018 • SEA TO SKY BALLROOM B**

Posters will be available for viewing 12:00 p.m. – 7:00 p.m. on Tuesday.  
Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters should be set up by 11:30 a.m. on Tuesday and must be removed by 8:30 p.m. on Tuesday.

**Tu1. Modulation of Kappa Opioid Receptor Activity by Nicotine and Ethanol in Adolescent and Adult Male Rats**

*Sarah Cross*

**Tu2. Training Future Clinicians Through Clinical Encounters in Neuroscience**

*Bradley Tanner*

**Tu3. Alcohol in the Central Nucleus of the Amygdala: Sex Differences, Effect of Adolescent Alcohol Consumption, and Modulation by Neuropeptides**

*Zachary Rodd*

**Tu4. Forebrain Dopamine Value Signals are Independent of Midbrain Dopamine Cell Firing**

*Jeffrey Pettibone*

**Tu5. Net Gains and Losses: How Daily Fluctuations in Perineuronal Net Intensity may Impact Behavior**

*John Harkness*

**Tu6. Sex Differences in Optogenetic Self-Stimulation of Excitatory Inputs to the Nucleus Accumbens Shell and Subsequent Locomotor Sensitization to Morphine**

*Erin Larson*

**Tu7. Adaptive Immunity in Depressive Mood States**

*Miles Herkenham*

**Tu8. Dysregulation of Non-CG Methylation by Child Abuse**

*Gustavo Turecki*

**Tu9. Effects of Outcome Devaluation on Sign- and Goal-Tracking**

*Jonathan Morrow*

**Tu10. The Contribution of Rodent Secondary Motor Cortex to Feedback Guided Actions**

*Drew Schreiner*

**Tu11. A Prefrontal-Basal Forebrain Circuit Shapes Neuroendocrine and Behavioral Stress Responses**

*Shane Johnson*

**Tu12. Lactobacillus Reuteri Administration Alters Social Affiliation and Neurochemical Marker Expression in the Brain in Female Prairie Voles**

*Meghan Donovan*

**Tu13. Laminar Distribution of High Frequency Oscillations in the Epileptic Brain Induced by Focal Cortical Dysplasia in Mice**

*Qian-Quan Sun*

**Tu14. More Severe Clinical Deficits are Associated With Greater Disruption of the Blood Brain Barrier During the First 24 Hours After Brain Hemorrhage**

*Richard Leigh*

**Tu15. Voltammetry for Studying Neuroenergetics: A Progress Report**

*Greg McCarty*

**Tu16. Reelin Signal Activation is Associated With Motor Function Recovery in the Neuron Transplantation of Hemiplegic Mice**

*Nagisa Nakata-Arimitsu*

**Tu17. Gi/o Protein-Coupled Receptors Inhibit Neurons but Activate Astrocytes and Stimulate Gliotransmission**

*Caitlin Durkee*

**Tu18. Homeostatic Mechanisms and the Nerve-Muscle Interaction**

*Sonsoles de Lacalle*

**Tu19. The Role of Endogenous Chaperone Protein RTP4 in Opioid Receptor Heteromer Regulation**

*Wakako Fujita*

**Tu20. Peptide Based Inhibitor of the Scaffolding Protein PICK1 Underlying Maladaptive Synaptic Plasticity**

*Kenneth Madsen*

**Tu21. New Insights Into Mechanisms Regulating Central Release of Neuropeptides**

*Javier Stern*

**Tu22. A Mechanistic Approach to Neuroprotective Potential of Zonisamide in Seizures: Pharmacokinetic & Pharmacodynamic Link**

*Baldeep Kumar*

# POSTER SESSION III

**WEDNESDAY, JANUARY 17, 2018 • SEA TO SKY BALLROOM B**

Posters will be available for viewing 12:00 p.m. – 7:00 p.m. on Wednesday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters should be set up by 11:30 a.m. on Wednesday and must be removed by 8:30 p.m. on Wednesday.

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|---|---|
| <p><b>W1. Unbiased Profiling of the Cellular Targets of Low-Dose Ethanol</b><br/><i>Daniel Bloodgood</i></p> <p><b>W2. <math>\alpha</math>-MSH-Mediated Regulation of VTA MC3R Neuron Activity</b><br/><i>Katherine West</i></p> <p><b>W3. Altered Dopamine-Stimulated Reward Seeking and Endocannabinoid Activity due to Adolescent Cannabinoid Receptor Stimulation</b><br/><i>Adam Manooogian</i></p> <p><b>W4. Acute Chemogenetic Inhibition of Accumbal Dopamine has Sexually Dimorphic Effects in a Rat Analogue of the Iowa Gambling Task</b><br/><i>Tristan Hynes</i></p> <p><b>W5. The Importance of Identifying the Endogenous Peptides Released and the Receptors They Act on in the VTA</b><br/><i>Elyssa Margolis</i></p> <p><b>W6. Perineuronal Nets may Have Time Dependent Effects Following Cocaine Exposure in Modulating the Firing Properties of Fast Spiking Interneurons in the Medial Prefrontal Cortex</b><br/><i>Emily Jorgensen</i></p> | <p><b>W7. Identification of Novel CACNA1C Splice Variants in Human Brain Using Nanopore Sequencing</b><br/><i>Elizabeth Tunbridge</i></p> <p><b>W8. Orbitofrontal Cortex Controls State-Dependent Value Updating for Action Control</b><br/><i>Emily Baltz</i></p> <p><b>W9. Time-of-Day and Time Spent Awake Affect Alertness and Performance Levels of Ship Pilots on Irregular Schedule</b><br/><i>Philippe Boudreau</i></p> <p><b>W10. Is Netrin-1 a Long-Range Chemoattractant?</b><br/><i>Celina Cheung</i></p> <p><b>W11. Effects of Prostacyclin Signaling on Alzheimer's Disease Associated-Pathologies</b><br/><i>Jason Eriksen</i></p> <p><b>W12. Loss of Neuronal Chaperone 7B2 Reduces A<math>\beta</math> Plaque Burden in APP/PS1 Alzheimer's Model Mice</b><br/><i>Timothy Jarvela</i></p> <p><b>W13. Small Molecule Modulation of Nerve Growth Factor Receptor in the Brain Using MRI-Guided Focused Ultrasound</b><br/><i>Kelly Markham-Coultes</i></p> |
|---|---|

**W14. Shifting Patterns of Synaptic and Extrasynaptic GABA-A Receptor Activation Explain the Loss of Inhibition and Emergence of Synchrony During Seizure Evolution**

*David Naylor*

**W15. Verbal Learning and Memory Outcome in Selective Amygdalohippocampectomy Versus Temporal Lobe Resection in Patients With Hippocampal Sclerosis**

*Olaf Paulson*

**W16. Analysis of Brainstem-Derived Neural Stem Cell Populations in Adult Zebrafish After Spinal Cord Injury**

*Jeffery Plunkett*

**W17. Progressive Multifocal Leukoencephalopathy in the Absence of Immunosuppression**

*Sybil Stacpoole*

**W18. Three GRIPs 1 Spot: Critical Determinants for the Binding of Three GPCR-Interacting Proteins Within the Same Six-Residue Region of the Dopamine D2 Receptor**

*Kim Neve*

**W19. Effect of Hormonal Contraceptive Phase on Default Mode Network Activity During Working Memory Under Stress**

*Alexandra Ycaza Herrera*

**W20. Potassium Channel Inactivation Drives Nonlinear Acceleration of Motoneuron Activity**

*Ronald Harris-Warrick*

**W21. The Effects of Real-Time Biofeedback Integrated Into Neuromuscular Training on Knee Motor Resting-State Connectivity**

*Jed Diekfuss*

**W22. Reliability of Functional Neuroimaging for Lower Extremity Motor Control**

*Dustin Grooms*

## POSTER SESSION IV

**THURSDAY, JANUARY 18, 2018 • SEA TO SKY BALLROOM B**

This is a special session displaying the highest-ranked posters by young investigators. A grand prize and several other prizes will be presented to the best posters. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. and return for the special session from 7:30 p.m. – 9:30 p.m. Posters must be removed by 10:00 p.m. on Thursday.

**Th1. Phasic Dopamine Release in the Nucleus Accumbens Core Differentially Alters Drug-Taking and Drug-Seeking**

*Ryan Farero*

**Th2. Diet-Induced Obesity Impairs Outcome Devaluation and Alters Excitability of the OFC**

*Lauren Seabrook*

**Th3. Neural Circuit Mechanisms Underlying Drug-Induced Changes in Motivated Behaviors**

*Johannes de Jong*

**Th4. Optogenetic Activation of the Central Amygdala Generates Addiction-Like Preference for Reward Despite Adverse Consequences**

*Mike Robinson*

**Th5. Divergent Behavioral and Synaptic Changes Caused by Different Patterns of Morphine Exposure in Mice**

*Emilia Lefevre*

**Th6. Sweet Tooth or Neophile? Evaluating Developmental Risk Factors for Cocaine Seeking in Male and Female Rat**

*Chloe Jordan*

**Th7. Effects of Genetic Deletion of Mu Opioid Receptors From Kölliker-Fuse and Prebötzing Complex Neurons on Morphine-Induced Respiratory Depression**

*Adrienn Varga*

**Th8. Generality and Mechanism of RMTG Responses to Aversive Stimuli**

*Hao Li*

**Th9. Using the Intermittent Access Self-Administration Procedure to Assess Sex Differences in the Motivation for Cocaine**

*Alex Kawa*

**Th10. Role of Anterior Dorsal Lateral Hypothalamic Area Perineuronal Nets in Cue-Induced Reinstatement of Cocaine-Seeking Behavior**

*Jordan Blacktop*

**Th11. Understanding the Neural Mechanisms of Enhanced Incentive Motivation in Obesity Prone Rats**

*Rifka Derman*

**Th12. Effect of Oxytocin on Stress-Induced Reinstatement of Alcohol-Seeking Behavior in Male and Female Mice**

*Courtney King*



**Th13. Chronic Ethanol Exposure Alters Dorsomedial Striatal D1 Receptor Function Disrupting Goal-Directed Actions**

*Rafael Renteria*

**Th14. Modulation of Endocannabinoid-Mediated Synaptic Plasticity Within the Orbitofrontal Cortex by a Palatable Diet**

*Benjamin Lau*

**Th15. AMPA Receptor Translation is Altered Following the Incubation of Cocaine Craving**

*Michael Stefanik*

**Th16. Selective Manipulation of Inhibitory Signaling in Dopamine Neurons of the Ventral Tegmental Area Alters Drug-Related Behavior**

*Nora McCall*

**Th17. Cocaine Alters Circuit-Specific Synaptic Connectivity in the Nucleus Accumbens**

*Corey Baimel*

**Th18. The Influence of the Mediodorsal Thalamus on Orbitofrontal Cortex Processing**

*Ege Yalcinbas*

**Th19. Parvalbumin-Positive Interneurons in the Nucleus Accumbens Inhibit Impulsive Behavior**

*Marc Pisansky*

**Th20. Noradrenergic Transmission in the Ventral Periaqueductal Gray Modulates Arousal**

*Kirsten Porter-Stransky*

**Th21. Bound and GAGed: Molecular Mechanisms Localizing Netrin-1 in Neural ECM**

*Stephanie Harris*

**Th22. The Filum Terminale of the Spinal Cord is a Source of Autologous Neural Progenitor Cells**

*David Cardozo*

**Th23. Identification of Novel Targets for Parkinson's Disease Levodopa-Induced Dyskinesia**

*Roberta Marongiu*

**Th24. Dominant Negative Variant of the Dopamine Transporter Associate With Early-Onset Parkinsonism and Psychiatric Disease**

*Freja Hansen*

**Th25. Investigation Into Presymptomatic Huntington's Disease Patients' Views on Preventative Drugs**

*Marcus Parrish*

**Th26. Predicting the Valence of Active and Passive Affective States Using FNIRS**

*Lucas Trambaiolli*

**Th27. Testing the Transition From Positive to Negative Reinforcement in Alcoholism: Application of a Novel Experimental Paradigm in a Clinical Sample**

*Spencer Bujarski*

**Th28. Global and Cell-Type Specific Disruptions of Psychiatric Risk Gene CACNA1C Alter Ascending Serotonin System Activity**

*Daniel Ehlinger*

**Th29. An Early-Life Traumatic Event Alters Hippocampal Theta, Low Gamma, and High Gamma Power and Theta-Gamma Comodulation During an Episodic Memory Task in Adulthood**

*Sarine Janetsian-Fritz*

**Th30. A Prospective Study of Brain Functional Connectivity in Females With Anterior Cruciate Ligament Rupture**

*Jed Diekfuss*

**Th31. The Effects of Insulin Excitatory Transmission in the Nucleus Accumbens of Lean and Obese Rats**

*Max Oginsky*

**Th32. Localization of Dopamine D2 Autoreceptors on Dopamine Neurons**

*Brooks Robinson*

**Th33. Novel LTP at an Opioid-Sensitive GABAergic Synapse in the VTA**

*Robyn St. Laurent*

**Th34. Pharmacotherapeutic Potential of NDGA Against 6-OHDA Induced Parkinson's Disease in Mice**

*Baldeep Kumar*

# Panel Session Abstracts

**MONDAY, JANUARY 15, 2018**

## *Opening Plenary*

**PLENARY • MONDAY, 8:00 A.M. – 9:30 A.M. • SEA TO SKY BALLROOM A**

### **1. Using Memory to Guide Decisions**

*Presenter: Daphna Shohamy*

From robots to humans, the ability to learn from experience turns a rigid response system into a flexible, adaptive one. This lecture will discuss the neural and cognitive mechanisms by which learning shapes decisions. The lecture will focus on how multiple brain regions interact to support learning, what this means for how memories are built, and the consequences for how decisions are made. Results emerging from this work challenge the traditional view of separate learning systems and advance understanding of how memory biases decisions in both adaptive and maladaptive ways.

## *Monday Pioneer Session # 1: Lakshmi Devi*

**PIONEER SESSION • MONDAY, 9:45 A.M. – 10:45 A.M. • FITZSIMMONS**

### **2. Exploring the Mysteries of the Endogenous Opioid System**

*Pioneer: Lakshmi Devi*

*Chair: James Zadina*

*Investigators: Wakako Fujita, Elyssa Margolis*

Opioid peptides and their receptors comprise a signaling system still rich with mysteries to unravel, and with important implications for behaviors such as emotion, pain, food reward, and substance use disorder. When WCBR Pioneer Awardee, Dr. Lakshmi Devi (Mount Sinai), became interested in the opioid system several decades ago, many endogenous opioid peptides had been discovered and multiple receptor subtypes had been characterized. Yet it remained unknown whether each peptide had unique function, was generated by a specific enzyme, or whether the receptor subtypes were encoded by distinct genes. The dedicated work of Dr. Devi has contributed critical answers to many of these questions. For example, all neuropeptides are generated by a small set of processing enzymes; receptors associate to form dimers; receptors

signal through more than one transduction pathway, even after endocytosis; and each opioid peptide can activate more than one receptor subtype. Dr. Devi will describe her journey in the field, with interesting excursions and diversions in this peptide system. Dr. Wakako Fujita (Nagasaki University) will follow with a focused exploration of the role of a chaperone protein, receptor transporter protein 4 (RTP4), in the regulation of mu opioid receptor (MOR) and delta opioid receptor (DOR) heteromers. RTP4 mRNA is selectively increased after opioid receptor activation, in a brain region-specific manner that correlates with increases in MOR-DOR levels. On the other hand, RTP4 knock-down increases stress and body weight. These results will be considered in light of long-term opioid treatment, as well as stress and reward. Dr. Elyssa Margolis (UC San Francisco) will conclude by comparing cellular responses to met-enkephalin, leu-enkephalin, and b-endorphin, using ex vivo whole cell recordings from VTA neurons. Some cells show similar hyperpolarizations to all three peptides, but others show varied activity including opposing responses to met- and leu-enkephalin. Moreover, different combinations of selective agonists and antagonists reveal that concurrent binding of ligands to MOR and DOR can produce either synergistic or opposing effects on cellular excitation and behavior. Together, these panelists will bring both breadth and depth to our understanding of the endogenous opioid system.

## *Career Development Workshops*

**SPECIAL SESSION • MONDAY, 2:00 P.M. - 3:30 P.M. • HARMONY A**

### **3. Being a Research Scientist in Academic and Non-Academic Settings: What are the Challenges and Rewards?**

*Chair: Gretchen Snyder*

*Presenters: Carrie Ferrario, Warren Hirst, Joel Kleinman, Amy Newman, Kyle Smith*

Neuroscientists conduct scientific research in diverse settings, including in traditional academic institutions, in innovative biotech and pharmaceutical companies, and in government. Each environment has different demands and rewards. This workshop brings together scientists representing each of these scientific arenas to compare and contrast their research experiences. Participants will compare the unique demands of academic research in medical school versus liberal arts institutions and at institutes with translational programs linking academic-style research labs to industrial drug development programs, as well as the differing goals and requirements of biotech/industry science with commercial goals. Participants will discuss issues including obtaining funding/support for their science, hiring scientific staff, demands and hurdles to publication and collaboration, opportunities for mentoring and achieving work/life balance, as well as the unique challenges and rewards they face being a scientist in their setting.

Gretchen Snyder, Executive Director at Intra-Cellular Therapies Inc., will introduce the speakers and lead the discussion. The speakers and their affiliations are: Carrie Ferrario, Assistant Professor at the University of Michigan Medical School; Warren Hirst, Director and Preclinical Lead for Parkinson's Disease Research, Neuromuscular and Movement Disorders at Biogen; Joel Kleinman, Associate Director and Co-Director at the Lieber Institute for Brain Development and Professor at the Johns Hopkins University School of Medicine; Amy Newman, Senior Investigator, Deputy Scientific Director and Chief, NIDA-IRP; and Kyle Smith, Assistant Professor at Dartmouth College.

**SPECIAL SESSION • MONDAY, 2:00 P.M. - 3:30 P.M. • HARMONY B**

## **4. Enhancing Scientific Rigor and Reproducibility: Are We Doing Better?**

*Chair: Lique Coolen*

*Presenters: Molly Lucas, Yavin Shaham, Lori Isom*

There is increasing awareness of the need to improve scientific rigor and reproducibility. This has resulted in many changes in guidelines and best practices that apply to work at the bench, needs for training and mentoring, writing applications for funding, and how research findings are reported. In this workshop, a panel of speakers will discuss improvements in laboratory record keeping with an emphasis on the use of online resources, in research reporting and changes in journal guidelines for authors, and in training and mentoring of faculty and trainees. Short presentation by the speakers will be followed by discussion with the audience. The presentations and discussion will be of value for scientists at all career stages.

The session will be chaired by Lique Coolen, who is a professor and Associate Dean at the University of Mississippi Medical Center. Molly Lucas, a graduate student at Stanford University, will review use of RedCap as well as other online tools for record keeping in studies using animal or human subjects. Yavin Shaham, Senior Editor Journal Neuroscience and NIDA-IRP Branch Chief, will discuss best practices of scientific reporting with emphasis on recent changes that have been implemented. Lori Isom, Department Chair and Professor at the University of Michigan, will discuss best practices and thoughts on training and mentoring of faculty and trainees to further enhance awareness and implementation of best practices of scientific rigor.

## *Monday Afternoon Panel Sessions*

**PANEL • MONDAY, 4:30 P.M. - 6:30 P.M. • FITZSIMMONS**

### **5. A Slippery Slope to Addiction: A Role for Neuroinflammation**

*Chair: Christopher Evans*

*Presenters: Anna Taylor, Sandra Comer, Spencer Bujarski, Catherine Cahill*

The transition to a drug-dependent state is accompanied by neuroplasticity in various brain structures and neuroimmune mechanisms contribute to such changes, impacting abuse liability. This panel will discuss recent pre-clinical and clinical data that neuroinflammation contributes to outcomes of drug misuse with new evidence that there's a gut biome link. Dr. Chris Evans (UCLA) will chair and provide a brief overview of the session. Dr. Anna Taylor (University of Alberta) will present pre-clinical data showing how opioid use and cessation impacts the gut microbiome and how opioid-induced changes in the gut microbiome contribute to inflammation-driven hyperalgesia and negative affect of opioid withdrawal. Dr. Sandra Comer (Columbia University) will present clinical data on the ability of pioglitazone and minocycline to alter the abuse liability of oxycodone in participants with opioid use disorder. In separate studies, the reinforcing, subjective, and analgesic effects of oxycodone were examined when participants received active or placebo study medication. Both medications appeared to reduce subjective ratings of drug craving, but did not alter the other pharmacodynamic effects of oxycodone. Dr. Spencer Bujarski (UCLA) will present data showing that neuroinflammation contributes to alcohol misuse in human subjects. Treatment with the neuroimmune modulator ibudilast was associated with mood improvements on the secondary measures of stress exposure and alcohol cue exposure, as well as reductions in tonic levels of alcohol craving. Exploratory analyses revealed that among individuals with higher depressive symptomatology, ibudilast attenuated the stimulant and mood-altering effects of alcohol as compared with placebo. Finally, Catherine Cahill (UCLA) will present data on the overlap in neuroinflammation-induced adaptations of neuroplasticity induced by chronic pain and effects of chronic opioid exposure.

## 6. Non-Mammalian Animal Models for Neuroscience Research

*Chair: Lloyd Fricker*

*Presenters: Monte Westerfield, Sean McBride, Michael Aschner, Catharine Rankin*

Non-mammalian species have several advantages over the traditional mammalian animal models such as mice, including lower costs, faster breeding cycles, easier genetics, and less regulatory paperwork. Many genetic mutations have been identified in non-mammalian species and these provide a simple system to study genes and pathways that are conserved through evolution. This short course will focus on three widely used non-mammalian animal models for neuroscience research: zebrafish (*Danio rerio*); fruit fly (*Drosophila melanogaster*); and nematode (*Caenorhabditis elegans*). Non-mammalian animal models will be briefly introduced by Lloyd Fricker (Albert Einstein College), who has used both rodent and non-mammalian animal models. Zebrafish will be described by Monte Westerfield (Univ. Oregon, Eugene), who uses this organism to identify genes involved in ear and eye development and pathogenesis. The fruit fly (*Drosophila melanogaster*) will be presented by Sean McBride (Rowan Univ.), with emphasis on learning and memory. The nematode (*Caenorhabditis elegans*) will be described by Michael Aschner (Albert Einstein College), who will focus on neurodegeneration, and Catharine Rankin (Univ. of British Columbia), who will focus on learning and memory. Each presenter will describe the strengths and limitations of the animal model. The overall goal of the session is to provide a general background on the optimal uses of non-mammalian animal models for neuroscience research and provide links to databases so that interested attendees can learn more. Ample time will be allowed for questions and discussion.

## 7. What About Me? The Paraventricular Thalamic Nucleus in Reward Circuitry

*Chair: Jacqueline McGinty*

*Presenters: Morgan James, Paolo Campus, James Otis, Xiaoke Chen*

The paraventricular thalamus (PVT) has undergone a renaissance in recent years with respect to its role in motivated behaviors. PVT receives diverse input from a number of brainstem, cortical, and hypothalamic regions and relays these signals to various components of the classic reward circuitry. This panel will discuss the latest approaches that are revealing how PVT acts as a key interface between cortical, hypothalamic, and striatal signaling to regulate arousal and reward processes. Morgan James (Rutgers U) will introduce the connections

and functions of PVT and discuss the role of orexin/hypocretin and cocaine- and amphetamine- regulated transcript input to PVT in the context of cocaine seeking behaviors and addiction. Paolo Campus (U MI) will present data supporting a role for the PVT orexin/hypocretin system in encoding the incentive value of reward cues, as well as chemogenetic evidence highlighting a role for the prelimbic-PVT circuit in differentially mediating “sign-tracking” (attracted to cues predicting reward) and “goal-tracking” (attracted to actual reward) behaviors. Jim Otis (UNC Chapel Hill) will discuss how PVT→NAc neurons integrate signals from hypothalamic and prelimbic regions to control reward-seeking behavior. He will show how PVT→NAc neurons, and their inputs, encode reward-predictive stimuli to control appetitive learning, using two-photon calcium imaging and optogenetics in vivo. Xiaoke Chen (Stanford U) will discuss how PVT orchestrates the formation and maintenance of opioid-associated memories through its connections with the central nucleus of the amygdala and NAc. His opto- and chemogenetics data indicate that morphine evokes cell type-specific plasticity in the PVT→NAc pathway that underlies opiate withdrawal. Together, these data, all generated by rising-star young scientists, indicate that PVT not only is a critical node of the “motive circuit” that acts to encode the motivational value of both appetitive and aversive stimuli.

**PANEL • MONDAY, 4:30 P.M. - 6:30 P.M. • HARMONY A**

## **8. Harnessing Metabolic Systems to Treat Epilepsy**

*Chair: Chris Dulla*

*Presenters: Mark Beenhakker, John Huguenard, Susan Masino, Jong Rho*

Metabolic activity and epilepsy are intimately linked. First, seizure activity consumes large amounts of cellular energy. Restoring ionic gradients, replenishing synaptic resources, and dealing with cellular damage during and after seizures can deplete energy reserves. Second, modulation of cellular energy resources has long been a treatment for epilepsy, as demonstrated by the ketogenic diet. Shifting the brain from glycolysis to ketolysis is powerfully and rapidly anticonvulsant. The underlying mechanisms by which metabolic activity links to seizure activity remains enigmatic. Recent discoveries, however, suggest that changes in metabolic state may have unique effects on cellular signaling systems, cell-type specific effects on neuronal activity, and differential consequences on regional circuit function. In this session we will explore the variety of ways in which the brain responds to disrupted metabolic activity and how metabolic pathways can be harnessed for their anticonvulsant effects. First, Dr. Mark Beenhakker (University of Virginia) will discuss how brain ketosis alters oscillatory network activity in the thalamus, a brain region important in generalized epilepsy. Second, Dr. John Huguenard (Stanford University) will present novel findings indicating that metabolic stress increases the release of



endozepines, endogenous chemicals that modulate GABA receptor function and suppress over-excitation. Third, Dr. Susan Masino (Trinity College) will discuss her work on how the ketogenic diet alters purinergic signaling to promote brain homeostasis and suppress seizure activity. Finally, Dr. Jong Rho (University of Calgary) will present his work on how ketone bodies can directly mediate anti-convulsant effects. Overall, our panel will highlight advances in neuro-metabolic coupling using cutting edge approaches and will discuss how we can better harness metabolic systems to treat specific forms of epilepsy.

**PANEL • MONDAY, 4:30 P.M. - 6:30 P.M. • HARMONY B**

## **9. A Novel Role for Mitochondrial Metabolism in Fragile X Autism Spectrum Disorder**

*Chair: Elizabeth Jonas*

*Presenters: George Porter, Richard Levy, Elizabeth Jonas, Thomas Jongens*

Fragile X disorder (FX) is a well-studied cause of intellectual disability caused by CGG repeats in the gene for FMRP on the X chromosome. The full FX mutation produces aberrantly functioning synapses and abnormally enhanced neuronal excitability, seizures, sensory hypersensitivity and loss of normal learning in humans and animal models. FMRP is partially understood as an mRNA binding protein the loss of which leads to elevated protein synthesis, yet previous studies have also suggested that rodents and flies lacking FMRP have metabolic defects. We now further describe the metabolic role for FMRP. We find loss of FMRP alters mitochondrial metabolism which in turn affects protein synthesis, resulting in delayed development and immature synapses. In this session, we will describe how the interaction of FMRP with mitochondria is required for normal brain development. George Porter will set the stage by describing the role of mitochondrial maturation in normal embryonic development. Rick Levy will then present evidence for the loss of coenzyme Q10 activity in the developing *Fmr1* KO forebrain and discuss targeting mitochondrial dysfunction with treatment with coenzyme Q<sub>10</sub> which he finds rescues behavioral defects in the mice. Elizabeth Jonas will present data that FMRP interacts directly with mitochondria, producing an increase in efficiency of mitochondrial metabolism required for the normal rate of protein synthesis. Her lab finds that reagents that improve bioenergetic function rescue protein synthesis defects in FX mouse neurons and human cells and support synaptic plasticity in the FX mouse brain. Thomas Jongens will present his compelling data that alterations in NAD metabolism may lead to the severe defects in neuronal function in the *drosophila* model lacking FMRP. Our group will attempt to suggest that a time dependent switch in mitochondrial metabolism is necessary for the normal maturation of synapses and neuronal connectivity in the developing brain.

## 10. High Excitability: Cannabinoids, Neural Excitability and Implications for Neurological Disorders

*Co-chairs: Matthew Hill, Lynn Raymond*

*Presenters: Gordon Teskey, Istvan Katona, Marja Sepers, Roger Thompson*

Cannabinoids (both plant derived and endogenous) are known to be potent regulators of synaptic transmission and neural excitability, particularly with respect to their ability to gate the release of the neurotransmitters glutamate and GABA. In pathological states, the ability of cannabinoids to modulate synaptic transmission could be important for diseases associated with excess glutamate release and neural excitability, such as epilepsy and Huntington disease (HD). The aim of this symposia is to discuss recent, exciting and unpublished findings regarding the impact of endocannabinoid (eCB) signaling at excitatory synapses and how this relates to diseases associated with elevated neural excitability. First, Cam Teskey will describe novel findings regarding the release of eCB molecules during hyperexcitable and hypersynchronous events (seizures) and how the metabolism of these molecules produces bioactive signals which modulate blood flow and the development of both short- and long-term behavioral dysfunction. Second, Istvan Katona will discuss novel findings using super resolution microscopy to map out the localization of cannabinoid receptors on glutamatergic and GABAergic axon terminals and how the micro-architecture of where CB1 receptors reside relative to calcium stores can have a dramatic impact on their ability to modulate transmitter release. Next, Marja Sepers will present novel data regarding altered cortical-striatal presynaptic glutamate release in animal models of HD and how long-term depression at these excitatory synapses is deficient in the YAC128 model of HD but can be rescued by modulation of the eCB system. Finally, Roger Thompson will discuss novel findings regarding how the pannexin-1 channel can regulate synaptic levels of the eCB anandamide, and how modulation of pannexin-1 function can elevate anandamide signalling at TRPV1 synapses to promote neural excitability and accelerate the development of epileptogenesis.

## 11. Targeting Cyclic Nucleotides for Improving CNS Function: A Black Diamond Descent?

*Co-chairs: Jos Prickaerts, Arjan Blokland*

*Presenters: Lawrence Wennogle, Michy Kelly, Arjan Blokland*

The second messengers cyclic GMP (cGMP) and cyclic AMP (cAMP) have crucial roles in controlling intracellular signaling pathways linked to neuroplasticity, neuroprotection or neuroinflammation. Regulating the levels

of cAMP and cGMP is mostly achieved by inhibiting their breakdown by specific phosphodiesterases (PDEs). An alternative approach is to increase their synthesis via stimulation or activation of adenylate or guanylate cyclases, respectively. A major drawback of both approaches is the appearance of drug-induced side effects. Clearly, we need more understanding of the role of PDEs and cyclases in modulating intracellular levels of cyclic nucleotides to control specific functions in the CNS. This panel will focus on less understood PDEs including PDE1, PDE2 and PDE11, as well as cyclases. Jos Prickaerts and Arjan Blokland (Maastricht University) will lead the discussion. First, Lawrence Wennogle (Intra-Cellular Therapies, New York) will discuss that the PDE1 inhibitor ITI-214 is able to reverse inflammation in LPS-induced mouse models of neuroinflammation, both in vivo and in vitro. These studies demonstrated unique expression signatures. Michy Kelly (University of South Carolina) will show that an age-related increase in PDE11A4 expression in the brain is largely accounted for by the formation of PDE11A4 aggregates. She also identified intramolecular signals, such as phosphorylation and homodimerization, which bimodally control the ability of both mouse and human PDE11A4 to aggregate. Finally, Arjan Blokland will discuss the effects of the soluble guanylate cyclase (sGC) stimulator Riociguat on cognition in both rodents and humans. He will show that stimulating sGC can be considered as an interesting target to improve cognition, despite translational hurdles.

**PANEL • MONDAY, 4:30 P.M. - 6:30 P.M. • WEDGEMOUNT**

## **12. Dissecting the Heterogeneity of Clinical Outcomes Associated With Mood-Altering Treatments: From Drugs to Neurostimulation**

*Chair: Anil Malhotra*

*Presenters: Melanie Blair, Daphne Voineskos, Miklos Argyelan, Anil Malhotra*

Recent research has suggested that variability in clinical outcomes of individuals administered mood altering treatments may be predicted by novel neuroimaging and electrophysiological biomarkers. These treatments include stimulants, repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT), amongst others. In this panel, we will highlight several of these biomarkers and their relationship to clinical outcomes such as treatment response. First, Melanie Blair (CUNY) will describe work using task-based fMRI to predict adverse response to psychostimulant use in 110 subjects followed for three years after baseline scanning. Results indicate that subjects who developed stimulant abuse patterns exhibited lower activation in frontal executive control, sensory, and emotional processing regions during decision making as well as greater sensitivity to risky rewards. Daphne Voineskos (University of Toronto) will report on using electrophysiological biomarkers to predict response to rTMS in depressed individuals, in which a

biomarker indexing cortical inhibition was significantly associated with clinical response. Miklos Argyelan (Hofstra Northwell) will continue this theme by examining the relationship between fMRI biomarkers and rTMS in patients scanned at baseline and followed for five weeks. Preliminary results suggest that key circuitry associated with mood regulation is linked to antidepressant response. Finally, Anil Malhotra (Hofstra Northwell) will report on the use of structural and functional neuroimaging to predict response to ECT. First, he will discuss resting state MRI biomarkers associated with ECT response in depressed patients, and then the use of electrical field modeling based on structural imaging to optimize electrode placement in ECT. Taken together, these presentations will provide an overview of novel precision medicine approaches to understanding the considerable variation in response to mood-altering treatments.

## *Monday Evening Panel Sessions*

**PANEL • MONDAY, 7:00 P.M. - 8:30 P.M. • FITZSIMMONS**

### **13. Selective Hypothalamic Inputs to the Lateral Habenula Underline Differential Motivated Behaviors**

*Co-chairs: Marisela Morales, David Barker*

*Presenters: David Barker, Meghan Flanigan, Salvatore Lecca, Richard O'Connor*

Heterogeneous cell types within the hypothalamus participate in maintaining homeostasis and guiding motivated behaviors by communicating with the central nervous system through an intricate network of neurotransmitters and neuropeptides. Recent evidence has implicated dense inputs from the preoptic and lateral hypothalamus to the lateral habenula in a wide variety of motivated behaviors including feeding, defensive behaviors, stress, and reward processing. This panel will cover recent findings regarding the anatomical connections, signaling molecules, and functional roles of hypothalamic inputs to the lateral habenula. Dr. Marisela Morales (National Institute on Drug Abuse/NIH) will provide general remarks. Dr. David Barker (National Institute on Drug Abuse/NIH) will discuss his discovery of converging neurotransmission by lateral preoptic area glutamate and lateral preoptic area GABA neurons onto single LHb neurons, and the role of these converging pathways in motivated behavior. Meghan Flanigan (Icahn School of Medicine at Mount Sinai) will present her data showing that a novel orexin input from the lateral hypothalamus to the lateral habenula controls the motivational aspects of aggressive behavior. Dr. Salvatore Lecca (University of Lausanne) will present his work investigating the role of lateral hypothalamic projections to the lateral habenula in signaling aversive stimuli that are ultimately important to guide escape behavior. Dr. Richard O'Connor (Icahn School of Medicine at Mount Sinai) will present his

work showing that lateral habenula projecting lateral hypothalamus neurons play a role in controlling food-related motivation and can differentially modify food intake in a palatability-dependent manner.

**PANEL • MONDAY, 7:00 P.M. - 8:30 P.M. • GARIBALDI A**

## **14. Assessment of the Health Impacts of Circadian and Sleep-Wake Disruption in Human**

*Chair: Diane Boivin*

*Presenters: Diane Boivin, Philippe Boudreau, Guy Dumont*

The session is intended for researchers and clinicians concerned with the health impacts of disturbed circadian and sleep-wake cycle. Recent advances in the field of chronobiology underline the complexity of the circadian system. This system is comprised of a master clock located in the suprachiasmatic nuclei of the hypothalamus and of peripheral clocks located in virtually all cells of the body. Circadian rhythms affect most mental and physical parameters and their disturbances can significantly deteriorate health. Despite their importance, the prevalence of circadian misalignment in clinical populations remains largely unknown due to the lack of reliable and easily accessible circadian markers in field conditions. Even less information is available on the prevalence and health impacts of peripheral clocks in humans.

The session will provide state-of-the-art presentations that will gather world leaders who made substantial contributions to this field. The session chair, Diane B. Boivin, M.D., Ph.D., Douglas Institute, McGill University, will present the impact of circadian misalignment that occurs in night shift work on sleep-wake, physiological, clock genes, and immune function disturbances. Philippe Boudreau, Ph.D., Douglas Institute, McGill University, will present evidences from highly controlled laboratory experiments that circadian phase and sleep affect cardiovascular parameters as well as results of field studies of police officers working nights. Guy A. Dumont, Ph.D., Department of Electrical Engineering, University of British Columbia will present a number of techniques that have been developed to estimate circadian phase non-invasively in humans. Although some of those methods have been shown to perform well in a controlled environment, none of them are used for ambulatory monitoring. He will review some of the challenges that have to be addressed before we can use these techniques reliably. The panel addresses the translational aspect of circadian disturbances for human health. This work has potential applications for the study and treatment of populations such as shift workers, patients with sleep and circadian rhythms disorders, as well as patients suffering with a variety of neurological and psychiatric conditions.

## 15. What's Down That Slope? Orbitofrontal Cortex and Amygdala Contributions to Outcome Anticipation

*Chair: Kate Wassum*

*Presenters: Nicolas Schuck, Peter Rudebeck, Alicia Izquierdo, Kate Wassum*

The ability to accurately anticipate potential future events is crucial to adaptive decision making and disruptions can lead to the core symptoms of several psychiatric diseases. The orbitofrontal cortex (OFC) may be one key region involved in this process. We will discuss recent evidence on the contribution of the OFC to decision making and its function in representing future outcomes. Additionally, there are major gaps in understanding how the OFC achieves this function within the broader circuitry. The OFC shares dense and reciprocal excitatory projections with the basolateral amygdala (BLA). Presentations will also address how the OFC and BLA function as a circuit to guide adaptive behavior. The overarching goal of this panel is to clarify the function of the OFC for reward-guided decision making through discussion of converging evidence collected in rodents, monkeys, and humans with multiple technical and theoretic approaches and across behavioral tasks. Results using both traditional and modern systems neuroscience techniques will be included. Computational modeling of OFC and BLA function will also be discussed. First, Nicolas Schuck will describe a novel theory that the OFC's role in decision making is to provide an up-to-date representation of important task information, e.g. a state representation, and will present fMRI and simulation studies to support this theory. Next, Peter Rudebeck will describe recent work examining the contribution of the amygdala to stimulus-reward encoding in the macaque medial and orbital frontal cortex during learning. Alicia Izquierdo will discuss evidence of BLA, OFC, and anterior cingulate cortex function in responding to value learning under uncertainty. Lastly, Kate Wassum will present data on the contribution of bottom-up BLA-OFC and top-down OFC-BLA projections to the updating of specific outcome values and to the use of detailed expectancies, both self-generated and cue-triggered, to guide choice behavior.

## 16. New Approaches for Finding Novel Anti-Seizure Drugs for Pharmacoresistant Epilepsy

*Chair: Francis Dudek*

*Presenters: Yevgeny Berdichevsky, Francis Dudek, Chris Dulla*

Although the classical approaches to finding novel anti-seizure drugs (ASDs) continue to identify compounds that could serve as new ASDs, the present methods have been criticized on the grounds that this approach has not

improved the proportion of patients who become seizure-free when given these ASDs. This panel will explore the pros and cons of new in vitro methods for screening possible ASDs and in vivo approaches for potentially validating their efficacy in models of chronic epilepsy. Berdichevsky will describe in vitro experiments testing potential ASDs on long-term field-potential recordings from organotypic hippocampal slices with spontaneous recurrent seizure-like activity. Dudek and Dulla will present work on in vivo studies concerning potential ASDs using long-term continuous electrographic methods from animal models with chronic acquired epilepsy (i.e., after brain injury). Although the brief presentations will discuss data, the panel will focus on issue of through-put, cost, feasibility, and reproducibility. Discussion will also include the issue of clinical validation.

**PANEL • MONDAY, 7:00 P.M. - 8:30 P.M. • HARMONY B**

## **17. Let's Make This Clear: 3D Analysis of Neural Circuits**

*Chair: Lique Coolen*

*Presenters: Lique Coolen, Aleisha Moore, Jonathan Epp*

A major challenge in anatomical investigations of the central nervous system (CNS) is the complex three-dimensional (3D) structure of the brain, containing heterogeneous cell groups expressing arrays of different neurotransmitters and interconnections. Therefore, the ability to visualize the complete 3D structure of the CNS is of great importance to understanding its functional connections and complexity. In recent years, new techniques for tissue clearing were developed that allow visualization of fluorescent signals throughout large tissue samples. In addition, microscopic techniques have been optimized for rapid imaging of such large samples. These techniques have revolutionized the field of neuroanatomy, enabling 3D analysis of the morphological complexity of the whole brain. In this panel, several large scale optical clearing techniques used in conjunction with confocal, multiphoton and light sheet microscopy will be reviewed.

The first speaker, Dr. Lique Coolen, will provide a brief overview introducing main concepts of optical clearing and microscopy techniques. Next, Dr. Aleisha Moore will present the use of immunolabelling and iDISCO to achieve high-resolution imaging of complete neuronal populations in the intact mouse and rat brain, and the intact sheep and primate hypothalamus. Her studies focus on the hypothalamic control of reproductive function. The third speaker is Dr. Jonathan Epp, who will present optimized protocols for CLARITY in the context of his research in rodents on hippocampal neurogenesis as it relates to memory and neuronal plasticity. Finally, the speakers will address questions from the audience in an open forum discussion. Attendees are encouraged to share their data and experiences with these approaches in a single slide, after obtaining approval from the panel chair prior to the conference.

## 18. Simplifying Big Data in Neuroscience and Brain Research

*Chair: Andrew Jaffe*

*Presenters: Jeff Leek, Andrew Jaffe, Barbara Engelhardt, John Muschelli*

Huge datasets in neuroscience and brain research have emerged in the last decade from centralized efforts in data collection and generation that include genomics and imaging. However, the sheer size of these datasets, particularly in raw/unprocessed forms, has been limiting to most researchers and clinicians. In this session we present new tools, resources and software for handling large genomics and neuroimaging datasets to make them more accessible to the scientific community. Dr. Jeff Leek (Johns Hopkins University) will describe the Recount2 project and accompanying software (<https://jhubiostatistics.shinyapps.io/recount/>) for downloading and analyzing over 70,000 human uniformly processed RNA sequencing samples, including over 3000 samples from human brain tissue. Dr. Andrew Jaffe (Lieber Institute for Brain Development, LIBD) will describe new publicly-available resources of expression quantitative trait loci (eQTLs) from dorsolateral prefrontal cortex and hippocampus around unannotated transcribed sequences focusing on genetic variants associated with genetic risk for brain disorders ([eqtl.brainseq.org](http://eqtl.brainseq.org)). Dr. Barbara Engelhardt (Princeton University) will describe new efforts by the Genotype-Tissue Expression (GTEx) project to better characterize gene expression levels and their association with nearby genetic variation in 14 brain regions and other central nervous system (CNS) tissues (<https://www.gtexportal.org>). Lastly, Dr. John Muschelli (Johns Hopkins University) will describe the new Neuroconductor software repository for rapid testing and dissemination of reproducible computational imaging software (<https://neuroconductor.org/>). This session will provide practical resources, tools and software for making big data more manageable for neuroscience and brain researchers across the globe.

## 19. Neuroleptics for ALS: From Chemical Genetics to Clinical Trial

*Chair: Pierre Drapeau*

*Presenters: Alex Parker, Kessen Patten, Elsa Tremblay, Lawrence Korngut*

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing, fatal disorder with no effective treatment. We used simple genetic models of ALS to screen phenotypically for potential therapeutic compounds. We screened libraries of compounds in *C. elegans* (Alex Parker), validated hits in zebrafish (Kessen



Patten) and tested the most potent molecule in mice (Elsa Tremblay) and in a small clinical trial (Lawrence Korngut). We identified a class of neuroleptics that restored motility in *C. elegans* and in zebrafish and the most potent was pimozide, which blocked T-type calcium channels in these simple models and stabilized neuromuscular transmission in zebrafish and enhanced it in mice. Finally, a short randomized controlled trial of sporadic ALS subjects demonstrated stabilization of motility and evidence of target engagement at the neuromuscular junction. Simple genetic models are thus useful in identifying promising compounds for the treatment of ALS such as neuroleptics, which may stabilize neuromuscular transmission and prolong survival in this disease.

**PANEL • MONDAY, 7:00 P.M. - 8:30 P.M. • WEDGEMOUNT**

## **20. Remembering the Brain in Orthopedic Rehabilitation: Translational Neuroscience to Understand Musculoskeletal Injury**

*Chair: Dustin Grooms*

*Presenters: Alan Needle, Adam Lepley, Dustin Grooms*

Musculoskeletal injuries such as those to ligaments, tendons, or muscle have commonly been considered structural injuries, requiring surgical reconstruction or rehabilitation focused on recovery of mechanical joint stability or muscle strength. However, this specific focus on structural properties in musculoskeletal medicine has ignored the effects of damage to highly innervated ligament and tendinous tissue on the central nervous system capacity for sensorimotor control. The failure to consider the neurological deficits in conjunction with mechanical instability induced by common orthopedic trauma has led to an inability to adequately restore patient function with recurrent injuries commonplace. Our group has completed novel work to quantify the nervous system changes induced by musculoskeletal trauma and the effects of interventions targeted to enhance not only joint and muscle function, but the nervous system that controls them. The focus of this panel will be the discussion of modern human neuroscience techniques to quantify musculoskeletal injury induced neuroplasticity. Dr. Alan Needle (Appalachian State University) will discuss the impact of acute and chronic musculoskeletal injury on peripheral and central somatosensory dysfunction. Dr. Adam Lepley (University of Connecticut) will highlight alterations in motor cortex excitability following lower extremity musculoskeletal injury. Dr. Dustin Grooms (Ohio University) will discuss neuroimaging of knee motor control tasks to quantify brain changes from anterior cruciate ligament injury. The panel will finish with a discussion of new research directions and avenues for novel neuroplastic integrated therapies for orthopedic trauma.

**TUESDAY, JANUARY 16, 2018**

## *Tuesday Morning Panel Sessions*

**PANEL • TUESDAY, 7:30 A.M. - 9:30 A.M. • FITZSIMMONS**

### **21. Instructive Signals for Aversive Learning and Memory**

*Chair: Joshua Johansen*

*Presenters: Sung Han, Bo Li, Joshua Johansen, Sabine Krabbe*

Aversive experiences powerfully shape our behavior by triggering learning and long-lasting memories. This occurs because aversive events activate dedicated brain circuits and mechanisms which instruct changes in neural connectivity underlying memory formation. While we are beginning to understand where aversive memories are stored and how they are expressed, we understand much less about the neural circuits responsible for aversive instructive signaling. In this symposium, four speakers at the cutting edge of this field will present exciting recent advances in our understanding of aversive instructive signaling from a well-studied form of associative learning termed fear conditioning. Sung Han will discuss a role for the parabrachial nucleus, a canonical pain pathway, in conveying aversive signals to the central nucleus of the amygdala during fear learning. Bo Li will examine how these signals are integrated in central amygdala circuits and broadcast to other amygdala subregions to produce synaptic plasticity. Joshua Johansen will reveal how aversive information is encoded in fear circuits and conveyed to the lateral nucleus of the amygdala to trigger fear learning. Sabine Krabbe will explore how aversive events engage different subclasses of interneurons in the amygdala to initiate fear learning. Together these talks will provide a comprehensive and up-to-date model of instructive signaling during aversive associative learning. This knowledge is important for understanding psychiatric disorders associated with exaggerated fear learning and could provide a template for understanding instructive signaling across a wide range of learning systems.

**PANEL • TUESDAY, 7:30 A.M. - 9:30 A.M. • GARIBALDI A**

### **22. One Size Does Not Fit All: Individual Differences in Substance Abuse**

*Chair: Jessica Barson*

*Presenters: Jessica Barson, Donna Calu, Anushree Karkhanis, Sarah Leibowitz*

While many individuals are exposed to palatable foods and drugs of abuse, only a small proportion go on to consume these substances in excess. These individuals may have underlying differences in the functioning of their limbic system, either intrinsically or due to extrinsic factors. This panel will describe

how different components of the limbic system may be dysregulated in individuals that overconsume various substances. Jessica Barson will discuss her work on behavioral predictors of excessive ethanol drinking. She will present her discovery that a neuropeptide in the paraventricular thalamus, pituitary adenylate cyclase-activating polypeptide (PACAP), participates in this excessive intake. Donna Calu will describe her work probing the role of divergent basolateral amygdala pathways in supporting Pavlovian approach behaviors. She will present data investigating the role of the basolateral amygdala to insular cortex pathway in driving individual differences in approach behavior of sign- and goal-trackers. Anushree Karkhanis will focus on adolescent chronic stress-induced alterations in the kappa opioid receptor and dopamine systems within the nucleus accumbens. She will demonstrate that these stress-induced neuroadaptations increase cocaine seeking and sensitivity to cocaine. Sarah Leibowitz will present her new findings showing sex differences in the effects of prenatal exposure to ethanol on the brain and behavior. She will demonstrate how maternal ethanol stimulates the hypothalamic neuroimmune system which in turn stimulates neuropeptide neurons and the consumption of ethanol and anxiety-like behavior in the adolescent offspring, with all effects significantly and consistently stronger in females. These presentations will highlight the diverse ways that the limbic system may be dysregulated in specific individuals to drive their excessive intake and should facilitate the efforts of precision medicine to treat those with substance use disorders.

**PANEL • TUESDAY, 7:30 A.M. - 9:30 A.M. • GARIBALDI B**

## **23. Associative Thalamic Control of Reward Seeking**

*Co-chairs: Xuan Li, Brian Mathur*

*Presenters: Bernard Balleine, Brian Mathur, Gavan McNally, Xuan Li*

The midline and intralaminar thalamic nuclei have long been implicated in generalized arousal. However, emerging evidence has demonstrated unique roles for these nuclei and associated circuits in reward seeking behaviors. Our panel will present recent findings that highlight the importance of the midline and intralaminar thalamic as a critical component of the brain circuits that regulate action reinforcement and drug seeking. Bernard Balleine (U Sydney, Australia) will discuss the role of the parafascicular nucleus of the thalamus in the control of cellular processes in the dorsomedial striatum and in the acquisition of goal-directed action. Brian Mathur (U Maryland School of Medicine) will discuss the role of the anterior intralaminar thalamic nuclei in controlling local striatal dopamine release. Gavan McNally (U New South Wales, Australia) will describe the role of paraventricular nucleus of the thalamus in interactions between reward and fear learning. Xuan (Anna)

Li (U Maryland College Park) will discuss the role of anterior intralaminar nucleus of thalamus to dorsomedial striatum projections in incubation of methamphetamine craving.

**PANEL • TUESDAY, 7:30 A.M. - 9:30 A.M. • HARMONY A**

## **24. Post-Traumatic Stress Disorder in the 21st Century: Genes, Environment, and Treatment**

*Co-chairs: Thomas Hyde, Joel Kleinman*

*Presenters: Rachel Yehuda, Thomas Hyde, Felicia Gould, Allison Feduccia*

Post-traumatic Stress Disorder (PTSD) increasingly has entered the public discourse, mostly with respect to its impact on members of the military and their families. Although PTSD has been recognized in one form or another since the 17<sup>th</sup> century, the American Psychiatric Association only formally recognized it as a diagnostic entity in 1980. This session will review current trends in research and treatment in this disabling and chronic disorder. Dr. Joel Kleinman will present a brief overview of the disorder. Dr. Rachel Yehuda will discuss gene co-expression networks in induced neurons derived from stem cells from individuals with and without PTSD. She also will discuss the use of lymphocytes as a proxy for neuronal gene expression in the study of PTSD. Dr. Thomas Hyde will review findings from RNA sequencing studies of postmortem human brain regions associated with PTSD, in relationship to genetic risk variants identified from GWAS. Dr. Felicia Gould will present findings from a prospective study of over 600 individuals, examining biomarkers/ epigenetic markers for PTSD and the development of PTSD within the first year following an Emergency Department admission resulting from a traumatic event. She also is involved in the identification of genetic variants associated with an increased risk of PTSD. Finally, Dr. Allison Feduccia will present clinical research data demonstrating that MDMA-assisted psychotherapy was effective in reducing symptoms of PTSD in six controlled Phase 2 single-site clinical trials. After 2-3 MDMA sessions, improvements in PTSD symptoms were accompanied by reductions in depression symptoms and increases in overall sleep quality, thus indicating the utility of MDMA as an adjunct to psychotherapy. Safety outcomes for MDMA use in a PTSD population were good, with transient increases in vital signs and expected reactions of MDMA. Advancing research into the genetics and neurobiology of PTSD will lead to better targeted treatments and outcomes for patients with this chronic and disabling disorder.

## 25. Neuronal Circuit Basis for Auditory Cortical Function

*Co-chairs: Li Zhang, Daniel Polley*

*Presenters: Alfonso Junior Apicella, Hysell Oviedo, Patrick Kanold, Robert Liu*

The panel will focus on discussing the latest progress in elucidating specific functional contribution of the auditory cortex. In the past couple of years, the detailed dissection of specific intracortical circuits and corticofugal projections has opened an opportunity to examine how information can be specifically processed and transformed by the auditory cortex under certain behavioral contexts. Here, the panel will cover a few representative research topics, including the functional difference between the two hemispheres and the underlying neural circuit basis, the modulation of auditory processing by long-range cortical projections, and the role of various corticofugal projections in auditory behaviors. First, Dr. Apicella from UTSA will present evidence for long-range GABAergic projections in the cortical circuit and discuss their roles in physiological and pathological conditions. Second, Dr. Oviedo from CCNY will discuss the functional lateralization of auditory cortex and reveal circuitry differences between the two hemispheres that may underlie specialization of one hemisphere in extracting the valence and meaning of animal vocalizations. Third, Dr. Kanold (Univ. Maryland) will talk about how auditory cortical circuits are the target of top-down projections from the prefrontal cortex and how interlaminar and intralaminar circuits can be modulated by experience. Fourth, Dr. Liu (Emory Univ.) will discuss auditory cortex's role in auditory learning, drawing on work with both positive valence (pup-mother communication) and negative valence (fear conditioning) paradigms. Led by two organizers (Dr. Polley from Harvard and Dr. Zhang from USC), the panel will further discuss recent studies on functional roles of corticofugal projections, e.g. corticothalamic and corticocollicular projection. Together, these presentations will provide a diversified view on current research approaches to understanding the functional contributions of auditory cortex, especially at the neuronal circuit level.

## 26. Frontiers in Aging Brain Research: Determining Neurobiological Substrates of Age-Related Cognitive Decline Towards Enhancing Cognitive Resilience

*Chair: Natalie Ebner*

*Presenters: Jennifer Bizon, Mara Mather, Peter Rapp, Natalie Ebner*

Cognitive decline is a major concern in our aging population as it compromises quality of life and independent living. The neurobiological substrates of age-related decline remain understudied and are essential to elucidate for devising interventions to enhance cognitive resiliency. Experts in this panel will present recent advances in aging brain research, integrating innovative neuroimaging, pharmacological, neurophysiological, and neuropsychological methodologies in a cross-species comparison. Dr. Bizon will highlight circuit and molecular mechanisms that mediate age-related changes in decision-making. She will present data showing that temporally specific optogenetic inactivation of basolateral amygdala shifts young rats towards an “aging-like” pattern of choice behavior. She will also discuss possible molecular substrates of altered amygdalar activity and decision-making in aging. Dr. Mather uses computational modeling to demonstrate age differences in how much the locus coeruleus-norepinephrine system increases information selectivity under arousal. From an fMRI study, she then concludes that aging is characterized by the inability to rely on increases in selective attention during high-stake moments of arousal. Dr. Rapp leverages an individual difference approach to present evidence from animal models, including non-human primates, that cognitive resilience may be mediated by trajectories of active neuroadaptation. Dr. Ebner (chair) will introduce a novel framework to study the involvement of the oxytocin system in enhancing cognitive, social, and affective capacities in aging. She will present hormonal, neural, and behavioral data supporting oxytocin’s beneficial role in social-cognitive aging and will conclude the session with a brief discussion of the translational potential of novel aging brain research in healthy aging and aging-related disease.

## 27. Circuit Trails of Kappa Opioid Involvement in Affect and Pain

*Chair: Catherine Cahill*

*Presenters: Jose Moron-Concepcion, Daniel Bloodgood, Jordan McCall, Catherine Cahill*

Chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses. Co-occurring psychopathology in chronic pain patients significantly impacts pain perception (heightened pain intensity),

increases pain-related disability, decreases response to treatment and increases risk of prescription opioid misuse. In humans, kappa opioid receptor (KOR) activation causes anxiety, discomfort, agitation, depression and dysphoria. This panel will discuss the circuitry modulated by kappa opioid receptors that contributes to affective like behaviors and the involvement of this receptor system in motivated behavior and pain aversion. Catherine Cahill (UCLA) will chair and provide a brief overview of the session and introduce the speakers. Jose Moron-Concepcion (WashU) will present data using a wide range of complementary cutting-edge techniques including pharmacology, optogenetics, chemogenetics, physiology, biochemistry and rodent PET imaging. His presentation will show that the recruitment of the dynorphin neurons acting through KOR in the NAc shell is both necessary and sufficient to drive in vivo pain-induced negative affect. Dan Bloodgood (a graduate student from Tom Kash's lab at UNC Chapel Hill) will present new, unpublished data that genetic manipulations of Dynorphin/KOR signaling in the central amygdala, but not the basolateral amygdala, alter heavy ethanol consumption. Jordan McCall (WashU) will present data showing that distinct patterns of c-fos expression were identified in a subset of neurons in the CeA following stress, pain, and alcohol exposure. Further, selective photostimulation of dynorphinergic neurons in the CeA produces a frequency-dependent real-time aversion. Together these data provide a base knowledge for further cell-type selective manipulation and observation in vivo and suggest that CeA dynorphin neurons may play a role in negative affective, rather than appetitive behaviors. Catherine Cahill will round out the session and show her most recent data that kappa opioid receptors modulate mesolimbic circuitry and contribute to the tonic aversive component of pain in sex-dependent manner.

**PANEL • TUESDAY, 7:30 A.M. - 9:30 A.M. • WEDGEMOUNT**

## **28. The Synapse and Neuropsychiatric Disorders**

*Chair: Amelia Gallitano*

*Presenters: Shenfeng Qiu, Yi Zuo, Amelia Gallitano, Kuan Hong Wang*

Convergent findings from psychiatric genetic and basic neuroscience research suggest that dysfunction at the synapse may underlie numerous neuropsychiatric disorders. This panel will focus on developmental and environmentally factors that regulate synapse formation and function, and influence local circuitry, in the mammalian forebrain. The genetic and behavioral links with neuropsychiatric illness will be emphasized. Dr. Gallitano (University of Arizona) will provide introductory remarks. Dr. Qiu (University of Arizona) will present work in progress demonstrating that MET receptor tyrosine kinase, an established risk factor for autism spectrum disorders, controls the timing of synapse maturation and plasticity of cortical circuits during development. Dr. Zuo (UC Santa Cruz) will present recent work

demonstrating how stress, a major risk factor for many psychiatric disorders, affects synaptic structure and local inhibitory circuits and impairs cortical function and behavior. Dr. Gallitano will present work demonstrating that the physiologic stress of sleep deprivation induces a rapid change in prefronto-cortical serotonin receptor expression that is mediated by the immediate early gene *Egr3*. Dr. Wang (NIMH) will present recent studies on the functional organization of frontal cortical circuits, which play crucial roles in behavioral control, a processes disrupted in neuropsychiatric disorders. He will present data examining the roles of dopaminergic input and activity-dependent Arc gene expression in shaping circuit structure and function. The panel will conclude with discussion and questions.

## *Tuesday Afternoon Panel Sessions*

**PANEL • TUESDAY, 4:30 P.M. - 6:30 P.M. • FITZSIMMONS**

### **29. Mechanisms by Which Viruses Impact the Brain and Behavior**

*Chair: Gretchen Neigh*

*Presenters: Gretchen Neigh, Jason Paris, Jaclyn Schwarz, Javier González-Maeso*

Exposure to viruses is pervasive and multiple viruses have lasting effects on the brain and behavior. This panel will examine the mechanisms by which HIV, Zika, and influenza can alter neural function and thereby behavior. The presentations in this panel will demonstrate multiple mechanisms by which viruses alter neural function and provide information about multiple potential points of intervention for mitigation of viral effects on the brain. Dr. Gretchen Neigh of Virginia Commonwealth University will chair the panel and lead off the session with a presentation examining the potential for glucocorticoid resistance to contribute to HIV-induced cognitive impairment. Dr. Jason Paris of The University of Mississippi will continue the focus on HIV and neuroendocrinology with a presentation demonstrating that the combined neurotoxic effects of HIV-1 Tat and opioids can be modulated by neurosteroids. Dr. Jaclyn Schwarz of the University of Delaware will then shift the discussion to the Zika virus with focus on using a rat model of maternal ZIKV infection to examine the interaction of pregnancy and immune activation on maternal and fetal outcomes. Finally, Dr. Javier González-Maeso of Virginia Commonwealth University will provide evidence for the influence of maternal influenza viral infection on schizophrenia-related phenotypes with a focus on underlying mechanisms. The long-term survival of individuals infected with HIV and the increasing prevalence of Zika have increased the proportion of the global population coping with the neural and behavioral effects of viral infection. Increased awareness of the mechanisms by which viruses impact the brain and



increased interest among the neuroscience community will ultimately lead to improved understanding of viral effects on the brain and better treatment interventions.

**PANEL • TUESDAY, 4:30 P.M. - 6:30 P.M. • GARIBALDI A**

### **30. Metabolic Dysregulation in Animal Models of Autism Spectrum Disorders**

*Co-chairs: Sean McBride, Thomas Jongens*

*Presenters: Sean McBride, Ilse Gantois, Jelena Popic, Thomas Jongens*

The focus will be on metabolic dysregulation in animal models of autism spectrum disorders (ASD). Dr. McBride will be discussing *Drosophila* models of Fragile X syndrome (FXS) and tuberous sclerosis type 2 (TSC2). Each model has cognitive impairments, similar to the human conditions. Exploring strategies to normalize neural signaling, it was discovered that HDAC inhibitors could rescue memory impairments in both the FXS and TSC2 models. There are clinically available strategies that provide some HDAC inhibition. Dr. Gantois will focus on the metabolic derangement in the mouse FXS model impairing neuronal and behavioral plasticity. Metformin treatment in adulthood that rescues behavioral and electrophysiology in the FXS mouse model. This adulthood metformin treatment is due to selective normalization of MEK/ERK signaling pathway and consequently reduction of phospho-eIF4E and MMP-9, while levels of phospho-S6 remained elevated. Dr. Popic will present work demonstrating dysregulation of mTOR and ERK signaling pathways, as well as imbalances in chloride homeostasis in the Eif4ebp2 knockout mouse model of ASD. These signaling changes lead to a delay in the shift of GABAergic transmission during synaptogenesis in Eif4ebp2 knockout mice could be the one of the causes of the autism-like phenotypes observed in these mice. Dr. Jongens, the Co-chair, will present work on the neurofibromatosis type 1 (NF1) fly model, which is another common monogenic disorder with that has an association with ASD as well as intellectual disability, learning disabilities and attention hyperactivity disorder. In characterizing this model, his work has uncovered dysregulation of the cAMP and mTOR signaling pathways in the brain leading to metabolic dysregulation. He will present work demonstrating that genetic and pharmacologic manipulation of these pathways can rescue memory impairments in the NF1 fly model.

### 31. It's All in Your Head: Neurobiological Mechanisms of Anxiety

*Co-chairs: Matthew Hill, Zoe McElligott*

*Presenters: Zoe McElligott, Matthew Hill, Bitá Moghaddam, Michael Bruchas*

Anxiety, while adaptive in nature to ensure survival, can become pathological when its impact significantly compromises the functionality of an individual. While convergent data from neuroimaging studies and biological assays in humans have generally paralleled findings from animal studies, limitations in technology have restricted the level of analysis with which scientists have been able to probe neural substrates and chemical signals regulating anxiety. Advances in neurotechnology (including opto/chemogenetics, voltammetry and ensemble unit recordings) over the past decade have allowed us to develop a greater understanding of the neurobiology of anxiety. The aim of the current symposia is to bring together a diverse group of scientists who are approaching the study of anxiety from different perspectives to present novel findings regarding the current state of science regarding the neurobiology of anxiety. First, Zoe McElligott will discuss recent findings using *ex vivo* voltammetry regarding changes in biogenic amines in an animal model of anxiety. Second, Matthew Hill will present novel data regarding a mechanistic understanding of how a disruption of endocannabinoid signaling within the amygdala can produce a behavioral state of anxiety in response to sustained peripheral inflammation. Next, Bitá Moghaddam will describe novel findings regarding neural synchrony between the prefrontal cortex and VTA and how this influences behavioral actions during aversive stimuli presentation. Finally, Michael Bruchas will detail new data regarding how communication between the locus coeruleus and dentate gyrus may encode the contextual representation of environments associated with stressful and anxiety-provoking stimuli.

### 32. Pathway-Specific Modulation of Neuronal Activity in Relapse to Drug-Seeking

*Chair: Giuseppe Giannotti*

*Presenters: Stephen Mahler, Giuseppe Giannotti, Aaron Garcia, Marco Venniro*

In the last decade, DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technology has emerged as a powerful chemogenetic tool to manipulate neural activity in the rodent brain with a spatial resolution, and cell-type specificity beyond the capabilities of pharmacological manipulation approaches. This strategy has yielded important insights into the cell-types

and neural circuitry driving drug use, and relapse to drug-seeking. Accordingly, the aim of this panel is to highlight the value of modulating specific neuronal subpopulations in a projection-specific manner in rodent models of relapse. First, Stephen Mahler (University of California, Irvine) will introduce the application of DREADD technology in the field of addictive behaviors, discussing new directions in the pathway-specific modulation of neuronal activity and showing data comparing behavioral efficacy of DREADD agonist drugs. Next, Giuseppe Giannotti (Medical University of South Carolina) will talk about his recent data showing that chemogenetic inhibition of the prelimbic cortex–nucleus accumbens core pathway immediately after the last cocaine self-administration (SA) session prevents BDNF-mediated attenuation of cocaine-seeking behavior. Aaron Garcia (University of Washington) will discuss the role of two distinct striatal-projecting cortical cell types in anterior cingulate on cocaine-induced place preference and reinstatement of drug-seeking following cocaine SA. Finally, Marco Venniro (NIH/NIDA) will discuss how activation of monosynaptic glutamatergic projections from anterior insular cortex to central amygdala, is critical to relapse after cessation of contingency management. These presentations will characterize cutting-edge approaches to resolving the contribution of cell- and projection-specific pathways in reward circuitry to addictive behaviors.

**PANEL • TUESDAY, 4:30 P.M. - 6:30 P.M. • HARMONY B**

### **33. Neuroimaging Psychiatric Biotypes**

*Chair: Marco Leyton*

*Presenters: Marco Leyton, Hugh Garavan, Yuliya Nikolova, Patricia Conrod*

Serious psychiatric disorders commonly begin in adolescence and young adulthood, co-varying with accumulating neurobiological and psychosocial impairments. Recent studies by members of the present panel raise confidence that it may be possible to identify neuroimaging based markers of these risk features. Marco Leyton will present evidence that susceptibility to substance use disorders arises along at least two pathways, one characterized by elevated striatal reactivity, the other by hyper-active amygdala responses to threat. Both biotypes might be influenced by pre-existing perturbations to dopamine and glutamate. Hugh Garavan will provide evidence that diverse internalizing disorders can be predicted by a combination of psychological indices and brain markers. Yuliya Nikolova will provide evidence that transcriptome based polygenic risk scores predict cortical brain reactivity which, in turn, predicts stress-related depressive symptoms and alcohol use problems. Finally, Patricia Conrod will present evidence that risk for psychosis is associated with elevated amygdalar responses to neutral stimuli, while her ongoing work investigates whether targeting vulnerability features with preventative measures not only diminishes adverse clinical outcomes but is related to altered corticolimbic

regulation. Together, these observations make important contributions to our understanding of the neurobiology of salience attribution, mood, and motivational states, and have the potential to refine diagnostic constructs, identify those in need of early intervention, and develop precision prophylaxis based on an improved understanding of etiology.

**PANEL • TUESDAY, 4:30 P.M. - 6:30 P.M. • RAINBOW THEATER**

### **34. Recent Progress From Human Stem Cell Models of Neuropsychiatric Disease**

*Chair: Kristen Brennand*

*Presenters: Sergiu Pasca, Karun Singh, Tracy Young-Pearse, Kristen Brennand*

Given the heterogeneity of neuropsychiatric disease and the limited cohort sizes feasible with human induced pluripotent stem cell (hiPSC)-based studies, our panelists will share their successes and struggles in developing cohorts defined by shared clinical or genetic features. They will discuss molecular and phenotypic insights uncovered in neurons and glia, from case/control and genetically-edited isogenic cohorts. Our overall objective is to consider the role of hiPSC-based studies to dissect the genetic origins of autism and schizophrenia, validate causal variants identified through ongoing genetic analyses, and serve as a personalized medicine approach to screen for novel therapeutics. Sergiu Pasca, Stanford University, will present work from his lab describing novel technologies to develop three-dimensional models of human brain development (brain region specific organoids/spheroids) and their application to study the impact of genetic events contributing to autism and schizophrenia. Karun Singh, McMaster University, will describe progress towards a high-throughput drug screening platform using hiPSCs generated from autism spectrum disorder patients with rare genetic variants. Tracey Young-Pearse, Harvard University, will discuss the convergence of multiple risk genes into common pathways; focusing on rare variants such as DISC1. Kristen Brennand, Icahn School of Medicine at Mount Sinai, will share data concerning the applicability of hiPSC-based models for the study of common variants underlying schizophrenia risk, focusing on the integration of stem cell findings with larger datasets generated from recent genomic and post-mortem studies of large patient cohorts.

### **35. Does Phasic Dopamine = Excess Value or Might it Serve a Broader Role in Error-Based Learning?**

*Chair: Geoffrey Schoenbaum*

*Presenters: Thorsten Kahnt, Geoffrey Schoenbaum, Ronald Keiflin, Paul Phillips*

Phasic dopamine activity has become synonymous with the cached value error signals contained in computational learning algorithms. This powerful proposal has become so entrenched that the two phenomena – phasic dopamine and cached value prediction errors - are often used interchangeably. Yet the learning based on cached value prediction errors - value in excess of what is predicted - is simple and does not encompass the richness and complexity of real world associative learning and behavior. One resolution to this conundrum is if dopamine – a biological signaling system – were capable of more than these models entail. Our panel will describe a variety of new data – in rats and primates – that suggest this may be true. First up, Thorsten Kahnt will describe BOLD signaling in human subjects learning to predict rewards that differed in their value or their identity. Geoffrey Schoenbaum will build on these data, discussing error signaling in putative dopamine neurons recorded in VTA in rats performing a similar task. Together their data will challenge the idea that value error signals exist independently of identity error signals and that dopamine neurons signal only the former. Ronald Keiflin will move from correlative studies to causal work, using optogenetics to ask what types of learning can be supported by transient activation of dopamine neurons in substantial nigra versus VTA. Finally, Paul Phillips will show data using voltammetry and optogenetics to examine how phasic dopamine signaling is involved in learning for drug rewards. Together, these data both confirm the current proposal that dopamine neurons signal (i.e., respond to) cached value errors, while also showing they are capable of signaling other types of errors and supporting much richer forms of learning. This suggests that cached value error signals may be a particularly strong example of a more general error signaling function supported by these neurons.

### **36. The Role of Oxidative Stress in Parkinson's Disease: From Origins to Outcomes**

*Chair: Leslie Sombers*

*Presenters: Eugene Mosharov, Louis-Eric Trudeau, Kristen Stout, Leslie Sombers*

The cardinal motor symptoms of Parkinson's disease (PD) result from the dysfunction and slow degeneration of the dopamine projection from the substantia nigra (SN) to the dorsal striatum. There is no specific known cause

for idiopathic PD; however, multiple lines of evidence implicate oxidative stress in neuronal vulnerability associated with the disease. It is well established that mitochondria generate reactive oxygen species in cellular respiration, and the phenotype of SN dopamine neurons creates a significant mitochondrial burden. Furthermore, many of the toxins, genetic mutations, and even treatments associated with PD can compromise mitochondrial function or generate oxidant stress. However, fundamental questions remain unanswered, including where and why aberrant oxidative stress originates, and how precise fluctuations of reactive oxygen species relate to the pathological and phenotypical hallmarks of PD. We will present work that sheds light on these questions. Eugene Mosharov will discuss mechanisms of MPP<sup>+</sup> toxicity in cultured SN and ventral tegmental area neurons, describing the role of L-type Ca<sup>2+</sup> channels, ryanodine receptors, and alpha-synuclein in selectively mediating toxicity in SN neurons. Louis-Eric Trudeau will describe how bioenergetics and the complexity of the axonal compartment contribute to neuronal vulnerability. Kristen Stout will discuss estrogen modulation of neuronal vulnerability due to oxidant stress as a result of dopamine metabolism, and where this is localized in the cell. Finally, Leslie Sombers will present data on hydrogen peroxide and DA fluctuations at single micron-scale recording sites in a rat model of PD (unilateral 6-OHDA lesion) over several weeks of L-DOPA administration. Overall, these talks will demonstrate that a better understanding of aberrant oxidative stress is paramount to the development of improved antiparkinsonian therapeutic interventions and neuroprotective/neurorestorative strategies.

## *Brain Talk Town Meeting*

PLENARY • TUESDAY, 7:00 P.M. – 8:30 P.M. • SEA TO SKY BALLROOM A

### **37. Champions of Illusion**

*Presenter: Susana Martinez-Conde*

Visual illusions are those perceptual experiences that do not match the physical reality. Our perception of the outside world is generated by brain mechanisms, so all visual perception is illusory to some extent. The study of visual illusions is critical to understanding the basic mechanisms of sensory perception, as well as to cure visual and neural diseases. The illusion community includes visual scientists, ophthalmologists, neurologists, painters, sculptors, magicians, mathematicians and graphic designers that use a variety of methods to unveil the underpinnings of illusory perception. This lecture will feature the most exciting novel illusions created by the best and most cutting-edge illusion innovators of the new millennium.

**WEDNESDAY, JANUARY 17, 2018**

*Wednesday Morning Panel Sessions*

**PANEL • WEDNESDAY, 7:30 A.M. - 9:30 A.M. • FITZSIMMONS**

**38. The Neglected Nuclei of Addiction: Putting Understudied Brain Regions in the Limelight**

*Co-chairs: Elizabeth Glover, Candice Contet*

*Presenters: Christopher Chen, Elizabeth Glover, Candice Contet, Christelle Baunez*

Substance use disorders are highly prevalent and constitute a significant public health concern. Pharmacotherapeutic options are limited and lack long-term efficacy. The consumption of drugs of abuse is initially driven by their rewarding properties, but negative reinforcement plays a gradually more prominent role as dependence develops, with the drug user seeking relief from the aversive state associated with withdrawal. Accordingly, studies investigating the neurobiological mechanisms of addiction have explored the role of neural circuits mediating reward and aversion, with a disproportionate emphasis on striatal, cortical, and extended amygdala subregions. The goal of this panel is to call attention to previously understudied brain regions and demonstrate their involvement in addiction-related phenotypes. First, Dr. Christopher Chen (Harvard University) will present data demonstrating involvement of cerebellar inputs to the ventral tegmental area in reward-related behavior. Dr. Elizabeth Glover (Medical University of South Carolina) will discuss the role of the rostromedial tegmental nucleus and its inputs in mediating aversive signaling and withdrawal-induced negative affect. Dr. Candice Contet (The Scripps Research Institute) will present data implicating the parasubthalamic nucleus as a new node in the neuronal network driving excessive ethanol drinking and negative affect during withdrawal from chronic ethanol exposure. Finally, Dr. Christelle Baunez (CNRS and Aix-Marseille Universite) will discuss how manipulation of activity within the subthalamic nucleus can affect various addiction-related outcomes across multiple drugs of abuse in rats and monkeys. Together, these panelists will introduce new data highlighting the need to explore previously neglected brain regions in an effort to improve our understanding of the neurobiological underpinnings of addiction and facilitate the development of new treatment targets for recovery.

### 39. Treatments for Intellectual Disability and Autism Targeting Protein Synthesis: The Prospects for Individualized Treatments

*Chair: Francois Bolduc*

*Presenters: Francois Bolduc, Eric Klann, Carolyn Beebe Smith, Sebastien Jacquemont*

Intellectual disability (ID) and autism spectrum disorders (ASD) are now at the forefront of translational research. ID and ASD cause significant burden on families and lead to costs of over \$20 billion per year in the US alone. Studies on animal models showed that many behavioral features of ID and ASD could be reversible, but despite these advances, clinical studies in humans have highlighted the challenges of treating cognitive disorders.

Our panel will focus on a biomarker-based approach to treatment. Despite the genetic heterogeneity of ID and ASD made evident by genome-wide sequencing methods, dysregulation of protein synthesis is at the core of cognitive pathology for many genes.

Our panel is composed of leaders in the field of translational control and ID/ASD. Francois Bolduc will present evidence for how protein synthesis can be regulated by FDA approved drugs which could help rescue defects in a wide range of ID/ASD genes clustering with Fragile X syndrome (FXS) gene FMR1. Eric Klann will discuss studies on the identification and characterization of autism spectrum disorder (ASD)-associated single nucleotide variants in genes encoding translational control proteins. These include ASD-associated genes in the eIF2 and the eIF4E translational control pathways. Carolyn Beebe Smith will discuss the use of brain imaging techniques to measure rates of protein synthesis in vivo. Results demonstrate a dysregulation of protein synthesis in both Fmr1 KO mice and in human subjects with fragile X syndrome. Sebastien Jacquemont will present evidence of the variability in levels of excess protein synthesis in FXS patients, how they may relate to clinical severity and discuss their use in clinical trials. Our multidisciplinary panel will discuss the impact of genetic background and the need for cross-talk between disciplines for the development of quantitative biomarkers in planning treatment trials targeting protein synthesis for ID and ASD.



## 40. Rodent Models of Cannabinoid Administration: Novel Approaches and Surprising Findings

*Co-chairs: Barry Setlow, Mary Torregrossa*

*Presenters: Barry Setlow, Ryan McLaughlin, Michael Taffe, Mary Torregrossa*

Cannabis is the most widely used illicit drug, and its use is expected to grow with recent and pending changes to its legal status. Despite its widespread use, basic research on cannabis has been hampered by a paucity of animal models that capture important features of human intake. The participants in this panel will review recent data from several novel rodent models of cannabis use, which reveal unexpected effects of cannabinoid administration on cognition, affect, and other aspects of behavior. Barry Setlow will present data in rats showing that acute exposure to cannabis smoke causes a sex-dependent enhancement in performance on a delayed response working memory task. This enhancement is not likely due to arousal caused by smoke exposure per se, as it is absent following exposure to smoke from “placebo” cannabis. Ryan McLaughlin will present data in rats showing that offspring exposed prenatally to vaporized cannabis extracts exhibit decreased anxiety-like behavior, but make significantly more regressive errors in an attentional set-shifting task, coinciding with impairments in reversal learning when tested in adulthood. Michael Taffe will discuss models of the self-administration of THC via e-cigarette vapor inhalation in rats, as well as an unexpected failure of SR141716 and AM251 to block hypothermia caused by vapor inhalation of THC in male and female rats. Mary Torregrossa will discuss results from studies investigating the cognitive consequences of intravenous self-administration of the synthetic cannabinoid agonist WIN 55,212-2 (WIN) in rats. Adolescent WIN self-administration can enhance working memory in adulthood, particularly in males, while adult WIN self-administration can cause temporary working memory impairments. Collectively, these data demonstrate the complexity of cannabinoid effects and highlight the importance of considering dose and method of administration for understanding how cannabinoids affect physiology and behavior.

## 41. Chronic Behavioral Effects of Neurological and Psychological Trauma

*Chair: Christopher Olsen*

*Presenters: Christopher Olsen, Cole Vonder Haar, Alana Conti, Carrie Jones*

This panel will explore the long-term effects of traumatic brain injury (TBI) and psychological trauma with an emphasis on chronic behavioral outcomes. Chris Olsen (Medical College of Wisconsin) will present data describing the effects

of a blast model of mild TBI on addiction-related phenotypes using intravenous drug self-administration. Cole Vonder Haar (University of West Virginia) will present data on the impact of repeated mild TBI on impulsive behaviors in rats. Alana Conti (Wayne State University) will present data focused on the effects of single prolonged stress exposure, as a model of PTSD. Specifically, her talk will describe how traumatic stress alters behavioral responding to a variety of alcohol exposure paradigms and identify potential molecular mediators of these outcomes. Carrie Jones (Vanderbilt University School of Medicine) will present data on the effectiveness of a VU0409106, a novel metabotropic glutamate receptor 5 (mGlu5) negative allosteric modulator, in reducing the exacerbated threat response following traumatic stress. She will also present evidence that VU0409106 reduces stress-associated increases in frontal cortex theta power and REM sleep, suggesting that selective mGlu5 antagonism early after trauma may be a safe and effective means of inhibiting or preventing the development of PTSD symptoms.

**PANEL • WEDNESDAY, 7:30 A.M. - 9:30 A.M. • HARMONY B**

## **42. When Roads Converge: What Integrative Homeostatic Circuits Teach Us About Brain Plasticity in Health and Disease**

*Chair: Carie Boychuk*

*Presenters: Javier Stern, David Mendelowitz, Jeffrey Tasker, Jasenka Zubcevic*

Homeostasis refers to the process by which the body maintains a constant internal environment. In the orchestration of homeostasis, brain networks involved in autonomic and neuroendocrine function coordinate multiple peripheral physiological systems through complex network processing. In this panel, we will discuss how interconnected brain regions sense and respond to physiologically relevant signals. Each speaker will discuss how disruptions of this integrative processing lead to physiological disease states, particularly of the cardiovascular system. Dr. Javier E. Stern (Georgia State University) will begin the session examining how mitochondria orchestrate intracellular calcium homeostasis and neuronal excitability in hypothalamic neurosecretory and presympathetic neurons. Dr. Stern's presentation will focus on how altered mitochondria function may contribute to increased neurohumoral activation after congestive heart failure. Dr. David Mendelowitz (George Washington University) will follow with a discussion on how the brain integrates longer distance projections from the hypothalamus to descending hindbrain cardiovascular regulating regions. Dr. Mendelowitz's presentation will highlight the use of oxytocin, an important signaling neuropeptide for these long distance projections, as a promising therapeutic target in the treatment of cardiovascular disease. Dr. Jeffrey G. Tasker will discuss crosstalk between the central control of feeding and fluid homeostasis. Dr. Tasker will present data on the regulation

of vasopressin neurons by the feeding peptide ghrelin. Dr. Jasenka Zubcevic (University of Florida) will finish the session discussing sympathetic nervous system regulation of immune function through adrenergic receptor activation of bone marrow. Dr. Zubcevic will discuss an elegant interplay between the sympathetic nervous system and the immune system in the regulation of inflammatory status that potentially contributes to neurogenic hypertension.

**PANEL • WEDNESDAY, 7:30 A.M. - 9:30 A.M. • RAINBOW THEATER**

### **43. GPCR Functional Selectivity: When Bias is a Good Thing**

*Chair: Amy Newman*

*Presenters: Laura Bohn, Marc Caron, David Sibley, J. Robert Lane*

Biased agonism describes the ability of ligands to stabilize different conformations of a G-protein coupled receptor (GPCR) linked to distinct functional outcomes and offers the prospect of designing pathway-specific drugs that avoid on-target side effects. Laura Bohn will introduce the topic of biased agonism and how it varies in cell based signaling assays. She will discuss the challenges in determining whether in vivo effects are due to bias or simply differences in drug potency, efficacy or pharmacodynamics/kinetics. She will then describe her work with the opioid receptor systems, and discuss how some of their biased agonists at the mu (MOR) and kappa opioid receptor (KOR) differentially effect dopamine-mediated behaviors in vivo. Marc Caron will discuss the concept of functional selectivity/biased signaling at the various dopamine receptors to provide proof-of-concept for the development of more efficacious therapies for both neurological and neuropsychiatric conditions like Parkinson's disease and schizophrenia. He will describe a new beta-arrestin2 biased-D2R compound (UNC9994A) that presumably functions as an antagonist in the striatum, but an agonist in GABAergic cortical fast spiking interneurons. In addition he will outline efforts to develop dopamine receptor selective compounds that could mimic the beneficial effects of L-DOPA while sparing its dyskinesia liability. David Sibley will describe the characterization of a novel G-protein-biased dopamine D2 receptor agonist and mutagenesis studies leading to the identification of residues in the receptor's fifth transmembrane-spanning domain that regulate signaling through either G proteins or beta-arrestin2. Finally, Rob Lane will discuss the influence of 'kinetic context', as determined by ligand-binding kinetics and the temporal pattern of receptor-signaling processes on the apparent bias of a series of dopamine D2 receptor agonists, including the antipsychotics aripiprazole and cariprazine. The concept of biased signaling is gaining momentum toward an increasingly prominent role in GPCR drug discovery. This panel of experts will provide highlights of their research in this arena as well as their view of future directions and therapeutic promise in the field.

## 44. Alzheimer's Disease and Comorbidities: Modelling and Treatment Strategies

*Chair: Isabelle Aubert*

*Presenters: JoAnne McLaurin, Jerome Robert, Cheryl Wellington, Isabelle Aubert*

This panel will address Alzheimer's disease (AD), comorbidities, in vitro and in vivo modelling, and treatment strategies. AD is a multifactorial neurodegenerative disorder, with characteristic amyloid- $\beta$  peptides ( $A\beta$ ) and tau pathologies. Known risk factors of AD are aging and, in rare cases, inherited genetic mutations. Prominent contributors to AD have been identified and they include cerebrovascular and cardiovascular diseases, diabetes, and traumatic brain injury (TBI). These topics will be introduced by Dr. McLaurin, followed by her research on interactions between hypertension, covert stroke and AD pathologies. Dr. Robert will focus on the role of cerebral amyloid angiopathy (CAA) in AD. He will present a unique functional 3D model of CAA in engineered human vessels. His findings show that lipoproteins synergize to facilitate  $A\beta$  transport across engineered human vessels. The utility of this innovative in vitro platform to study key mechanistic questions relevant to AD will be discussed. Dr. Wellington will describe relationships between TBI and AD, and the importance to develop animal models that accurately replicate human TBI pathophysiology. She recently developed CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) to model a wide range of severities. Preliminary data reveal complex interactions between age at injury with inflammation, axonal damage and  $A\beta$  metabolism. Treatment strategies promoting neural and vascular health, in addition to reducing  $A\beta$  pathology, may be required to counter AD. Dr. Aubert will present data on the impact of running on the hippocampal vasculature in a mouse model of AD. She will also discuss neural plasticity  $A\beta$  reduction mediated by focused ultrasound, alone and in combination with immunotherapy or neurotrophin receptor (TrkA) stimulation. The panel will conclude on the importance of understanding the interplay between risk factors and AD pathophysiology for the development of successful therapies.

## 45. Organization and Plasticity of Excitatory and Inhibitory Synapses

*Chair: David Bredt*

*Presenters: Elva Diaz, Susumu Tomita, David Bredt, Andres Maricq*

Organization of receptors at postsynaptic sites is precisely controlled during development. Furthermore, receptor density at synapses is dynamically regulated in the plasticity that underlies learning and memory. This panel will describe molecular pathways that determine the distribution and function of synaptic neurotransmitter receptors. Diaz will present data showing that SynDIG4 modifies AMPA receptor biophysical properties in a subunit dependent manner and that SynDIG4 knockout (KO) mice show complete loss of tetanus-induced long-term potentiation while mEPSC amplitude is reduced by only 25%. As synaptic AMPA receptor channel kinetics are unchanged in SynDIG4 KO mice, these results imply that SynDIG4 establishes a pool of extrasynaptic AMPA receptors necessary for synapse development and plasticity. Tomita will describe their discovery of GARLH family proteins as GABAA receptor auxiliary subunits that occur together with neuroligins in native GABAA receptors complexes. He will present roles for this tripartite complex of GABAA/GARLH/neuroligin in regulating inhibitory transmission. Bredt will describe recent discoveries concerning the trafficking and function of neuronal nicotinic receptors. He will provide molecular details for regulation of nicotinic receptor assembly by the protein chaperone NACHO and how this participates in neuropsychiatric disorders. Maricq will discuss the identification and characterization of a novel NMDA receptor auxiliary protein. In contrast to the AMPA and kainate receptor, no auxiliary proteins that modify the function of NMDA receptors have been found. He will describe a genetic approach in *C. elegans*, that identified NRAP-1, a NMDAR auxiliary protein. Importantly, NMDA receptor-mediated currents were not detected in nrp-1 mutants and reconstitution of NMDA-gated current in *Xenopus* oocytes depends on NRAP-1.

## *Wednesday Pioneer Session #2: Daniel Weinberger*

**PIONEER SESSION • WEDNESDAY, 9:45 A.M. – 10:45 A.M. • FITZSIMMONS**

### **46. Sex, Signaling and Human Brain Development**

*Pioneer: Daniel Weinberger*

*Chair: Thomas Hyde*

*Investigators: Elizabeth Tunbridge, Alexandra Ycaza Herrera*

Our current conceptualization of schizophrenia as a neurodevelopmental disorder with genetic underpinnings is based largely on the work of WCBR Pioneer, Dr. Daniel Weinberger (Lieber Institute for Brain Development). After providing historical perspectives on the challenges of identifying genetic mechanisms for disruptions in cognition and emotion, Dr. Weinberger will explore how early brain development mediates genetic and epigenetic risk for schizophrenia. For example, RNA seq analyses show preferential expression of genes implicated in susceptibility for developmental neuropsychiatric disorders, at both pre- and postnatal time points. Similarly, epigenetic variations associated with prenatal development are enriched for schizophrenia GWAS loci. Finally, polygene risk scores for schizophrenia interact with obstetrical complications, likely because some risk genes are dynamically regulated in placenta from complicated pregnancies, with greater effects in placentae from male offspring than females. Dr. Elizabeth Tunbridge (University of Oxford) will focus further on voltage-gated calcium channels (VGCCs) as potential therapeutic targets emerging from genomic studies of psychiatric illnesses. She is using nanopore sequencing to characterize the strongest GWAS VGCC target, CACNA1C in human post-mortem brain, and has revealed multiple novel exons, of which five have been validated using Sanger sequencing. These data reveal the complexity of human brain CACNA1C isoform profiles, and chart the path for identifying those most relevant for psychiatric illness. Dr. Alexandra Ycaza Herrera (University of Southern California) will extend the session to the interplay of stress and hormonal signaling on working memory. After completing a stressful cold pressor test, women using hormonal contraception (HC) show greater activation of the Default Mode Network (DMN) during control trials (0-back blocks), compared with working memory trials (2-back blocks). This difference is attenuated, particularly in the posterior cingulate, when HC hormones are absent, suggesting that exogenous hormones promote more efficient switching between DMN and working-memory networks. Together these panelists explore genetic, molecular, and cellular mechanisms for neuropsychiatric disorders of cognition and emotion.

## *Wednesday Afternoon Panel Sessions*

**PANEL • WEDNESDAY, 4:30 P.M. - 6:30 P.M. • FITZSIMMONS**

### **47. Net Gain and Loss: Perineuronal Nets, Plasticity, and Drugs of Abuse**

*Co-chairs: Barbara Sorg, John Harkness*

*Presenters: Carolyn Johnson, Amy Lasek, Jordan Blacktop, Travis Brown*

Perineuronal nets (PNNs) are specific extracellular matrix structures that wrap around the surface of certain neurons during development and are involved in controlling plasticity in the adult central nervous system (CNS). They are found primarily around fast-spiking, parvalbumin interneurons, which can profoundly influence output from many brain regions, making PNNs an exciting and emerging target for therapies. Recent studies show that PNNs and the surrounding extracellular matrix contribute to memories associated with drugs of abuse and are themselves altered after exposure to these drugs. Dr. John Harkness (Co-chair) will give a brief introduction of the structure and function of PNNs. Dr. Carolyn Johnson will discuss the role of PNNs in the prefrontal cortex on inflexible/compulsive behavior. Dr. Amy Lasik will discuss how alcohol exposure produces changes in PNNs in the insula, and, in turn, how ethanol consumption is reduced after removing PNNs in this region. Dr. Jordan Blacktop will discuss how PNNs in reward-related circuitry in the medial prefrontal cortex and the lateral hypothalamus regulate cocaine-associated memories, and Dr. Travis Brown will describe electrophysiological changes in principal neurons and fast-spiking neurons with PNNs after cocaine exposure. In summary, this panel will discuss how PNNs alter plasticity in their underlying neurons that are critical to maintaining excitatory-inhibitory balance of cortical output.

**PANEL • WEDNESDAY, 4:30 P.M. - 6:30 P.M. • GARIBALDI A**

### **48. Two Sides of the Same Slope: Dissecting Separate and Shared Neural Substrates of Reward and Aversion**

*Chair: Sade Spencer*

*Presenters: Rachel Smith, Sade Spencer, Stan Floresco, Peter Vento*

The ability to appropriately modify behavior in the face of a dynamic environment is a critical tool for survival. The brain is wired normally to seek out rewards and avoid negative consequences, and these opposite processes engage overlapping neural circuitry. Environmental and physiological factors can modify these circuits to change behavioral output in both beneficial and maladaptive ways. This panel will focus on circuit mechanisms of decision-making using both traditional and novel techniques for circuit dissection.

First, Rachel Smith (Texas A&M) will present research describing roles for dorsal striatum in habitual cocaine seeking and punishment resistance. Next, Sade Spencer (MUSC) will present work examining how activity of ventral tegmental area dopamine neurons modulates key relapse-dependent neurobiological adaptations in nucleus accumbens associated with cue-induced drug seeking. Then Stan Floresco (University of British Columbia) will show that the nucleus accumbens does not promote reward seeking, highlighting dissociable contributions of the shell and core in various aspects of aversively motivated behavior including punished reward seeking, discriminative fear conditioning and active/passive avoidance. Finally, Peter Vento (MUSC) will describe research showing how activity of GABAergic projection neurons from the rostromedial tegmental nucleus facilitates learning from aversive events through transient inhibition of midbrain dopamine transmission. Collectively, these presentations will highlight the mesolimbic neuron populations involved with decision-making, reward-seeking, and aversively motivated behaviors.

**PANEL • WEDNESDAY, 4:30 P.M. - 6:30 P.M. • GARIBALDI B**

## **49. Novel Brain Stimulation Techniques to Optimize Plasticity Induction in Humans**

*Chair: Corey Keller*

*Presenters: Faranak Farzan, Corey Keller, Cammie Rolle, Molly Lucas*

Neurological and psychiatric disorders are increasingly thought as arising from abnormalities in distributed brain networks. Recent brain stimulation therapies such as transcranial magnetic stimulation (TMS) target specific cortical regions, but attempts to do so in a one-size-fits-all approach and with no objective measurement of brain changes. Having a better mechanistic understanding of how current treatments elicit lasting changes in the brain, and exploring how these treatments compare to newer treatment modalities are needed. The goal of this symposium is to discuss the leading-edge basic science and translational neurostimulation projects in the field. Speakers will present their most recent unpublished data that have the potential to understand brain plasticity in humans and transform clinical practice. Projects included aim to improve the field of human non-invasive brain stimulation by: better understanding the mechanism of action of neurostimulation techniques; developing tools to track brain network changes during treatment; and improving the strength, duration, and focality of plasticity in the human brain. Dr. Faranak Farzan will first provide an overview of concurrent TMS-EEG markers of brain health in enhancing the precision of brain stimulation therapies. Using intracranial EEG, Dr. Corey Keller will present on the mechanistic effects of standard repetitive stimulation and the utility of real-time monitoring. Cammie Rolle will present data using theta burst stimulation (TBS) to induce plasticity in circuits involved



in emotion regulation to modulate cognitive function. Molly Lucas will discuss the use of multi-coil TMS to induce spike timing dependent plasticity in cortical networks.

**PANEL • WEDNESDAY, 4:30 P.M. - 6:30 P.M. • HARMONY A**

## **50. New Therapeutic Approaches to Epilepsies Caused by Sodium Channelopathies**

*Chair: Peter Ruben*

*Presenters: William Catterall, Lori Isom, Steven Petrou, Charles Cohen*

Channelopathies are a group of diseases caused by ion channel mutations and range from annoying to fatal. Voltage-gated sodium channel mutants underlie a number of channelopathies including epilepsy. An explosion of genetic data has provided new opportunity for discovery of therapies targeted at disease mechanisms. The panel will discuss research to understand and treat epilepsy caused by sodium channel mutations. Haploinsufficiency of Nav1.1 causes Dravet Syndrome (DS). Electrophysiological and mouse genetic studies show DS is caused by specific loss of excitability in GABAergic neurons, altering the ratio of excitation and inhibition in brain circuits. Catterall will discuss the pathogenic roles of different classes of interneurons causing epilepsy in DS, and beneficial effects of cannabidiol, a non-psychotropic component of cannabis. Isom will discuss a pediatric epileptic encephalopathy, EIEE13. Testing an FDA approved drug, in use for other diseases, on patient-derived iPSC neurons and a mouse model with a knock-in mutation, led to a recommendation to pediatric neurologists for a drug trial. Two EIEE13 patients, previously out of seizure control, are currently having little to no seizures. Petrou will discuss strategies to target mechanisms underlying excitability changes in neurons expressing Nav1.2 in epilepsy of infancy with migrating focal seizures. Nav1.2 mutants show both gain- and loss-of-function; however, clear genotype-phenotype relationships are emerging. Cohen will discuss gain-of-function Nav1.6 mutants causing severe childhood epilepsies. Carbamazepine and other non-selective sodium channel blockers are widely used as anticonvulsants, but have modest therapeutic indices. Reasoning that compounds selective for Nav1.6 would have a superior therapeutic index, Cohen's group used a privileged binding site on VSD4 to develop isoform-selective compounds with anticonvulsant activity, effective in transgenic mice that express one of these mutations.

## 51. Dissecting the Hypothalamic Arcuate Nucleus – Epicenter of Steroid Action in the Brain

*Chair: Paul Micevych*

*Presenters: Paul Micevych, Kevin Sinchak, Oline Ronnekleiv, Stephanie Correa*

Over the years, our understanding of sex steroid signaling in the brain has greatly expanded due to experiments that have demonstrated membrane-initiated actions in addition to the classical direct nuclear actions. Perhaps no other region in the brain has been so intensely studied in terms of steroid actions as the arcuate nucleus of the hypothalamus (ARH). This small nucleus controls numerous sexually dimorphic physiological actions including energy balance, luteinizing hormone release, and reproductive behavior – all affected by sex steroids. The ARH expresses a variety of steroid receptor, including estrogen receptor- $\alpha$  (ER $\alpha$ ), an alternatively splice variant, ER $\alpha\Delta 4$ , Gq coupled membrane ER (Gq-mER) G protein-coupled estrogen receptor 1 (GPER) and progesterone receptor (PGR). This panel will discuss the physiological interactions and effects of these receptors. Micevych will describe the downstream signaling of ER $\alpha$  and ER $\alpha\Delta 4$  that determines whether membrane estradiol actions are stimulatory or inhibitory. These actions affect morphological plasticity and activation of microcircuits that regulate female sexual receptivity through modulation of NPY and POMC ARH neurons. Sinchak expands the discussion of steroid actions on female reproductive behavior by discussing the integration of membrane estradiol and progesterone signaling. While ER $\alpha$  mediated initial estradiol actions, facilitation of lordosis behavior requires either activation of GPER or PGR-Src signaling. Ronnekleiv will discuss her results about estradiol signaling through ER $\alpha$  and Gq-mER to regulate ARH kisspeptin neurons in females, which integrate the control of reproduction and metabolism. Correa will discuss her work on transcriptional profiling and ER $\alpha$  deletion. The elimination of ER $\alpha$  has a potent action on bone density, but not food intake. These results suggest a female specific ARH controller involving dopamine neurons that can divert energy from bone to maintain pregnancy or lactation.

## 52. Examining the Role of Autophagy in Animal Models of Intellectual Disability and Autism Spectrum

*Co-chairs: R. Suzanne Zukin, Sean McBride*

*Presenters: R. Suzanne Zukin, Leonard Kaczmarek, Elizabeth Jonas, Sean McBride*

Suzanne Zukin will chair the session and make introductory remarks. The presentation order will be Suzanne Zukin, Leonard Kaczmarek, Elizabeth Jonas and Sean McBride. Zukin and McBride will lead discussion of presentations. Fragile X syndrome (FXS) is the most common form of heritable intellectual disabilities and the leading single gene cause of autism. Cognitive deficits associated with FXS remain an unmet medical need. Autophagy is a process of programmed degradation and recycling of cellular components via the lysosomal pathway which is increased during periods of cellular stress. mTOR plays a pivotal role in cell growth, autophagy, and cell survival. Zukin will discuss her research demonstrating that autophagy is impaired and causally related to aberrant spine morphology and impaired cognition observed in Fragile X mice. Kaczmarek will discuss his finding that mutations in the Kv3.3 potassium channel cause spinocerebellar ataxia type 13, a disorder associated with ataxia and mild intellectual disability. Activation of Kv3.3 stimulates activity of Tank Binding Kinase 1 (TBK1), an enzyme that controls autophagy and mitophagy. A disease-causing mutation in Kv3.3 induces overstimulation of TBK1 in animal models, leading to an accumulation of multivesicular bodies that contain cell-survival proteins linked to Kv3.3 channels, release of exosomes, and eventual neuronal death. Chronic loss of the mitochondrial membrane potential results in pathological levels of mitophagy. Jonas will discuss the role of a macromolecular complex that includes the Parkinson's protein DJ1 and FMRP (Fragile X mental retardation protein), regulate ATP production and mitochondrial membrane potential, suggesting that interaction of these proteins with mitochondria regulates mitophagy. McBride will discuss genetic and pharmacological manipulation of macro-autophagy in the brains of the *Drosophila* FXS model. He finds that normalizing autophagy in the fly brain rescues social and memory impairments in the FXS fly.

### 53. Cues for Bad Behaviour: The Role of Aberrant Motivation Elicited by Conditioned Stimuli in Addictive and Compulsive Disorders

*Co-chairs: Catharine Winstanley, Kathryn Cunningham*

*Presenters: Kathryn Cunningham, Catharine Winstanley, Roshan Cools, Valerie Voon*

The ability of drug-paired cues to exert a dominant influence over goal-directed behaviour is a central tenet in the highly influential “incentive sensitization” theory of drug addiction. Recent data posit that the aberrant control of behavior by reward-paired cues may also play a role in non-drug compulsive disorders. However, the degree to which cue-induced incentive motivation contributes to other cognitive processes central to such psychopathologies, including impulsivity and poor cost/benefit decision making, remains unclear. The panel will therefore present recent and novel data to indicate a broader role for maladaptive, cue-driven biases across a range of psychiatric disorders, and consider whether these are unitary or dissociable neurocognitive mechanisms precipitating psychiatric vulnerability. Dr. Kathryn Cunningham will highlight the importance of serotonin receptors mediating impulsivity that precipitates addiction risk, and the degree to which such cognitive changes may be representative of greater incentive motivation to drug or reward-paired cues in rodents and humans. Dr. Catharine Winstanley will discuss data from studies using both rodents and human subjects in which the addition of reward-concurrent cues to laboratory-based gambling tasks skews choice in favour of risky or uncertain outcomes, alters the neurochemical regulation of choice, and also renders rats more sensitive to the risk-promoting effects of cocaine self-administration. Dr. Roshan Cools will then review recent studies combining psychopharmacology, dopamine PET and patient work evidencing a key role for both dopamine and trait impulsivity in the detrimental effects of incentive motivational cues on human cognitive control. Finally, Dr. Valerie Voon will consider recent data regarding the impact of affective valence on the role played by serotonin in model-based learning, and the implications of these findings for disorders associated with a breakdown of goal-directed behaviour.

## 54. Circuit and Synaptic Mechanisms of Stress Responses: Towards an Integration of Neuroendocrine and Behavioral Responses

*Chair: Jason Radley*

*Presenters: Victor Viau, Jaideep Bains, Jamie Maguire, Jason Radley*

The past quarter century has seen a substantial degree of progress in unraveling the neural pathways mediating maladaptive behavioral and endocrine responses to emotional stressors. Emphasis on studying these systems is based upon the far-reaching adverse health consequences that result from severe or chronic stress exposure. Further insight into stress-related disease susceptibility will invariably derive from, not only the application of more sophisticated techniques, but also by constructing frameworks for understanding the basis for individual differences in adaptive and maladaptive responses. This symposium will highlight recent advances in differential adaptations to stress system by researchers employing physiological, circuit and synaptic level approaches. Victor Viau (University of British Columbia) will discuss adaptive neuroendocrine responses as a consequence of sex differences in mechanisms of central serotonin synthesis and signal transfer. Jaideep Bains (University of Calgary) will present data showing how social interactions can both transmit and buffer signals that promote plasticity in brain circuits following stress. Jamie Maguire (Tufts University) will discuss how stress facilitates the recruitment of a neural circuit involved in the behavioral expression of anxiety and the implications for neuropsychiatric disorders. Jason Radley (University of Iowa) will implicate an emerging role for the limbic forebrain in mediating proper emotional and sensory information for successful stress coping.

### *Wednesday Evening Panel Sessions*

## 55. Dexterity: A Problem for Robotics and Biology

*Chair: Andrew Schwartz*

*Presenters: Neville Hogan, Gerald Loeb, Marco Santello, Francisco Valero-Cuevas*

Dexterity is the pinnacle of motor behavior. The use of the hand and fingers to manipulate objects demands precise control of the way the hand and fingers move as well as the forces they apply to the targeted object. To impart this control, it is necessary to have a high-level understanding of the target object's properties (e.g. size, weight, and texture), the way it's situated in the environment, and the desired outcome of the manipulation. The control signal itself must have the resolution to provide precise control of fine displacement,

small incremental changes in force, and elaborate coordination of the many degrees of freedom in the arm, hand and fingers. Equally important is the sensory feedback needed to gain knowledge of the object and to monitor progress of the ongoing behavior. In biological systems, feedback comes from visual, cutaneous, and proprioceptive receptors. This intricate control problem has been a topic of interest for robotic manipulators and information gained from research in this field is useful in guiding nascent studies of the behavioral and neurophysiological characteristics of primate dexterous behavior. Andrew Schwartz will give an overview of the control needed to successfully manipulate objects. Neville Hogan will discuss some surprising limitations of human control that arise in physical interaction with robots. Gerald Loeb will show how exploratory actions must be selected and with tactile data to identify familiar objects in the absence of vision. Marco Santello will describe an experimental framework for identifying neural mechanisms underlying dexterous manipulation. Francisco Valero-Cuevas will explain how experimental/clinical metrics can be used to quantify the sensorimotor integration used during dexterous movement in health and disease.

**PANEL • WEDNESDAY, 7:00 P.M. - 8:30 P.M. • GARIBALDI A**

## **56. Secreted Axon Guidance Cues, Proteoglycans, and Perineuronal Nets in the Developing and Adult CNS**

*Chair: Timothy Kennedy*

*Presenters: Jessica Kwok, Timothy Kennedy, Stephanie Harris*

Perineuronal nets (PNNs) are a specialized extracellular matrix that develops relatively late during the maturation of the central nervous system (CNS) to ultimately envelop many neuronal cell bodies, dendrites, and synapses in a dense web of glycosaminoglycans (GAGs). PNNs exert a potent influence on plasticity and regeneration. Major molecular components of PNNs include the chondroitin sulfate proteoglycans (CSPGs): aggrecan, neurocan, versican, brevican, phosphocan; in combination with hyaluronan and tenascins. PNN formation correlates with the closure of developmental critical periods. Degradation of PNNs by digestion with chondroitinase ABC (ChABC) increases axon regeneration in the CNS, enhances synaptic plasticity, and can prolong memory. The session will focus on recent evidence that netrins and semaphorins, proteins initially described as secreted axon guidance cues, are GAG binding proteins and key components of PNNs. Jessica Kwok (University of Leeds, UK) will discuss the localization and function of semaphorins at PNNs in the mature brain, Tim Kennedy (McGill University, Canada) will address synaptic plasticity in the adult brain regulated by neuronal expression of netrin-1, and Stephanie Harris (McGill University, Canada) will describe functional roles for netrin-GAG interactions during embryonic development and at PNNs in the adult brain.

## 57. Ketamine and Depression

*Chair: Mohamed Kabbaj*

*Presenters: Chadi Abdallah, Christine Ann Denny, Mohamed Kabbaj*

As the global burden of depression continues its rise as the leading cause of disability worldwide, the urgent need for more effective treatments is dire. A new wave of excitement, however, has been generated by recent discovery that the N-methyl d-aspartate receptor (NMDAR) antagonist, ketamine, rapidly relieves depressive symptoms and suicidal ideation, particularly amongst those with treatment-resistant depression. Since then, a significant amount of effort has gone into understanding the underlying mechanisms by both preclinical and clinical researchers alike, with the hope of developing novel rapid-acting treatments effective in a broader range of patients.

Here, we propose this symposium to highlight recent research in animal models and humans assessing the risks and benefits of treating depression with ketamine. Dr. Chadi G. Abdallah will discuss how the antidepressant drug ketamine alters brain functioning in the human population. Dr. Christine A. Denny will present some of her recent work identifying the mechanisms by which ketamine may protect against stress-induced depression and alter how a stressor is encoded into an aversive memory. Dr. Mohamed Kabbaj (Chair) will then discuss the safety of ketamine use in the treatment of depression-like behaviors, with a focus on its potential addictive properties when used repeatedly.

We believe that these speakers will provide a complimentary and comprehensive overview of this timely, important research topic, which is novel and innovative and will be of great interest to the WCBR members.

## 58. Novel Neuroprosthetic Technologies for Diagnosis, Monitoring, and Treatment of Psychiatric Illness

*Co-chairs: Darin Dougherty, Alik Widge*

*Presenters: Thilo Deckersbach, Alik Widge, Todd Herrington, Christopher Salthouse*

Mental illnesses arise from specific brain circuits, but most treatments act on the whole brain at once. At the same time, the psychiatric diagnostic system hinders treatment development. Categorical, “pick K of N symptoms” diagnoses have substantial biological heterogeneity. Brain stimulation may be a solution to the treatment side of this equation; we can modulate the activity of most brain areas or connections by focal energy injection. The challenge is that we do not know the optimal circuit targets or stimulation methods to effectively relieve symptoms. This panel describes an integrated approach to circuit validation,

electrophysiologic biomarker discovery, and biomarker-driven (closed-loop) neurostimulation. The TRANSFORM DBS collaboration has developed frameworks for phenotyping, monitoring, and modulating behavior in humans. Our work uses a transdiagnostic framework -- objectively measurable behaviors that can define a patient's illness not as a set of diagnoses, but as a distance from the "healthy" origin in a multi-dimensional space.

Dr. Dougherty, as chair, will introduce the framework and lead discussion. Dr. Deckersbach, a neuro-imager and clinical psychologist, will describe a pipeline for measuring patients' behavior and circuit impairments through functional imaging. He will show how circuit impairments detected in this pipeline connect back to clinical rating instruments. Drs. Widge and Herrington, both young investigators, will describe their approaches to modulating function in two domains. Dr. Widge will describe mathematical models of flexible decision-making and enhancement of that decision-making through DBS-like stimulation. Dr. Herrington will describe related approaches for bidirectional control of a risk/reward tradeoff. Finally, Dr. Salthouse, an electrical engineer, will describe the development of an implantable system that can be targeted to the identified circuits and can deliver these closed-loop therapies to patients.

**PANEL • WEDNESDAY, 7:00 P.M. - 8:30 P.M. • HARMONY B**

## **59. The Role of Activity-Dependent Neuronal Ensembles in Learning**

*Chair: Leslie Whitaker*

*Presenters: Leslie Whitaker, Zoe Donaldson, Rajtarun Madangopal, Joseph Ziminski*

Learned behaviors are often directed by complex sets of highly specific stimuli. Neural mechanisms mediating learned associations in these behaviors must contain sufficient storage capacity to encode high resolution information and must distinguish among thousands of different associations. In the past, our understanding of circuitry mediating learned behavior has been based primarily on region-wide or cell-type specific inactivation regardless of neuronal activation state during cue-specific behavior. However, activation of all or most cells in a brain area lacks sufficient resolution to distinguish complex learned associations. Instead, associations are likely encoded within specific patterns of sparsely distributed neurons, or neuronal ensembles, that are selectively activated by cues. The advent of novel technologies including calcium imaging and transgenic animals have allowed investigators to study activity dependent neuronal ensembles and their role in learning and memory processes. This panel will present recent findings employing novel technologies for identifying, characterizing, and manipulating activity-dependent neuronal ensembles. Panel chair Leslie Whitaker (National Institute on Drug Abuse) will discuss the role of intrinsic plasticity in prelimbic cortex neuronal ensembles that play a role in operant learning in rats. Zoe Donaldson (University of Colorado) will present



data demonstrating a role for nucleus accumbens (NAc) neuronal ensembles in selective social attachment in prairie voles using imaging and molecular-genetic approaches. Rajtarun Madangopal (National Institute on Drug Abuse) will show data suggesting a role for separate activity-dependent ensembles in distinguishing between learned associations using novel activity-dependent labeling strategies. Joseph Ziminski (University of Sussex) will discuss data showing excitability changes in NAc ensembles following reward-associated cue exposure that is reversed by extinction or devaluation.

**PANEL • WEDNESDAY, 7:00 P.M. - 8:30 P.M. • RAINBOW THEATER**

## **60. Microglial Targets to Treat Neuroinflammation in Neurological Disorders**

*Chair: Zoe Hughes*

*Presenters: Tsuneya Ikezu, Roland Staal, Zoe Hughes*

This panel focuses on the role of microglia in neurological disorders, the contribution of microglia to disease progression, and describes therapeutic approaches to modulate microglia to reduce the consequences of their aberrant activation. Prof Tsuneya will present his research on hyper-phosphorylated tau (pTau), the primary component of neurofibrillary tangles which epitomize Alzheimer's disease (AD). As AD progresses, pTau spreads from entorhinal cortex to the hippocampus. Prof Tsuneya will show that microglia transduce tau aggregates via exosomal secretion, and that inhibition of exosome synthesis or secretion reduces tau dissemination. The potential value of monitoring CSF exosomes as biomarkers will also be discussed. Dr. Staal will describe the contribution of calcium-activated potassium channel, KCa3.1 which is expressed in microglia upon injury. This channel potentiates Ca<sup>2+</sup> signals and subsequent sequelae including release of cytokines, nitric oxide and eicosanoids. Dr. Staal's studies have demonstrated that senicapoc is a CNS penetrant inhibitor of KCa3.1 channels and attenuates the production of these molecules in vitro and ameliorates pain behaviors in models of chronic and neuropathic pain. Finally, Dr. Hughes will describe how an isoform selective PDE4 inhibitor attenuates biochemical and behavioral effects of acute and chronic neuroinflammation as well as binding to translocator protein (TSPO), a clinically used surrogate of activated microglia.

## 61. Circadian Clocks in Biology and Medicine: Central Control of Peripheral Oscillator Function

*Co-chairs: Joseph Takahashi, Carla Green*

*Presenters: Carla Green, Joseph Bass, Gianluca Tosini, P. Michael Iuvone*

Circadian clocks are 24-hour physiological timing systems that are ubiquitous among organisms and govern behavior, metabolism, and cell and molecular function. The molecular mechanism of circadian clocks in mammals is generated by a set of genes forming a transcriptional autoregulatory feedback loop. The “core clock genes” include: Clock, Bmal1, Per1, Per2, Cry1 and Cry2. The discovery of “clock genes” led to the realization that circadian gene expression is widespread throughout the body and that the clock is cell autonomous. The cellular autonomy of circadian clocks has raised a number of questions concerning synchronization and coherence of rhythms at the cellular level as well as circadian organization at the systems level. The role of clocks in peripheral tissues has a number of important implications for disease. This panel will highlight the significance of circadian clocks for gene expression, metabolism and vision. Joseph Takahashi (Chair) will provide introductory comments and will lead the discussion of the presentations. Carla Green (Co-chair) will present work on post-transcriptional regulation of circadian gene expression and its role in metabolism. Joseph Bass will discuss genetic analysis of hypothalamic clock control of body weight. Gianluca Tosini will discuss the role of melatonin receptors in mediating brain signaling to the pancreas. Finally, Michael Iuvone will discuss the role of dopamine and circadian clocks in visual dysfunction.

## 62. The Cognitive Hypothalamus

*Co-chairs: Geoffrey Schoenbaum, Melissa Sharpe*

*Presenters: Mark Rossi, Yoav Livneh, Joey Burnett, Melissa Sharpe*

Current theoretical accounts of hypothalamic function restrict this nucleus to an innate drive to feed, where hypothalamic activity is argued to come under control of forebrain regions to elicit learned food-motivated behaviors. However, our panel will discuss recent findings showing that distinct populations play different and complex roles in food-directed behaviors, either in isolation or via powerful interactions with “cognitive” brain areas. First up, Mark Rossi will present data using calcium imaging that shows dynamic changes in glutamatergic neurons in the lateral hypothalamus with physiological state, a relationship which is altered following diet-induced obesity. Following on, Yoav Livneh will present data from a microprism-based cellular imaging

approach, suggesting state-dependent changes in hypothalamic activity contribute to alterations in the processing of food-paired stimuli in insular cortex. Then, Joey Burnett will present data garnered from optogenetics and fiber photometry to demonstrate a role for arcuate nucleus AgRP-expressing neurons in regulating a trade-off between feeding and two other homeostatic mechanisms: the need to interact with social conspecifics and the need to stay away from threat. Finally, Melissa Sharpe will show using optogenetics that GABAergic neurons in the lateral hypothalamus actively oppose learning about the general structure of the environment in favor of learning cue-food associations. This research suggests previous theoretical accounts of hypothalamic function have oversimplified a role for this nucleus in feeding. Rather, the hypothalamus plays a critical role in learning about cues and rewards in a state-specific manner where this information is relayed locally and throughout the brain to regulate an appropriate allocation of learning and behavior towards food-relevant stimuli.

## **THURSDAY, JANUARY 18, 2018**

### *Thursday Morning Panel Sessions*

**PANEL • THURSDAY, 7:30 A.M. - 9:30 A.M. • FITZSIMMONS**

### **63. The NMDA Receptor/CaMKII Complex is the Center of the PSD Universe**

*Chair: Roger Nicoll*

*Presenters: Andres Barria, Lonnie Wollmuth, Katherine Roche, Roger Nicoll*

This panel will address recent advances in our understanding of the wide-ranging roles of NMDA receptors and CaMKII in excitatory synapse function. Barria will discuss a new regulatory mechanism that controls synaptic NMDARs. He has found that noncanonical Wnt signaling regulates neuronal excitability and mobilizes Ca<sup>2+</sup> from internal stores. Activation of this novel Wnt signaling cascade specifically increases surface and synaptic expression of GluN2B containing NMDARs. Wollmuth will focus his presentation on the dynamics of rapid pore opening of ionotropic glutamate receptors, including NMDA receptors, in response to transient glutamate. Recent open state structures highlight the displacements required for pore opening. He will address the energetics of these displacements especially those instrumental to rapid pore opening. Roche will present her work on the phosphorylation of several key residues on the extreme C-terminus of GluN2B and how it exquisitely regulates synaptic NMDARs. She will discuss a new 'bedside to bench' approach to better understand structure/function relationships of NMDARs. In particular she has characterized several rare variants within the

C-terminus of GluN2B identified from deep sequencing of patient populations. One such variant, S1413L, has a profound effect on GluN2B surface expression as well as spine density supporting this approach for investigating receptor function. Finally, Nicoll will present recent work on the roles of CaMKII on basal and activity-dependent plasticity. These actions of CaMKII involve both kinase-dependent and independent processes. All of these actions are entirely dependent on the binding of CaMKII to NMDA receptors. These results emphasize the key role the CaMKII/NMDAR complex plays as a signaling hub for all aspects of excitatory synaptic function.

**PANEL • THURSDAY, 7:30 A.M. - 9:30 A.M. • GARIBALDI A**

## **64. Stress-Induced Alterations in Limbic Neurochemistry**

*Chair: Rodrigo España*

*Presenters: Matthew Wanat, Zachary Brodник, Lori Knackstedt, Brian Baldo*

Stress-induced neuropsychiatric disorders are a significant economic and social burden. Unfortunately, treatment strategies for many of these disorders are sub-optimal. Understanding the array of neurochemical changes that influence the development of stress-induced disorders, and the interplay between these changes, is critical for the development of effective treatment strategies. Presenters will discuss the role of corticotrophin releasing factor, dopamine, glutamate, and norepinephrine in mediating stress and behavior interactions. Dr. España will provide introductory comments and lead the discussion. Dr. Wanat will discuss how stressor controllability influences dopamine release to stress-paired cues, bouts of stress, and the removal of stress. Results indicate that dopamine encodes negative reinforcement prediction error signals. Zachary Brodnik (graduate student) will discuss evidence that susceptibility and resilience to traumatic stress correspond with distinct alterations in the dopamine system. He will provide a putative mechanism by which susceptibility to stress drives aberrant cocaine reinforcement. Dr. Knackstedt will present data describing a novel rodent model of comorbid post-traumatic stress disorder (PTSD) and cocaine addiction. Rats that develop a PTSD-like phenotype display deficits in extinction learning and enhanced cue-primed reinstatement of cocaine-seeking relative to both unstressed controls and resilient rats. Further, resilient rats display significantly greater mGlu5 gene expression in the PFC and amygdala, and targeting mGlu5 normalizes some deficits in PTSD-like rats. Dr. Baldo will present data showing that a model of trauma-like stress produces long lasting alterations in basolateral amygdala circuitry. He will show how corticotropin-releasing factor and noradrenergic systems interact in the aftermath of stress exposure to promote behavioral responses that are seen in psychiatric illnesses such as PTSD.

## 65. Mesoscopic Circuit Architecture at the Whole-Brain Level: How Structural Connectome can be Used for Functional Studies and for Disease Mechanisms

*Chair: Tianyi Mao*

*Presenters: Hongwei Dong, Tianyi Mao, Lindsay Schwarz, Bingxing Huo*

Understanding the connectivity of the brain circuitry has been at the heart of neuroscience. Decades of neuroanatomy studies have provided the framework for understanding many brain functions. However, traditional anatomy often does not capture all projections throughout the brain, or has limited number of animals that makes quantitative description and comparison across animals difficult. With recent development in novel imaging methods and computational algorithms, whole brain mapping at mesoscopic level has become feasible (e.g., Zingg et al., 2014; Oh et al., 2014; Hunnicutt et al., 2014; Mitra, 2014; Hintiryan et al., 2016; Hunnicutt et al., 2016). In the proposed panel, four speakers, each represents a forefront that this field has been pushing for. Dr. Hongwei Dong (USC) will present mouse cortico-cortical connectome and cortico-striatal connectome, and importantly, the defects of the connectome in two different mouse models (Huntington disease and monoamine oxidase A/B knockout mice). Dr. Tianyi Mao (Vollum Institute, OHSU) will present comprehensive excitatory connectivity maps the cortico-thalamo-basal ganglia circuits, and how such maps are used for studying the functional organization principles of the loop and the region-specific modulation by opioids. Dr. Lindsay Schwarz (St. Jude Children's Research Hospital) will present brain-wide mapping for locus coeruleus, a norepinephrine circuit, and her work in combining optogenetics, next-generation sequencing, and in vivo calcium imaging, to identify how heterogeneity within these circuits promote different behavioral outputs. Finally, Dr. Bingxing Huo (CSHL/RIKEN), representing Dr. Partha Mitra's group, will present the effort to map the whole-brain connectivity on mesoscale in marmoset. She will discuss how methods originally established for the mouse connectome has been custom developed to acquire large-scale, high resolution images of the entire marmoset brain sections.

## 66. The Apple Never Falls Far: Parental Exposure to Alcohol and Other Drugs of Abuse has Deleterious Consequences on Progeny

*Chair: Mathieu Wimmer*

*Presenters: Fair Vassoler, Chris Pierce, Gregg Homanics, Mathieu Wimmer*

Mounting evidence suggests that environmental insults in parents, such as exposure to alcohol or illicit drugs, produce long-lasting changes in offspring neurobiology and behavior. Epigenetic inheritance refers to these acquired traits and phenotypes that are caused by mechanisms independent of DNA sequence mutation. This panel will present ongoing animal studies exploring the impact of parental exposure to cocaine, opioids and alcohol on future generations. In all cases, presenters will focus on behavioral abnormalities caused by parental consumption of drugs or alcohol as well as the underlying epigenetic mechanisms driving these effects. The presenters use the latest techniques to address all three components of the epigenetic landscape: chromatin remodeling and histone modifications, methylation of DNA and small non-coding RNAs. Dr. Vassoler's research investigates the impact of adolescent opioid exposure prior to conception on future generations. Dr. Pierce will discuss recent studies showing that paternal cocaine ingestion produces learning deficits in male offspring. Dr. Homanics' research program examines alcohol-related behaviors in a multigenerational model of alcohol exposure. Dr. Wimmer will present ongoing work exploring the effects of paternal morphine taking on reward processing in male and female offspring. This panel aims to address two questions: 1) which germline epigenetic reprogramming events are critical for shaping development and produce long-term changes into adulthood? 2) what are the functionally relevant neuroepigenetic processes that govern gene expression and behavior in these multigenerational models? Discussion will be centered around the challenges associated with replicating behavioral findings and confirming the functional relevance of epigenetic remodeling events. We hope to engage in a lively and productive discussion encompassing the latest controversies in the emerging field of multigenerational behavioral epigenetics.

## 67. Bench to Bedside Drug Development for the Brain: Learning From Failures

*Chair: Nigel Greig*

*Presenters: Nigel Greig, Howard Feldman, Nick Brandon, Thomas Swanson*

Drug development is a long, expensive, uncertain process that is associated with many failures. The focus of preclinical drug discovery is to deliver one or more clinical candidate molecules, each with sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human evaluation. Once in clinical trials, however, CNS drugs have lower success rates (8.2% vs. 15% for all drugs combined) and take a longer time to develop, than do other drug classes. The success rate of neuropsychiatric drug candidates that enter human testing to effectively reach the marketplace is particularly low (0% for some neurodegenerative diseases), and the 'fail fast, fail early' strategy to eliminate key risks prior to making expensive late-stage investments has largely failed as CNS agents tend to die later during the clinical development process - making them amongst the most expensive to develop. It is hence important to optimize each piece of the preclinical and clinical development process to create the conditions that allow a drug the opportunity to demonstrate efficacy. Understanding and following mechanisms associated with this scientifically embeds the drug development process by allowing the evaluation of drug candidates and hypotheses. Nigel Greig (NIA/NIH) will overview the current CNS drug development dilemma. Howard Feldman (ADCS/UCSD) will describe how rigorous compound selection and innovative clinical trial design can optimize the screening and testing of drug candidates. Nick Brandon (AstraZeneca) will discuss lessons learnt from the AstraZeneca portfolio and strategies implemented to increase success rate as well as to share the risk described above. Finally, Tom Swanson (Montana Comprehensive Epilepsy Program) will define post launch issues that affect a drug's success in demonstrating efficacy in the general population.

## 68. Cannabinoid Signaling in Health and Disease

*Chair: Josée Guindon*

*Presenters: Daniel Morgan, Josée Guindon, Lakshmi Devi, Alex Straiker*

Within the nervous system, endocannabinoid signaling is involved in modulating a diverse range of physiological functions including pain, learning and memory, reward signaling, and mood. Pharmacological manipulation of endocannabinoid signaling using antagonists, agonists, and/or allosteric modulators represent promising therapeutic agents for the treatment of chronic

pain, anxiety, depression, drug abuse, glaucoma, and metabolic disease. In this panel symposium Josée Guindon will introduce speakers and lead a discussion regarding the role of cannabinoid signaling in disease states including visual system disease, pain, and cancer. Daniel Morgan will talk about the mechanisms of cannabinoid tolerance in pathological pain and the potential impacts on dependence and cannabis use disorder. He will discuss important agonist-specific differences in the mechanisms that underlie cannabinoid tolerance. Josée Guindon will present recent work demonstrating the profound effect that chronic exposure to cannabinoid agonists has on the estrous cycle and will discuss the impact of these findings on female health including potential impacts on estrogen-driven diseases more specifically chemotherapy and HIV-induced pain. Lakshmi Devi will discuss the interactions between cannabinoid and opioid receptor interactions in rodent models of neuropathic pain. They find that both in streptozotocin-induced neuropathic pain and paclitaxel-induced neuropathic pain, cannabinoid-opioid heteromers in the spinal cord are unregulated and exhibit unique signaling properties. It has been known for nearly 20 years that a cannabinoid signaling system is present in the retina. Alex Straiker will present evidence for cannabinoid signaling in retinal function and health. This symposium will shed light on the predominant role of the cannabinoid system in physiological and disease states such as hormonal regulation, vision, analgesic response in pathological disease, and cannabinoid tolerance. Sharpening our understanding of the involvement of the cannabinoid system will ensure better translation of preclinical findings to the clinic to ultimately improve patient health.

**PANEL • THURSDAY, 7:30 A.M. - 9:30 A.M. • SPEARHEAD**

## **69. Opioids in the Thalamo-Cortical-Striatal Pathway**

*Chair: John Williams*

*Presenters: William Birdsong, Matthew Banghart, Aya Matsui, Ream Al-Hasani*

The Thalamo-Cortical-Striatal pathway is a key system in the emotional aspects of pain and reward. Opioid receptors are among the molecules that modulate the activity of this important part of the CNS. This panel will discuss the opioid regulation of neurons within this system that have profound behavioral actions. Will Birdsong will discuss the opioid inhibition of transmitter (glutamate and GABA) release in the dorsal striatum, prefrontal cortex and anterior cingulate cortex that is initiated by activation of neurons in the midline thalamus.

Matthew Banghart will present work that demonstrates a local and pathway-specific action of delta opioid receptors on the inhibition of GABA release within the patches of the dorsal striatum. Aya Matsui will present work that examines acute opioid modulation on dMSN or iMSN axon terminals in the VP measuring GABA transmission and inhibition of calcium conductance and the modulation by alcohol. Ream Al-Hasani will discuss ongoing developments in



the dorsal/ventral segregation of dynorphin neurons in the nucleus accumbens and its implications on behavior. Retrograde tracing and in vivo microdialysis suggests that distinct inputs to dynorphin neurons may differentially regulate aversion and reward and selective release of endogenous opioids.

**PANEL • THURSDAY, 7:30 A.M. - 9:30 A.M. • WEDGEMOUNT**

## **70. Individual Differences and Biomarkers in Decision Making and Addiction Vulnerability**

*Chair: Nicola Grissom*

*Presenters: Alicia Izquierdo, Melanie Tremblay, Nicola Grissom, Stephanie Groman*

Addictions are defined in part by the continued seeking of a specific rewarding outcome despite the requirement of engaging in increasingly costly or harmful behaviors. Understanding the mechanisms of risky decision-making processes are essential in revealing how the brain prioritizes these costly drug-seeking behaviors over other goal-directed behaviors. However, one of the most striking features of addictions is that most individuals who sample a drug will not become addicted. Thus, considerable individual differences in how individuals react to drug exposure, driven by differences in the internal milieu of the brain in the form of intracellular signaling, gene expression, and protein networks, are likely to mediate the decision-making processes that go awry to drive addiction. In this panel, we will present data across diverse levels of analysis to identifying new biobehavioral markers of risky decision making in animal models as they relate to addiction-relevant phenotypes. First, Alicia Izquierdo will describe how cortical plasticity in drug-naïve animals or following methamphetamine intravenous self-administration may influence risky and effortful choices. Second, Melanie Tremblay will present data suggesting that differential intracellular signaling driven by D2 receptor activation mediates individual differences in the ability of chronic dopamine D2/3 agonist administration to boost preference for uncertain outcomes and elicit compulsive gambling-like behavior in rats. Third, Nicola Grissom will discuss sex differences in balancing the explore-exploit tradeoff in decision making in mice, and how differences in striatal transcriptional activation during outcome based learning contribute to differences in exploiting rewarding outcomes. Finally, Stephanie Groman will present proteomic work identifying novel protein targets linking aberrant decision making to addiction vulnerability in rats.

## *Thursday Afternoon Panel Sessions*

**PANEL • THURSDAY, 4:30 P.M. - 6:30 P.M. • FITZSIMMONS**

### **71. Opioid Alternatives to Opiates: New Approaches for Separating Analgesic From Adverse Effects Mediated by Opioid Receptors**

*Chair: James Zadina*

*Presenters: Elyssa Margolis, James Zadina, Wakako Fujita, Susruta Majumdar*

Treatments for moderate to severe pain have been dominated for a century by opium-derived (opiate) painkillers. Their “gold standard” analgesic effects are limited by adverse effects, including those contributing to an overdose epidemic. New ligands for, and insights into the functional mechanisms of, opioid receptors holds promise for the long-sought separation of analgesia from adverse effects. This panel will discuss novel compounds acting at opioid receptors with reduced side effects, and mechanisms of mu and delta opioid receptor interaction that could lead to new targets for therapy. Elyssa Margolis will contrast the contribution of opioid receptors in the lateral habenula and ventral tegmental area (VTA) to reward and pain relief, and discuss the contrasting effects of mu and delta opioid receptor activation on VTA neurons with different projection targets. James Zadina will discuss an endomorphin analog, ZH853, that provides longer antinociception than morphine in multiple pain models with substantial reduction of major side effects, including reward/abuse liability, respiratory depression, motor impairment, tolerance, and glial activation. Wakako Fujita will describe mu and delta receptor interactions and regulation of mu-delta receptor heteromers in vivo. She will also discuss the identification and characterization of ligand targeting mu-delta opioid receptor heteromers. Susruta Majumdar will discuss a novel kratom analog, mitragynine pseudoindoxyl (MP) that is a mu agonist, delta antagonist, and does not recruit  $\beta$ -arrestin. MP exhibits antinociceptive activity in multiple pain models, shows no reward behavior, and has attenuated respiratory depression, constipation, tolerance, and dependence compared to morphine. In summary, these four talks are geared towards addressing two major issues: the lack of adequate treatment for millions in pain, and the epidemic of overdose deaths from currently used opioids.

## 72. Riding High With Buds in BC: Recent Advances in Cannabis/Cannabinoid Science

*Chair: Alan Budney*

*Presenters: Brian Thomas, Ryan Vandrey, Evan Herrmann, Marcel Bonn-Miller*

Over the past two decades, the landscape of cannabis and cannabinoid use has been rapidly changing. The number of jurisdictions permitting lawful use of medical and/or recreational cannabis, the types of natural or synthetic cannabis products available, and the prevalence of Cannabis Use Disorder have all increased dramatically. As a result, cannabis/cannabinoid science is behind in four key areas, i. e., few controlled studies have: characterized synthetic cannabinoids, examined the effects of cannabis administered via non-smoked routes, identified promising medications for Cannabis Use Disorder, and provided sufficient data for medicinal cannabis use indications. This symposium brings together a diverse panel of speakers that have made recent advances in these four areas. Dr. Thomas will present an overview of the structure and function of synthetic cannabinoids, their role in facilitating research that increases understanding of the endogenous cannabinoid signaling system, and data from several recent studies characterizing a number of novel synthetic cannabinoid allosteric ligands. Dr. Vandrey will present data from a series of laboratory studies that directly compared the pharmacokinetics and pharmacodynamics of cannabis following oral, smoked, and vaporized routes of administration. Dr. Herrmann will present data from two recent within-subjects; placebo-controlled, human laboratory studies examining two different medication combinations for the treatment of Cannabis Use Disorder; zolpidem+nabilone and varenicline+nabilone. Dr. Bonn-Miller will present data from the largest and most comprehensive a priori study conducted on the short-term and long-term effects of cannabis in individuals with Post Traumatic Stress Disorder. The symposium will be chaired by Dr. Budney, who is internationally renowned for his pioneering work in characterizing the Cannabis Withdrawal Syndrome and developing interventions for Cannabis Use Disorder.

## 73. Decision-Making and the Amygdala: Implications for Drug Addiction

*Co-chairs: Mike Robinson, Caitlin Orsini*

*Presenters: Caitlin Orsini, Mike Robinson, Yavin Shaham, Zoe McElligott*

Drug addiction is characterized by impaired decision-making abilities, often resulting in risky choices that lead to adverse outcomes. Impaired decision-making can contribute to initial drug intake and continued drug use, and can

also promote relapse. Decision-making, however, is a multifaceted process, comprised of multiple cognitive processes that guide choice behavior. Recent work has made great strides in uncovering the neurobiology underlying decision-making and drug-seeking, highlighting the contributions of the amygdala and its extended network in choice behavior. In particular, our studies have begun to dissect how these brain regions contribute to processes critical to decision-making, such as encoding the valence of potential choices and outcome evaluation. This symposium will highlight the work from such studies and will provide a forum for discussion between expert panelists and attending scientists. Caitlin Orsini will describe the unique contributions of the basolateral amygdala to the different processes involved in a decision-making task involving explicit punishment. Mike Robinson will describe the role of the central amygdala in making persistent addictive-like decisions when in situations that model various components of addictive criteria such as adverse consequences. Yavin Shaham will describe a new rat model of drug relapse after choice-based voluntary abstinence and present recent findings on the role of D1- and D2-receptor expressing neuronal ensembles in dorsomedial striatum and glutamatergic projections from anterior insula to central amygdala in this new form of relapse. Zoe McElligott will describe synaptic and behavioral changes following morphine exposure and withdrawal in male and female mice, focusing on the extended amygdala. Together these talks will discuss and provide evidence for the role of the amygdala and its extended network in the reward seeking and risky decision-making associated with drug addiction.

**PANEL • THURSDAY, 4:30 P.M. - 6:30 P.M. • HARMONY A**

## **74. Hitting the Brakes: Mechanisms of Inhibitory Control of Dopaminergic Signaling in the VTA**

*Co-chairs: Abigail Polter, Robyn St. Laurent*

*Presenters: Larry Zweifel, Abigail Polter, Alexey Ostroumov, Robyn St. Laurent*

Dopaminergic neurons of the ventral tegmental area play a critical role in encoding reward and aversion, and dysfunction of this circuitry is thought to contribute to the development of substance abuse and mood disorders. These neurons are dynamically regulated by a diverse array of GABAergic inputs from both local inhibitory neurons in the VTA itself as well as projections from more distal regions. Recent advances have highlighted the diversity of these inhibitory projections in modulating dopaminergic neurons and dopamine-dependent behaviors. However, there are still significant gaps in knowledge about the specific mechanisms governing these inputs and how their activity is shaped by experience. In this panel, speakers will present recent advances in understanding function, physiology, and plasticity of GABAergic signaling in the ventral tegmental area, with a particular focus on how these synapses may contribute to maladaptive states. First, Larry Zweifel (University of

Washington) will discuss recent work defining inhibitory networks (local and distal) that coordinately regulate dopamine neurons of the ventral tegmental area. He will describe the anatomical classification of these networks, their synaptic connectivity, and their role in regulating dopamine-dependent behaviors. Abigail Polter (George Washington University) will present data showing differences in plasticity and physiology between VTA-originating and RMTg-originating inhibitory synaptic inputs onto VTA dopamine neurons, and will highlight potential roles for these inputs in stress-induced behavioral adaptations. Alexey Ostroumov (University of Pennsylvania) will discuss recent work showing converging effects of alcohol and stress leading to blunted dopaminergic responses through excitatory GABAergic signaling onto VTA dopamine neurons. Preventing these circuit alterations prevents stress-induced increases in alcohol self-administration. Finally, Robyn St. Laurent (Brown University) will present data regarding a novel form of plasticity induced by low frequency stimulation at inhibitory synapses in the VTA and how opiates affect this type of long-term potentiation.

**PANEL • THURSDAY, 4:30 P.M. - 6:30 P.M. • HARMONY B**

## **75. Postsynaptic Mechanisms Regulating the Assembly and Stability of Neural Circuits Relevant to Neuropsychiatric Disorders**

*Chair: Gavin Rumbaugh*

*Presenters: Shernaz Bamji, Peter Penzes, Gavin Rumbaugh, Courtney Miller*

Synapses are fundamental to nervous system function. Thus, it is not surprising that synapse dysfunction is associated with most brain disorders. Various neuropsychiatric disorders are now linked to impairments in the dynamic processes within the postsynapse that promote the formation, stabilization, and plasticity of neural circuits. Our panel will therefore highlight the breadth of how postsynaptic biology contributes to the etiology of neuropsychiatric disorders, from single spine mechanisms to circuits and behavior. Shernaz Bamji (UBC) will discuss how genetic risk factors that impact palmitoylation within dendritic spines act to regulate excitatory/inhibitory balance. Her work provides molecular insight into a genetically-defined form of intellectual disability (ID) with comorbid epilepsy. Peter Penzes (NWU) will discuss how ubiquitination in dendritic spines acts as a mechanism to stabilize synapses. Alterations in ubiquitination through acquired genetic pathogenicity suggests that this may be a mechanism that disrupts the stabilization of cortical circuits, with relevance to several neuropsychiatric disorders. Gavin Rumbaugh (TSRI) will discuss how the neuropsychiatric risk factor, SYNGAP1, which is linked to four distinct disorders, disrupts signaling at the postsynapse with consequences for neural circuit connectivity, excitatory balance and cognitive function. His work suggests that this gene has complex, circuit-specific functions,

perhaps explaining the broad cognitive and behavioral deficits observed in patients with pathogenic SYNGAP1 variants. Courtney Miller (TSRI) will discuss how mechanisms driving dynamic actin within the postsynapse links synaptic plasticity to memory stabilization. Her work suggests that the molecular mechanisms that drive dynamic actin within the postsynapse may be a therapeutic target for disrupting maladaptive memories associated with substance abuse disorder.

**PANEL • THURSDAY, 4:30 P.M. - 6:30 P.M. • RAINBOW THEATER**

## **76. Inflammation and Alpha-Synuclein Aggregation Along the Gut-Brain Axis in Parkinson's Disease**

*Chair: Anurag Tandon*

*Presenters: Michel Desjardins, Kelvin Luk, Alain Dagher, Warren Hirst*

The selective vulnerability of specific central neuronal pathways in Parkinson's disease (PD) to developing Lewy body (LB) pathology was first noted by Braak and colleagues. LB appear initially in the dorsal motor nucleus and the olfactory bulb, both of which contain neuron bodies that project efferent fibers into the periphery. Since their seminal work, it is now clear that a broad range of nonmotor clinical symptoms can often be observed in PD patients prior to the appearance of classical PD motor features, and these correspond the manifestation of LB-like pathology in the peripheral and central nervous systems, particularly enteric and olfactory neurons. This panel will discuss recent studies suggesting that gut microbiome and inflammation pathways may represent early triggers to  $\alpha$ -synuclein misfolding, which then propagates by a self-templating process that spreads across connected neural networks. Anurag Tandon (U Toronto) will begin the session with a brief introduction of the PD field and the relationship between prodromal and pathological features. Michel Desjardins (U Montreal) will discuss how inflammation and gut infection induce mitochondrial antigen presentation (MitAP), triggering the engagement of autoimmune mechanisms leading to severe motor impairment in susceptible mice. Kelvin Luk (U Penn) will discuss the process of pathological  $\alpha$ -synuclein seeding and mechanisms for spread. Alain Dagher (McGill University) will show that MRI-derived longitudinal patterns of atrophy in humans are consistent with a network spread model, in which the disease propagates through the intrinsic brain connectome. He will show computational agent-based models of  $\alpha$ -synuclein propagation to test the effect of risk genes or interventions on disease progression.

Warren Hirst (Biogen) will describe BIIB054, a human-derived antibody against  $\alpha$ -syn that is being developed as an immunotherapy for PD, in addition to preclinical efficacy data with an  $\alpha$ -synuclein antisense oligonucleotide and how these diverse therapeutic modalities may influence the spread of  $\alpha$ -synuclein pathology providing new therapeutic strategies for PD.

## 77. The Pros and Cons of Modulating Prefrontal Cortical Function

*Chair: David Devilbiss*

*Presenters: Robert Spencer, David Devilbiss, Craig Berridge, Brian Baldo*

The prefrontal cortex (PFC) supports a variety of cognitive and behavioral processes that guide goal-directed behavior, appetitive motivation, and reward seeking behaviors. Dysregulation of such processes, including working memory and behavioral inhibition, are implicated in a variety of clinical disorders. Neuromodulation in localized subregions of the PFC act to regulate these PFC dependent functions. However, we currently lack a clear understanding of PFC functional heterogeneity, at both the neurochemical and anatomical levels. This panel will review recent evidence regarding the modulation of PFC-dependent cognitive and behavioral function, focusing on the functional diversity of catecholamine and peptide systems across anatomical PFC subregions. Robert Spencer will present evidence of neurophysiological mechanisms underlying the cognition-improving and cognition-impairing actions of psychostimulants. David Devilbiss will provide findings that the cognition-impairing effects of stress reflect impaired neural coding and functional connectivity across subregions of the PFC and between the PFC and dorsal striatum. Craig Berridge will describe evidence regarding topographically-organized cognitive actions of corticotropin releasing factor (CRF) within the PFC and the neural coding consequences of PFC CRF neuronal activation across frontostriatal circuitry. Brian Baldo will present work demonstrating that the inhibitory control of appetitive motivation is mediated through topographically-organized actions of the mu-opioid receptor across PFC subregions. Together, these findings provide important insight into the regulation of PFC-dependent cognitive function and provide potential direction for the development of new treatments for PFC-dependent cognitive and behavioral dysfunction.

## 78. A Tectonic Shift in Our Thinking: Understanding the Contribution of Glia to Neural Plasticity and Behavior

*Chair: Sade Spencer*

*Presenters: Michael Scofield, Kyle Brown, Alfonso Araque, Heather Boger*

Historically, glial cells were thought to play a peripheral role in the nervous system serving mainly as physical and metabolic support for neurons. More recently, we have begun to appreciate the more important and active role these cells play in the brain including regulation of synapse formation, function and synaptic plasticity ultimately modifying behavioral output. This panel

will show how neurons and glia, with a particular focus on astrocytes and microglia, interact in the brain to mediate synaptic plasticity and behavior under physiological and pathological conditions. Sade Spencer (MUSC) will provide a brief introduction and lead discussion of the presentations. Michael Scofield (MUSC) will discuss new methods of imaging and analysis to study astrocyte morphology at the single cell level. He will present work demonstrating dynamic changes in astrocytic complexity in response to drugs of abuse. Kyle Brown (University of Colorado Boulder) will provide evidence that innate immune signaling through Toll-Like Receptor 4 (TLR4) expressed on glia modulates reinstated drug seeking following cocaine self-administration. This work extends previous findings indicating that chronic cocaine produces maladaptive neuroinflammatory signaling. Alfonso Araque (University of Minnesota) will present work describing how astrocyte activity induces differential synapse-specific regulation of excitatory and inhibitory synapses in the centromedial amygdala. His work links these synaptic effects to behavioral changes in auditory fear conditioning. Finally, Heather Boger (MUSC) will discuss how dysfunction of glial glutamate transporters contributes to neuronal and behavioral degeneration in animal models of Parkinson's and Alzheimer's disease. She has used in vivo electrochemistry to assess glutamate neurotransmission in the healthy and diseased state.

## **FRIDAY, JANUARY 19, 2018**

### *Friday Morning Panel Sessions*

**PANEL • FRIDAY, 7:30 A.M. - 9:30 A.M. • FITZSIMMONS**

#### **79. Mixed Drinks: Alcohol Comorbidities**

*Chair: Alana Conti*

*Presenters: Alana Conti, Anna Lee, Bryan Yamamoto, Nick Gilpin*

Comorbidity affects treatment of both alcoholism and its comorbid condition, independently of when each presents clinically. Common comorbidities of alcoholism include stress, brain injury, anxiety, nicotine and poly drug use. Much is known about alcohol itself, but little is known about the neurobiological underpinnings of these common co-morbidities that will assist in improving the identification and treatment of alcohol misuse and alcoholism. The focus of this panel is the behavioral and molecular signatures of alcohol comorbidities. First, Dr. Alana Conti will discuss the intersection between traumatic brain injury and alcohol dependence. She will discuss data demonstrating the upregulation of Class IIa histone deacetylase expression by both chronic ethanol exposure and TBI, suggesting a final common pathway in these conditions. Secondly, Dr. Anna Lee will present data focused on the



effects of alcohol abstinence using a novel alcohol and nicotine co-consumption model developed in her lab. She will also present some unpublished data on the contribution of  $\alpha 4$  and  $\alpha 6$  nicotinic receptors in this model. Dr. Bryan Yamamoto will address the effects elicited by the co-abuse of ethanol and methamphetamine. He will discuss the role of inflammation produced by voluntary ethanol drinking in mediating and enhancing the neurotoxic effects of methamphetamine. Finally, Dr. Gilpin's talk will explore the effects of traumatic stress, re-stress, and stress reminders on corticotropin releasing factor in the amygdala and prefrontal cortex. His talk will also discuss the effects of brain site-specific pharmacology and circuit manipulations on post-stress avoidance, alcohol drinking, and hyperalgesia. Together, these talks aim to highlight the complexities associated with alcohol comorbidities and the importance of co-modeling in the pursuit of translationally-relevant alcohol research.

**PANEL • FRIDAY, 7:30 A.M. - 9:30 A.M. • GARIBALDI A**

## **80. Striatum Subregions and Motivated Behavior**

*Chair: Kyle Smith*

*Presenters: Kyle Smith, Stephan Lammel, Matthew Wanat, Stephanie Borgland*

The striatum is organized into subregions based on molecular makeup and anatomical connectivity. This panel will discuss a set of recent studies on distinct neurobiological and behavioral characteristics of striatal subregions. Kyle Smith (Dartmouth) will present data showing functional differences for motivation between regions of the nucleus accumbens and their connections with the ventral pallidum. Transitioning to dopamine interaction with the striatum, Stephan Lammel (UC Berkeley) will address how nucleus accumbens subnuclei exert direct inhibitory and disinhibitory influence over dopamine subpopulations in the ventral tegmental area (VTA) in order to regulate motivated behaviors. Matt Wanat (UT San Antonio) will discuss how a single episode of stress elicits a persistent enhancement in Pavlovian conditioned responding and alters cue-elicited dopamine release across ventral striatal subregions. Finally, Stephanie Borgland (Calgary) will describe how acute fasting, commonly associated with 'dieting', influences dopamine release in efferent targets using fast scan cyclic voltammetry in dorsal and ventral striatum. Results show that while fasting does not alter striatal dopamine in male mice, female mice have decreased evoked dopamine in the dorsal medial and dorsolateral striatum consistent with increased efficacy of D2 autoreceptors. Collectively, the data in these presentations will help paint a picture of heterogeneity for motivated behavior across striatal subregions and their interaction with midbrain dopamine system.

## 81. Crosstalk Between the Epigenome and Neural Circuits in Drug Addiction

*Co-chairs: Erin Calipari, Philipp Mews*

*Presenters: Chris Pierce, Erin Calipari, Philipp Mews, Marcelo Wood*

Addiction is characterized by dysregulated learning about drugs and associated cues that result in drug seeking and relapse. Learning about drugs and predictive cues is a complex process controlled by neural circuits that interact with transcriptional and molecular mechanisms within each cell to precisely guide behavior. The interplay between neuronal activation and long-term changes in transcription is of critical importance in the expression of appropriate, or in the case of drug addiction, inappropriate behaviors. This panel will present emerging data from diverse approaches that converge upon the notion that the complex interplay between epigenetic gene regulation and circuit connectivity is dysregulated in addiction. First, Chris Pierce (University of Pennsylvania), will outline epigenetic mechanisms, including histone turnover, underlying the incubation of cocaine craving. Erin Calipari (Vanderbilt University School of Medicine) will talk about how cocaine self-administration and withdrawal alters transcription across six reward-related brain regions and how specific transcriptional signatures are predictive of addictive behaviors. Philipp Mews (Icahn School of Medicine at Mount Sinai) will speak about his work using cell-type specific approaches to determine the role of epigenetic remodeling in D1 and D2 medium spiny neurons that prime specific responses in gene expression to drug re-exposure. Finally, Marcelo Wood (University of California, Irvine) will speak about the role of cholinergic activity in the medial habenula in controlling cocaine seeking and how epigenetic mechanisms, including changes in HDAC3 and downstream target NR4A2, underlie the changes in activity of this defined cell population. Together, this session will showcase how novel epigenetic and circuit technology have expanded the scope of addressable scientific questions and how these advances can be applied to the study of reward processing and its dysregulation in psychiatric disorders.

## 82. Biomarkers for Huntington's Disease: Why do We Need Them and What Can They Tell Us?

*Co-chairs: Elizabeth Thomas, Steven Potkin*

*Presenters: Elizabeth Thomas, Amit Joshi, Blair Leavitt, Steven Potkin*

Huntington's disease (HD) is a genetic, neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. The mutation responsible for HD is an abnormal CAG repeat expansion in the HTT gene.

Despite HD being a single gene disorder, there is enormous variability in disease onset and severity. Additionally, symptom presentation and course of illness also vary among patients. Hence, biomarkers are greatly needed to anticipate and monitor these features, as well as to track potential therapeutic effects. In this panel, researchers will discuss the latest findings in biomarkers for HD, which will include the use of CSF, blood and saliva as biospecimens for biomarker research. Beth Thomas (The Scripps Research Institute) will discuss salivary biomarkers that could be relevant HD prognosis and therapeutics. This work includes measuring levels of huntingtin, C-reactive protein and uric acid in saliva from HD patients along with correlations to clinical measures. The second speaker, Dr. Amit Joshi (Stanford University) will review studies investigating potential biomarkers to follow disease progression in HD. These studies include mitochondrial and inflammation biomarkers, which have been found in the brain and plasma of HD mice, as well as in human patients. The third speaker, Blair Leavitt (University of British Columbia) will discuss CSF biomarkers for HD. His talk will largely focus on the recent development of CSF Biomarkers for use in HD clinical trials. Finally, Steven Potkin (University of California, Irvine). Dr. Potkin will continue the topic of CSF biomarkers for HD, describing his work identifying a novel CSF screening assay that measures mutant HTT cell-to-cell transmission. This assay discriminates between symptomatic and pre-manifest symptomatic HD individuals and has implications with regards to new potential therapeutic strategies to treat this devastating disease.

**PANEL • FRIDAY, 7:30 A.M. - 9:30 A.M. • HARMONY B**

### **83. Mechanisms for Visual Cortical Plasticity and Reactivation of Plasticity**

*Co-chairs: Huizhong Tao, Aaron McGee*

*Presenters: Weifeng Xu, Aaron McGee, Joshua Trachtenberg, Hey-Kyoung Lee*

Synaptic connections in sensory cortices are highly sensitive to changes of sensory experience during a critical period in postnatal development. For example, in the primary visual cortex, monocular deprivation drives long-lasting changes in cortical connectivity that can result in deficits in vision such as amblyopia. The sensitivity to discordant vision declines after the critical period closes. 'Reactivating' cortical plasticity after critical period closure is thought to be essential for improving spatial vision in amblyopic adults. Thus, understanding the molecular mechanisms governing the timing duration of the critical period, and the molecular, neuronal and circuit changes induced by experience confined to the critical period as well as those sustained in adulthood thereafter, will generate insights into approaches to enhance cortical plasticity in adults. First, Dr. Xu will focus on cellular and molecular mechanisms underlying the experience-dependent equilibration of AMPA

receptor-mediated synaptic transmission during the critical period despite substantial remodeling of synaptic connectivity. Dr. McGee will discuss the differential effects of deleting the *nogo-66* receptor (*ngR1*) in different neuronal populations on the recovery of ocular dominance and visual acuity. Dr. Trachtenberg will describe a shift in dendritic integration and somatodendritic inhibition associated with critical period closure. And Dr. Lee will report how a loss of auditory modality induces recovery of visual cortical plasticity in adult animals. Dr. Tao will lead discussion of the presentations. Together, these presentations will provide a diversified view on molecular, neuronal and sensory manipulations that can be utilized to promote visual cortical plasticity.

**PANEL • FRIDAY, 7:30 A.M. - 9:30 A.M. • SPEARHEAD**

## **84. Cerebellar Modulation of Non-Motor Brain Functions**

*Co-chairs: Erik Carlson, Krystal Parker*

*Presenters: Hirofumi Fujita, Erik Carlson, Krystal Parker, Peter Tsai*

Cerebellar dysfunction has been increasingly linked to cognitive dysfunction in neuropsychiatric disorders. However, the underlying circuit mechanisms remain poorly understood. Non-motor functions have been linked not only with the cerebellar hemispheres, but also with the vermis, which is known as the 'spinocerebellum'. Hirofumi Fujita (Johns Hopkins University) has identified four major types of projection neurons that are molecularly and anatomically distinct in the output nucleus of the vermis, fastigial (medial) nucleus, which may organize cerebellar vermal functions into four major domains that correspond to postural coordination, orienting movement, vestibulo-autonomic function, and cognition. The dentate (lateral) nucleus of the cerebellum (LCN) is activated during performance of cognitive tasks involving complex spatial and sequential planning. Utilizing viral and genetic strategies in mice, Erik Carlson (Univ. of Washington), has identified an anatomically distinct region of the LCN that contains catecholaminergic innervation. Genetic inhibition of catecholamine release in the LCN impairs working memory, sensory discrimination, and alters affective state, demonstrating a functional link between the LCN in non-motor behavior. Krystal Parker (Univ. of Iowa) has shown that pharmacologic and optogenetic stimulation in cerebellum rescues performance on a timing task (which requires attention to the passage of time and estimation of the end of an interval) by reinstating specific frontal cortical neuronal activity in rodents. Here, she will discuss how a specific cell type, D1 dopamine receptor expressing neurons in the LCN, influence activity downstream in frontal cortex; and how targeting cerebellum with neuromodulatory interventions influences frontal activity and cognitive function in schizophrenia. Peter Tsai (UT Southwestern) has demonstrated that disruption of an autism-related gene specifically in cerebellar Purkinje cells results is sufficient to generate autism-relevant behaviors. Here, utilizing genetic

models, pharmacology, imaging, electrophysiology, and functional circuit manipulation, he will show that modulation of cerebellar regions and circuits modifies autism-related behavior, and implicates them as targets for therapeutic intervention.

**SHORT COURSE • FRIDAY, 7:30 A.M. – 9:30 A.M. • WEDGEMOUNT**

## **85. From Mapping to Modulation: Using Intrinsic Neural Architecture to Develop Clinically Useful Neuromodulation Tools for Psychiatry**

*Chair: Colleen Hanlon*

*Presenters: Katharine Dunlop, Jonathan Downar, Colleen Hanlon*

In the past decade advances in both clinical and preclinical neuroimaging have significantly expanded our understanding of the neuronal circuitry of psychiatric disease. In the next decade, our challenge is to use that knowledge to develop an efficacious treatment. Neural networks of Control and Reward: Through advances in computational modeling and large data repositories, we now know that the brain can be parsed into multiple independent and complementary networks which govern cognitive control and reward based behavior. Many of these functional connectivity networks are also well aligned with structural connectivity maps, as validated with diffusion tensor imaging. Tools available to modulate these Networks: Through advances in clinical imaging, we know that it is possible to independently activate frontal-striatal circuits that govern executive control and arousal with non-invasive transcranial magnetic stimulation (TMS). We also know that it is possible to change reward based behavior through realtime neural feedback using functional MRI (rtfMRI). We do not, however, know if rTMS or rtfMRI will be more effective as clinical tools through targeting repetitive TMS will be an effective therapeutic tool for substance dependent populations. We also do not know whether attenuating craving or amplifying cognitive control will likely be a more efficacious approach. This short course will thematically be linked by two questions - "Which neural circuits should we try to modulate?" & "What tools are available to modulate these circuits in our patients?" It will begin with an introduction to the neural circuits and candidate neural biomarkers involved in reward and control based disorders, and proceed to a summary of previous and new data on the efficacy of rTMS and rtfMRI as therapeutic tools. Finally, we will conclude the short course with an interactive panel discussion asking the hard questions: "What is needed for these techniques to actually be clinically relevant and useful."

## *Friday Afternoon Panel Sessions*

**PANEL • FRIDAY, 4:30 P.M. - 6:30 P.M. • FITZSIMMONS**

### **86. Neuroinflammation in Parkinson's Disease - The Chicken and the Egg**

*Co-chairs: Fredric Manfredsson, Malu Tansey*

*Presenters: Caryl Sortwell, Ashley Harms, Malu Tansey, Fredric Manfredsson*

Inflammation is increasingly recognized as playing a crucial role in Parkinson's disease (PD) disease etiology. Nevertheless, the classical view on the role of neuroinflammation in PD suggests that the appearance of chronic inflammation is merely a response to the progressive cell death that occurs in the dopaminergic neurons of the substantia nigra. However, more recent evidence suggests that neuroinflammation may be a triggering, and causative, event in parkinsonian neurodegeneration. The goal of this panel is to discuss these current views and to summarize recent findings. Dr. Caryl Sortwell will present and discuss unpublished data demonstrating the relationship between Lewy-body like inclusions, neuroinflammation, and nigrostriatal degeneration. Dr. Ashley Harms will present work highlighting the role of MHC-II mediated responses in synucleinopathy models, and the role of peripheral immune cells in central neurodegeneration. Dr. Malu Tansey will summarize recent patient data describing a role for the PD-associated gene LRRK2 in regulating peripheral immune cells and what this means for PD progression. Finally Dr. Fredric Manfredsson will talk about how neuronal dysfunction can lead to the expression of MHC-1 on nigral neurons, resulting in a neurogenic inflammatory response. Altogether, we will present a mechanistic view of the role of the immune system in neuronal degeneration and tie together genetic links with histopathological indices of PD. Importantly, one highlight of this panel will be to introduce the concept of immunomodulation as a potential therapeutic avenue in neurodegeneration.

**PANEL • FRIDAY, 4:30 P.M. - 6:30 P.M. • GARIBALDI A**

### **87. Rapid Trafficking in the Moguls: State Dependent Synaptic Plasticity**

*Chair: Victoria Luine*

*Presenters: Graham Knott, Victoria Luine, Kristen Harris, Lique Coolen*

LTP is known to elicit rapid changes in spine synapses in the hippocampus, however recent evidence shows that other stimuli cause activation of signaling cascades with concomitant changes in the distribution of spines, trafficking of proteins within spines and alterations in firing patterns. We highlight ultrastructural and neurochemical changes within spines and spine synapses

following diverse stimuli. Knott presents how dendritic spines are formed in the adult cortex and the influence of other synapses along the dendrite. Electron microscopy, imaged in the live mouse brain, shows that new spines always appear close to shaft synapses, and the longer that the spine persists then the further these two types are separated. This influence on the positioning of new connections may be general and present throughout development. Luine describes use of a 3-dimensional, Golgi-immunohistochemical staining allowing co-localization of synaptic markers within various spine shapes in CA1 of the hippocampus. Estradiol rapidly enhances recognition memory and analysis shows decreased GluA2-containing filopodial spines at 30 min and increased GluA2-containing mushroom spines at 120 min post injection which may contribute to enhanced memory consolidation. Harris discusses how synapses are modified initially by the induction of long-term potentiation and then grow silent to prepare for subsequent LTP augmentation. This process is balanced by homeostatic shrinkage of neighboring synapses that likely did not undergo potentiation. Each step during LTP results in dramatic remodeling of the synapses at short time scales from 5 to 120 min after induction. Coolen discusses transient effects of sexual reward, experience and abstinence on spinogenesis and glutamate receptor expression/trafficking in the nucleus accumbens. The underlying cellular mechanisms of these events and demonstrations of functional relevance for sex reward memory and cross-sensitization to drugs are discussed.

**PANEL • FRIDAY, 4:30 P.M. - 6:30 P.M. • HARMONY A**

## **88. There's Always Room for Dessert: Neural and Behavioral Alterations Contributing to Obesity**

*Chair: Carrie Ferrario*

*Presenters: Stephanie Borgland, Catharine Winstanley, Rifka Derman, Uku Vainik*

The global obesity epidemic shows no signs of abating, and in fact rates of obesity and the many diseases it perpetuates are still on the rise. While the solution seems easy- eat less, exercise more- this is far from the reality of the complex neuropsychological alterations induced by obesity, and by some of the tasty foods we eat. Speakers in this panel will provide an overview of behavioral and neurobiological factors that contribute to the obesity epidemic. Stephanie Borgland (University of Calgary) will present electrophysiological and structural studies examining how diet induced obesity alters synaptic plasticity in the orbitofrontal cortex. Catharine Winstanley (The University of British Columbia) will discuss how impulsivity is differentially affected by eating fatty foods vs. by gaining fat mass. Thus, these first two talks will address how diet and obesity interact to affect neural systems that influence and regulate feeding behaviors. The last two talks will address contributions of individual susceptibility to weight gain to the obesity epidemic. Rifka Derman

(The University of Michigan) will present studies examining differences in incentive motivation in obesity-prone and obesity-resistant rodents, followed by Uku Vainik (McGill University, Montreal Neurological Institute and University of Tartu) who will present human studies addressing the heritability of neurocognitive risk factors for obesity and quantification of obesity's behavioural similarity with drug addiction.

**PANEL • FRIDAY, 4:30 P.M. - 6:30 P.M. • HARMONY B**

## **89. Neural Circuit Disruption in Traumatic Brain Injury: Looking Beyond Pathology to Network Alterations Across Different Severities and Modalities**

*Chair: Akiva Cohen*

*Presenters: Cole Vonder Haar, Matthew Hemphill, Akiva Cohen, Kaitlin Folweiler*

Traumatic Brain Injury (TBI) is estimated to occur annually in ~295 per 100,000 people worldwide. Various modes of physical insult can initiate TBI, including acceleration, impact, and pressure, and ensuing pathologies are linked to a range of clinical severities. Although numerous models indicate cellular, synaptic, and network changes in hippocampal and limbic circuits, core circuit pathologies shared across injury types and severities and their relevance to neurobehavioral prognosis remain to be elucidated. This session will focus on circuit remodeling and related behavioral deficits observed in multiple animal models of TBI including controlled cortical impact (CCI), lateral fluid percussion (LFPI), and primary explosive blast (bTBI), across mild to severe injury spectrum. Cole Vonder Haar (WVU) will present findings from a rodent CCI model spanning mild to severe injury levels in which increased addictive and risky behavior is observed. Matthew A. Hemphill (UPENN) will present a murine model of bTBI that produces deficits in open field and spatial object recognition tasks with circuit impairment detected in CA1. Akiva Cohen (CHOP/UPENN) will present a mild rodent LFPI model in which circuit alterations due to excitatory/inhibitory imbalances are observed in both CA1 and DG which contribute to multiple behavioral impairments including contextual fear and spatial object recognition. Building on the notion that TBI is heterogeneous in injury mechanism and severity, Kaitlin Folweiler (CHOP/UPENN) will conclude with a translational discussion of machine learning strategies to stratify human TBI subpopulations and map injury features to prospective outcomes. This session will bring together three young investigators, who have not participated in a WCBR panel, to inform the neuroscience community on recent developments in physiological changes after TBI with a focus on translating these mechanisms to improve human behavioral outcomes after brain injury.



## 90. Enzymatic Control of Endocannabinoids: Budding Targets to Regulate Brain Function and Behavior

*Chair: Carl Lupica*

*Presenters: Andrea Hohmann, Aron Lichtman, Daniel Covey, Carl Lupica*

Endocannabinoids (eCBs) are lipid modulators produced in brain that influence a wide range of functions via actions at cannabinoid receptors. Recent work suggests that manipulation of enzymes regulating eCB metabolism represents a viable target for pharmacotherapies in human disease, pain management, and drug addiction. The best understood eCBs, N-arachidonylethanolamine (anandamide; AEA) and 2-arachidonylglycerol (2-AG), are derived from membrane phospholipids via phospholipases. 2-AG is synthesized from the precursor, diacylglycerol, via diacylglycerol lipase (DGL), and is primarily inactivated by monoacylglycerol lipase (MAGL). The mechanisms responsible for AEA biosynthesis are poorly understood, but AEA degradation by fatty-acid amide hydrolase (FAAH) is well-characterized. This panel will provide insight into eCB control of brain function and behavior using strategies targeting eCB metabolism. Andrea Hohmann (Indiana University) will discuss work exploring the analgesic therapeutic potential of augmenting eCB function through selective inhibition of FAAH peripherally, or within the CNS. Aron H. Lichtman (Virginia Commonwealth University) will discuss antinociceptive effects of DGL and MAGL inhibitors in neuropathic pain models, via cannabinoid receptor independent and dependent mechanisms. Dan Covey (University of Maryland) will discuss his recent data showing that behavior and dopamine neuron activity driven by reward-associated cues depends on 2-AG synthesis in midbrain dopamine (DA) neurons via DGL- $\alpha$ . Finally, Carl Lupica (NIDA) will show that DGL- $\alpha$  knockout in midbrain DA neurons alters cocaine-induced 2-AG release in the ventral tegmental area, and discuss the consequences of this for cocaine self-administration. Together, these investigators will explore how strategies designed to alter eCB production and degradation can be used to gain insight into roles of these molecules in the regulation of pain and reward-based behavior.

## 91. mGlu5 Receptors at the Intersection of Stress, Sex and Addiction: Tales of Rats and Humans

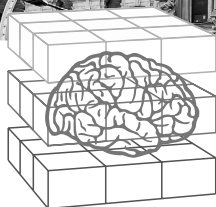
*Chair: Marek Schwendt*

*Presenters: Irina Esterlis, Marek Schwendt, Erin Larson, M. Foster Olive*

Metabotropic glutamate receptor subtype 5 (mGluR5) plays a key role in modulating synaptic plasticity, and its dysregulation has been associated with several neuropsychiatric conditions – including stress-related and substance use disorders. Presenters in this panel will discuss their findings on possible neural mechanisms of dysregulated mGluR5 function in clinical populations (individuals with PTSD) or in translational animal models that address the effects of traumatic stress or sex-differences on substance abuse vulnerability. Additionally, presenters in this panel will discuss emerging tools that allow for specific diagnosis and targeting of mGluR5 in vivo. First, Dr. Irina Esterlis will present data showing dysregulation in mGluR5 availability in human PTSD vs. healthy controls subjects as detected by positron emission tomography and postmortem tissue analysis, and discuss her findings in relation to co-occurring clinical symptoms and other protein expression changes. Second, Dr. Marek Schwendt will introduce a novel animal model of PTSD and cocaine abuse comorbidity and present the data on a dual role of mGluR5 in amygdala regulating both the vulnerability to develop PTSD-like anxiety and relapse to cocaine-seeking. Next, Dr. Erin Larson will extend the discussion on the role of mGluR5 in cocaine-seeking to include a recently discovered molecular mechanism (mGlu1/5 – estrogen receptor interaction) that may contribute to sex-differences in relapse vulnerability. Further, she will present data on the significance of this interaction for the emergence of cocaine-induced changes in behavior and dendritic morphology. Finally, Dr. Foster Olive will discuss recent developments in light-activated mGlu5 receptors (OptoXR-mGluR5), and show examples on how this molecular tool can be used to manipulate mGluR5 function in vivo to study cognitive performance and cocaine-related behaviors.



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# Poster Abstracts

MONDAY, JANUARY 15 • 3:30 P.M. – 4:30 P.M. • SEA TO SKY BALLROOM B

## M1. Assessment of “Stress-Responsivity” in Sign-Trackers and Goal-Trackers

*Sofia Lopez\*, Paolo Campus, Aram Parsegian, Marin S. Klumpner, Shelly B. Flagel*

Reward cues gain inordinate control and lead to maladaptive behavior when attributed with incentive motivational value. Yet, there is considerable individual variation in the propensity to attribute incentive value to reward cues. Rats that undergo Pavlovian conditioned approach (PCA) training may develop a sign- or goal-tracking conditioned response. For both sign-trackers (ST) and goal-trackers (GT) the cue attains predictive value, but only for ST does the cue also attain incentive value. Using the ST/GT model, we have shown that different neural circuits regulate predictive vs. incentive learning, with the latter—sign-tracking—dependent on dopamine. Relative to GT, ST also show higher levels of corticosterone (CORT), the major hormone mediating stress response, after a single session of PCA training. Given the known interactions between CORT and DA and the ability of both to regulate cue-motivated behaviors, we investigated whether there are differences in “stress-responsivity” between ST and GT that could in turn affect the propensity to attribute incentive salience to reward cues. CORT was assessed in ST and GT under baseline conditions, following PCA training, and in response to acute stressors. Anxiety-related behavior was also assessed in ST and GT using the elevated plus maze and locomotor response to novelty. Results suggest that there is no relationship between the propensity to attribute incentive salience to reward cues and anxiety-related behaviors. However, CORT does appear to mediate individual differences in cue-reward learning. Ongoing studies are assessing whether differences in glucocorticoid receptor (GR) mRNA expression throughout the mesocorticolimbic system might be mediating differences in CORT between ST and GT. These data will contribute to our understanding of stress responsivity in sign- and goal-tracking behaviors and prompt future investigations examining the interaction between CORT and dopamine during cue-reward learning.

## **M2. Decoding Ventral Striatal Oscillations Related to Feeding Behavior: Toward Real-Time Models That Generalize Across Individual Animals and Brain States**

*Lucas Dwiell\*, Michael Connerney, Jibran Khokhar, Wilder Doucette*

Background: Binge eating is a disruptive and treatment-resistant behavior complicating the management of obesity and many psychiatric disorders. The distributed circuit that governs feeding behavior has a nexus point in the ventral striatum (VS). The VS has been evaluated as a target for circuit-based interventions (deep brain stimulation) in appetitive disorders and as a source of information used to shape the characteristics of that intervention.

Here, we tested the hypothesis that VS electrical activity could be used to predict real-time feeding behavior, food palatability, and calories consumed in a pre-clinical model of binge eating. Methods: Sprague-Dawley rats had local field potentials (LFPs) recorded from bilateral VS with paired video during sessions of limited access to palatable food. Features extracted from LFPs were used in statistical modeling and machine learning approaches to build and test models to predict food type (palatability), calories consumed, and real-time feeding behavior. The models were tested across animals, hunger states, and food type. Performance was assessed using area under the curve (AUC) and effect size (ES) from permuted data.

Results: VS activity was able to predict calories consumed ( $ES=0.5$ ), the increase consumption due to food deprivation ( $ES=1.15$ ), and food type ( $ES=0.89$ ). Models built from any one rat did well at predicting its time of eating, but not that of other rats ( $AUC=0.91$  vs  $0.7$ ). Models built from all animals generalized better than individualized models in predicting time of eating during food deprivation. Lastly, models built from the pre-feeding period were able to classify brain activity that predicted imminent feeding up to 1 minute before feeding began ( $AUC=0.75$ ). Conclusions: Our findings suggest that the VS is a rich source of information about current and future feeding behavior, and that such information could help ensure the efficacy of circuit based interventions to regulate appetitive disorders.

## **M3. Dissecting Gene-Early Life Stress Interactions in Cocaine Responsiveness and Sensorimotor Gating**

*Tod Kippin\*, Jared Bagley, Rachel Bozadjian, Lana Bubalo, Kyle Ploense, Philip Vieira*

Early life stress has been implicated in a number of psychiatric conditions, including addiction and schizophrenia, and appears to be involved in complex gene X environment interaction leading to pathology. Identification of the alleles mediating these interactions is an important step in understanding the underlying neurobiology. To dissect this interaction, we have been

examining the impact of prenatal stress (PNS) on cocaine responsiveness and sensorimotor processing in the BXD inbred panel of mice. These strains possess unique combinations of B6 and D2 alleles and may allow for identification of quantitative trait loci (QTLs) that mediate the effects of PNS. Methods. BXD strains were subject to timed mating followed by assignment to PNS and control groups. PNS dams were placed in a restraint stress protocol (1 hour restraint, 3 times daily) starting between embryonic day (E) 11 and 14 and continued until parturition. PNS may affect developmental outcomes by altering maternal behavior in the post-natal period. Accordingly, the frequency of pup-dam contact was measured in the first 10 post-natal days. Adult control and PNS offspring (8 to 9 weeks) were tested in a PPI procedure (110 dB startle, 74 and 90 dB PPI) followed by cocaine (10 mg/kg, I.P.) CPP. Results. We have found PNS by strain interactions, indicating the effects of PNS are heritable in the BXD panel. Specifically, PNS interacts with strain to alter cocaine acute locomotion, locomotion sensitization and CPP, acoustic startle response and PPI. PNS interacts with strain to alter pup-dam contact, with the most frequent effect being a reduction in contact. Overall, these results suggest that the effects of PNS on cocaine reward/locomotion, sensorimotor processing and maternal stress response are heritable in the BXD panel and we have identified significant QTLs based on this data set. Ultimately, we will attempt to identify polymorphisms mediating the genetic susceptibility to PNS.

#### **M4. Endocannabinoids on Cortical Terminals Orchestrate Local Modulation of Dopamine Release in the Nucleus Accumbens**

*Yolanda Mateo\*, Kari Johnson, Daniel Covey, Brady Atwood, Marisela Morales, Joseph Cheer, David Lovinger*

Dopamine transmission mediates numerous aspects of behavior. Although dopamine release is strongly linked to firing of dopamine neurons, recent developments indicate the importance of presynaptic modulation at striatal dopaminergic terminals. The endocannabinoid system regulates dopamine release and is a canonical gatekeeper of goal-directed behavior. Here we report that extracellular dopamine increases induced by selective optogenetic activation of cholinergic interneurons in the nucleus accumbens are inhibited by CB1 agonists and endocannabinoids. This modulation requires CB1 receptors on cortical glutamatergic afferents. Dopamine increases driven by optogenetic activation of prefrontal cortex terminals in the nucleus accumbens are similarly modulated by activation of these CB1 receptors. We also demonstrate that this same population of CB1 receptors modulates optical self-stimulation sustained by activation of prefrontal cortex afferents in the nucleus accumbens. These

results establish local endocannabinoids actions on prefrontal cortex terminals within the nucleus accumbens that inhibit mesolimbic dopamine release and constrain reward-driven behavior.

## **M5. The Effect of Inhibited Dopamine Release in the Nigrostriatal Pathway on Risky Decision Making in Rats**

*Brett Hathaway\*, Mason Silveira, Melanie Tremblay, Catharine Winstanley*

Numerous studies have demonstrated that risky decision making is associated with the development and maintenance of addiction. Reward concurrent cues also appear to play a role in addiction, as previous results have indicated they enhance risky choice in rats. Despite extensive addiction research implicating the dorsal striatum in the maintenance of compulsive drug seeking, the role the nigrostriatal pathway plays in aberrant choice in the presence of reward-paired cues remains unclear. The present study examined the effects of both acute and chronic inhibition of the dopaminergic nigrostriatal pathway on risky decision making in rats. Female TH:Cre rats ( $n = 8$ ) and transgene negative litter mates ( $n = 7$ ) were trained on the cued rat gambling task (crGT), a rodent analogue of the human Iowa Gambling Task, to assess cue-enhanced decision making. This task was designed such that the optimal strategy for earning sugar pellets over time is to favor the low-reward options, as they are associated with a higher probability of winning. Consistently selecting the high-risk, high-reward options ultimately results in longer and more frequent time-out penalties, and therefore less reward overall. Adding salient reward-paired cues to this task results in a substantial proportion of rats establishing a risk-preferring choice profile. To assess nigrostriatal involvement in the crGT, inhibitory DREADD (designer receptor exclusively activated by a designer drug) hM4D(Gi) was infused into the substantia nigra prior to task training. After a statistically stable baseline was reached, rats were given an acute clozapine-N-oxide (CNO) challenge, followed by a chronic injection period in which CNO was given twice daily for 14 days. crGT performance was assessed while CNO was on board. CNO administration increased choice latency in all rats transfected with DREADDs. While acute CNO administration did not significantly affect choice, chronic administration shifted risk preference in rats who previously demonstrated a risk-averse choice profile. These results provide evidence for whether dopaminergic activity within the nigrostriatal pathway is involved in risky decision making, and therefore sheds light on its role in the development and maintenance of addiction.

## **M6. Cerebellar Activation During a Multisensory Stroop Task is Associated With Mood, Anxiety and Alcohol Use Disorder (AUD) Severity in AUD**

*Claire Wilcox\*, Andrew Mayer, David Braitman, Josh Clifford, Josef Ling, Michael Bogenschutz*

**Introduction:** Individuals with alcohol use disorder (AUD) have altered brain activation during Stroop-like tasks, which measure cognitive control. However, few studies have explored the relationship between Stroop tasks and AUD severity. Additionally, although impaired cognitive control is associated with deficits in emotion regulation, the relationship between brain activation during a non-emotional Stroop and emotionality in AUD has not been investigated.

**Methods:** 33 treatment-seeking participants with AUD enrolled in a clinical trial of prazosin ( $39.7 \pm 11.3$ , female  $n=12$ ) also underwent a multisensory Stroop task during fMRI (Mayer 2012) prior to initiating treatment. Percent signal change (PSC) estimates were calculated using deconvolution analysis in AFNI (details in Mayer 2013; 33Hz). Paired t-tests were performed [Incongruent (I) vs. Congruent (C)] and corrected for multiple comparisons for the whole brain using 3dClustsim ( $\alpha < .05$ , individual voxel  $p < .001$ ). PSC for I and C were extracted from significant clusters and their difference score was used for all subsequent analyses (I-C). Results: Significantly greater activation for I relative to C was observed in the cerebellum and left temporal gyrus (TG). I-C in the cerebellum was correlated with AUD severity as measured by the Alcohol Use Disorders Identification Test (AUDIT;  $\rho=.418$ ,  $p=.017$ ) and Drinkers Inventory of Consequences (DrInC;  $\rho=.518$ ,  $p=.002$ ) as well as scores on the Affective Lability Scale (ALS) ( $r=.568$ ,  $p=.001$ ), Perceived Stress Scale ( $r=.529$ ,  $p=.002$ ), and PROMIS anxiety ( $r=.515$ ,  $p=.002$ ), PROMIS anger ( $r=.447$ ,  $p=.023$ ) and PROMIS depression ( $r=.597$ ,  $p<.001$ ) scales. I-C in the TG correlated with PROMIS depression ( $\rho=.479$ ,  $p=.005$ ) and anxiety ( $r=.395$ ,  $p=.023$ ). Furthermore, I-C in the cerebellum was an independent predictor of most emotional measures, correcting for previous 7 day total drinks, AUDIT or DRINC, and years since AUD onset (e.g. using AUDIT as the AUD severity measure, ALS, I-C  $\beta=.530$ ,  $p=.015$ ). Moreover, change in I-C from baseline to a repeat scan at week 3 ( $n=23$ ) was correlated with change in PDA from baseline to the week prior to the scan ( $\rho=-.689$ ,  $p<.001$ ), and with change in DPW from baseline to a week prior to the scan ( $\rho=.340$ ,  $p=.113$ ).

**Conclusions:** Brain activation during a non-emotional Stroop task is related to both AUD severity and emotionality and deserves further exploration as a treatment target in AUD. Our findings also support previous research indicating that cerebellum may play an important role in tempering and modulating emotional reactions in the brain (Bodranghien et al. 2016, Koziol et al., 2014).



## **M7. Auditory Processing of Mate Choice Cues in the Female Songbird**

*Koedi Lawley\*, Jonathan Prather*

In its essence, decision making consists of two components – evaluating sensory signals and using that information to direct specific motor responses. The first step in this process is identifying and evaluating sensory signals, however, it remains unknown how the brain assigns value to sensory stimuli. In many songbird species, including the Bengalese finches (*Lonchura striata domestica*) studied here, females recognize individual males by their songs and evaluate the features and quality of those songs to choose one mate from among many suitors. A key experimental advantage is that song is a unimodal stimulus that is so effective in driving female preference that females will perform behavioral indicators of mate choice (i.e. copulation solicitation displays and calls) in response to song even if no male is physically present. Studies of female responses to song have implicated auditory cortical regions such as the caudal mesopallium (CM) and the caudomedial nidopallium (NCM) in the expression of mate preferences. Here we chemically lesioned CM and NCM bilaterally to investigate the degree to which they play a role in: 1) preference for conspecific over heterospecific songs, and 2) higher-resolution preference for one conspecific song over others. Preliminary results indicate that there is little to no change in preference for conspecific or heterospecific male song following lesions to CM and NCM when using call numbers as a measure of preference. Further investigations are ongoing to determine if the fibers of passage through and between these areas are intact and what occurs when they are damaged using electrolytic lesions.

## **M8. CB1 Receptor Signaling Enhances Associative Strength in Pavlovian and Instrumental Settings**

*Sam Bacharach, Helen Nasser, Natalie Zlebnik, Hannah Dantrassy, Joseph Cheer, Donna Calu\**

Prior studies suggest that dopamine (DA) release in the nucleus accumbens (NAc) plays a time-limited role in driving appetitive approach in sign-, but not goal-trackers. Endocannabinoids (eCBs) are critical gatekeepers of dopaminergic signaling and antagonists of the cannabinoid-1 (CB1) receptor alter DA dynamics in the NAc to influence cue-motivated behavior in instrumental procedures that resemble Pavlovian lever autoshaping. Here, we determine whether systemic CB1 receptor blockade during early and late phases of Pavlovian lever autoshaping resembles the previously reported effects of DA receptor antagonists on sign-tracking but not goal-tracking. We tested the prediction that systemic injections of the CB1 receptor inverse agonist, rimonabant, would block sign-, but not goal-tracking behaviors. We trained male and female rats in four Pavlovian lever autoshaping sessions to determine

their sign-tracking (ST), goal-tracking (GT) or intermediate-tracking (INT) phenotype. We then tested rats with systemic injections of rimonabant (0, 1, 3 mg/kg), during early (5-7) and late (15-17) reinforced Pavlovian lever autoshaping sessions. Rimonabant dose-dependently decreased both lever and food cup directed behaviors early in training. With continued task experience many previously goal-tracking and intermediate rats shifted towards lever-directed behaviors, which continued to be dose-dependently sensitive to the effects of rimonabant. In the same group of ST, GT, and INT rats we introduced an instrumental contingency by training rats to acquire a cued-instrumental nosepoke response. We examined the impact of rimonabant (0, 1, 3 mg/kg) on cued-instrumental performance under long ITI conditions that were identical to rats' previous reward history. Rimonabant did not affect the instrumental performance under long ITI conditions that theoretically limited changes in associative strength linking environmental stimuli, instrumental actions and reward. However, after additional training with short ITI (5 s), rimonabant (0, 1, 3 mg/kg) dose dependently impaired instrumental performance. The increased reward rate under short ITI conditions theoretically raises the ceiling on the associative strength linking cues, actions and outcomes. Together, our results suggest that CB1 receptor signaling impacts the associative strength of environmental stimuli to invigorate motivated behavior in both Pavlovian and instrumental contexts.

## **M9. Characterization of Behavioral and EEG Phenotypes in a Novel Rat Model of Angelman Syndrome**

*Anne Anderson\*, Luis Martinez, Julianah Ajose, Shellsea Fontenot, Sarah Harris, Patrick Breen, David Segal, Edwin Weeber, Heather Born*

Angelman Syndrome (AS) is a genetic neurodevelopmental disorder with unique behavioral phenotypes and seizures as key features of the disease. The most common genetic cause of AS is the deletion or mutation in the maternally imprinted Ube3a gene, encoding ubiquitin ligase (Ube3a). In this study, we sought to characterize the effect of the AS genetic lesion on behavior and electroencephalography (EEG) activity in a novel Ube3a maternal deletion rat model of AS. The increased brain size and complexity found in rats versus mice as a model of disease are advantageous for study, particularly for an examination of early post-natal development, and is beneficial for pre-clinical studies in support of developing novel therapeutic strategies. We performed behavioral tests during early postnatal development and in young adult AS rats. Our results indicate that abnormal behavioral phenotypes are present early during development, including significantly fewer ultrasonic vocalizations during isolation in AS rats compared to wildtype (WT) littermates ( $p < 0.05$ ). Young AS rats also show significantly increased speed during open field activity ( $p < 0.01$ ) and an age-dependent increase in distance traveled ( $p < 0.01$ ). Work

is ongoing to further study measures of anxiety, motor coordination, social interaction, and cognition. In parallel, rats were implanted for video EEG monitoring to assess differences in epileptiform activity and spectral power from early post-natal development into adulthood. Preliminary analysis indicates that abnormal EEG spiking is present in juvenile AS rats. Spectral power analysis of EEG activity suggests that, much like our previous findings in an AS mouse model and in humans with AS, the AS rats show significantly increased spectral cortical EEG power ( $p < 0.05$  at 1-3 Hz) primarily driven by increased power in delta frequencies. Together, these findings indicate that this AS rat model shows behavioral and electrographic abnormalities similar to symptoms of AS in the human disease.

## **M10. Comparison of Device Assisted Therapies for Parkinson's Disease**

*Neil Mahant\*, Han-Lin Chiang, Florence Chang, David Tsui, Yicheng Tai, Ainhi Ha, Jane Griffith, Donna Galea, Samuel Kim, Belinda Cruse, Hugo Morales-Briceno, Victor Fung*

Device assisted therapies (advanced therapies) for Parkinson's disease are important tools to control medication related motor fluctuations. Yet there are few data comparing the three options: apomorphine (Apo), levodopa-carbidopa intestinal gel (LCIG) and deep brain stimulation (DBS). Therefore, we prospectively followed consecutive patients who proceeded with a DAT for PD.

Patients chose which DAT on the basis of preference, with education and guidance of the specialised DAT team. Detailed assessments were performed prior to initiation and regularly after commencing DAT. Non-parametric statistics were used to compare group data.

The sample size was 45: 15 Apo, 15 LCIG and 18 DBS. Baseline characteristics were similar between groups, except for gender (M:F 6:9 Apo, 13:1 LCIG, 11:5 DBS,  $p = 0.008$ ), Addenbrook's Cognitive Examination III (ACE-III) scores ( $87 \pm 12$  Apo,  $87 \pm 18$  LCIG and  $94 \pm 6$  DBS,  $p = 0.03$ ) and Cambridge Behavioural Inventory (CBI) scores ( $36 \pm 26$  Apo,  $49 \pm 30$  LCIG and  $19 \pm 23$  DBS,  $p = 0.03$ ). Off medication MDS-UPDRS motor scores were  $50 \pm 27$  Apo,  $48 \pm 20$  LCIG and  $44 \pm 22$  DBS (median and IQR), and diary based Off time (hours per day) was  $5.8 \pm 4.7$  Apo,  $6.8 \pm 6.0$  and  $5.4 \pm 3.2$  DBS. Here we compare the baseline and 6 month post-treatment outcomes. In the DBS group, improvements were found in L-DOPA equivalent daily dose ( $-750$ mg LEDD,  $p < 0.001$ ), MDS-UPDRS (parts I [3.5 points,  $p = 0.003$ ], II [3.0 points,  $p = 0.02$ ] and IV [7.0 points,  $p = 0.001$ ]), HY scores ( $-0.5$  points,  $p = 0.02$ ), UDysRS (17 points,  $p < 0.001$ ), PDQ-39 (20 points,  $p = 0.003$ ), SEADL (10 points,  $p = 0.004$ ), new freezing of gait questionnaire (3 points, NFOG,  $p = 0.01$ ), BDI (3.5 points,  $p = 0.006$ ), HADS-A (1.5 points,  $p = 0.01$ ), HADS-D (2.5 points,  $p = 0.01$ ) and QUIP (Questionnaire for impulsive-compulsive control disorders in Parkinson's

disease, 5.5 points,  $p=0.03$ ). There was no change in ACE-III or MoCA, but a decrease in excluded letter fluency (5 points,  $p=0.04$ ). In the LCIG group, the LEDD increased (+540mg  $p=0.001$ ) and there were improvements were in HY (1 point,  $p=0.004$ ), UPDRS-IV (2 points,  $p=0.009$ ), PDQ-39 (15 points,  $p=0.003$ ), NFOG (4.5 points,  $p=0.01$ ) and CBI (12 points,  $p=0.04$ ). The Apo group had improvement in HY scores (1 point,  $p=0.03$ ). Between group differences were found in LEDD ( $p<0.001$ ), UPDRS-IV ( $p=0.001$ ), UDysRS ( $p=0.02$ ), PDQ-39 ( $p=0.04$ ) and SEADL ( $p=0.008$ ). The number of adverse events recorded in each group were 15 Apo, 14 LCIG and 16 DBS, the commonest being mood changes (6) and weight gain (2) in the DBS group; wound hypergranulation (5), neuropathy (2), pyridoxine deficiency (2) and depression (2) in the LCIG group; and somnolence (3), nausea (3), hallucination (2), skin nodules (2) and dizziness (2) in the Apo group. Four patients discontinued Apo during the study period due to inadequate benefit or adverse effects. This the first study to directly compare DATs in PD, and provides useful information to inform treatment decisions. The differences between groups needs to be interpreted with caution because of the study was not randomised and there were some differences in baseline characteristics between groups. All three DATs demonstrated significant improvements, the greatest improvements in the DBS and LCIG groups.

## **M11. Progranulin Loss Dysregulates Splenic and Peripheral Blood Immune Cells Populations and May Contribute to Neuroinflammation and Neurodegeneration in Early-Onset Dementia**

*Thomas Kukar\*, Kathryn MacPherson, George Kannarkat, Elizabeth Kline, Christopher Holler, Michelle Johnson, Malu Tansey*

Autosomal dominant mutations in the progranulin gene (GRN) cause a drastic reduction in progranulin (PGRN) and granulin levels contributing to the pathogenesis of familial frontotemporal degeneration (FTD), the most common form of early-onset dementia. Rare homozygous GRN mutations in humans have cause neuronal ceroid lipofuscinosis (NCL), which shares neuropathological features with FTD- GRN patients suggesting shared disruption of lysosomal pathways. Multiple studies have implicated PGRN as a key regulator of neuroinflammation and neurodegeneration. Genetic ablation of the GRN gene is associated with aberrant increases in phagocytosis and pro-inflammatory cytokine production in microglia. Further, global Grn KO and microglia-specific Grn KO mice have increased sensitivity to the neurotoxin MPTP. Most recently Grn deficiency was shown to promote circuit-specific synaptic pruning by microglia via complement activation. While intense focus has been placed on investigating the effect of GRN deficiency in microglia, we have focused our efforts on investigating the effects of GRN

loss in microglia and all major subsets of peripheral immune cells based on the rationale that peripheral-central immune cross-talk is key for brain health and disruptions in these pathways may promote degeneration. We performed deep-immunophenotyping using flow cytometry of brain, spleen, and peripheral blood of Grn KO and WT mice ages 18-30 months. We found that in aged Grn KO mice microglia make up a smaller fraction of Cd11b+ Ly6G- cells and a large fraction of microglia express higher levels of MHCII and lower levels of CD68 compared to WT mice. Further, the CD45int CD11b hi population in the brain is increased in Grn KO mice relative to that in WT mice and a large fraction of them is expressing MHCII and CD68 relative to WT mice. We also found a generalized increase in cell numbers in the blood with an increased frequency of T cells in Grn KO vs WT mice and decreased frequency of MHCII+ cells within Ly6Clo monocytes (alternative activation) and increased CD68 on Ly6C- monocytes. In addition, Grn KO mice displayed decreased NK cells, B cells, and macrophages in the spleen with decreased expression of MHC-II; and non-CD4/CD8 T-cells make up a larger proportion of CD3+ T cells in their spleen. These novel findings support a model for PGRN in regulation of central and peripheral immune cell populations and raise the interesting possibility that analysis of peripheral immune cells could shed light on the role of central-peripheral immune cross-talk in the pathogenesis of FTD/ALS patients with GRN mutations. [Funding provided by NIH/NINDS 5R01NS093362, 5R01NS092122, 1F31NS081830, and The Bluefield Foundation].

## **M12. Three-Dimensional Imaging of Kisspeptin Neurons in the Mammalian Brain Using Optical Tissue Clearing and Immunocytochemistry**

*Aleisha Moore\*, Kathryn Lucas, Robert Goodman, Lique Coolen, Michael Lehman*

Kisspeptin neurons of the arcuate nucleus are critical for the hypothalamic regulation of fertility. The ability to study changes in the expression and connections of kisspeptin neurons across reproductive states is essential for understanding the function of the population. Recently developed protocols for optical tissue clearing has permitted three-dimensional (3D) imaging of complete neuronal populations, however, these techniques have largely been reported in the mouse brain. We aimed to expand immunolabelling and optical tissue clearing techniques into larger mammalian species. Intact rat brains (n=4) and sheep hypothalamic blocks (n=4, 1.5cm x 1.5cm x 1cm) were immunolabelled with rabbit anti-kisspeptin (1:250, gifted by A. Caraty) and Alexa Fluor 647 (1:100-400, Life Technologies) antibodies before being rendered transparent through modification of a 3DISCO-based (Erturk et al 2012) protocol. Brains were imaged using a bi-directional light sheet microscope (LaVision Biotec) and images collected using ImspectorPro

software with magnification up to 6.3x. Mosaic stacks of images were stitched together using Fiji software and projected with IMARIS software to provide 3D visualization of the complete rostral to caudal extent of arcuate kisspeptin cell bodies. In the rat and sheep, large populations of kisspeptin neurons were observed in the caudal region of the arcuate nucleus, which may have been underestimated using traditional approaches in each species. In the sheep hypothalamus, a previously unreported kisspeptin population was identified in the lateral region of the mediobasal hypothalamus, demonstrating the ability of this technique to identify novel features of the kisspeptin system. In recent preliminary studies, we have successfully imaged kisspeptin immunolabelling within the transparent primate hypothalamic block, permitting future comparative analysis of the kisspeptin neuron population in the rodent and sheep brain with higher mammalian species.

### **M13. Activation of Hypothalamic Oxytocin Neurons Restores Oxytocin Release to Parasympathetic Cardiac Vagal Neurons of the Brainstem in Left Ventricular Hypertrophy Induced Heart Failure**

*David Mendelowitz\*, Jhansi Dyavanapalli*

Heart failure (HF), is characterized by an autonomic imbalance i.e., high sympathetic and depressed parasympathetic activities to the heart. Oxytocin, traditionally involved in promoting lactation and uterine contractions, has been known to improve stress induced changes in autonomic balance. Parasympathetic activity to the heart originates from cardiac vagal neurons (CVNs) in the brainstem, whose activity has been shown to be controlled, in part, by excitatory synaptic input co-releasing oxytocin from hypothalamic paraventricular nucleus oxytocin neurons (PVN). Activation of PVN oxytocin neurons is crucial for the activation of CVNs that increases parasympathetic activity to the heart. This study tests if activation of oxytocin neurons restores oxytocin release to activate CVNs and hence increases parasympathetic activity to the heart that is diminished in left ventricular hypertrophy induced heart failure. Left ventricular hypertrophy was elicited in rats by aortic pressure overload using a transaortic constriction (TAC) approach. Selective activation of PVN OXT fibers projecting to CVNs was achieved by chemogenetic DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) and optogenetic Channelrhodopsin (ChR2) approach. A cocktail of viral vectors, cre expression under OXT promoter (AAV1-OXT-Cre) + floxed DREADDS (AAV2-DIO-HM3Dq-mcherry) + floxed ChR2 (AAV1-EF1a-DIO-hChR2) were co-injected in to the PVN. 3 groups of animals Sham, TAC and TAC+Treatment (activation of DREADDS by daily injection of CNO) were used to assess oxytocin release upon photoactivation of PVN ChR2 fibers surrounding CVNs at 2,4 and 6 weeks post-surgery using cultured

Chinese hamster ovary cells co-expressing OXT receptors and Ca<sup>2+</sup> indicator, R-GECO. There were no changes in calcium responses in CHO cells triggered by photoactivation of PVN Chr2 fibers neighboring CVNs among 2, 4 and 6 weeks post sham. However, there is a blunted activation of CHO cells at 6 weeks post TAC compared to 2 and 4 wks post Tac groups (% increase in fluorescence:  $18.6 \pm 2.6$  at 2 wks,  $n=9$ ;  $19.2 \pm 2.0$  at 4 wks,  $n=16$  and  $10.5 \pm 1.5$ ,  $n=16$  at 6 wks post Tac). Further, the blunted CHO cell responses at 6 wks post Tac were completely restored by activation of PVN OXT neurons at 6 wks post TAC+Treatment ( $21.6 \pm 2.0$ ;  $n=22$  in sham,  $10.5 \pm 1.5$ ;  $n=16$  in TAC and  $25.1 \pm 1.6$ ;  $n=22$  in TAC+Treatment). These results indicate reduced PVN release of oxytocin onto CVNs likely contributes to depressed parasympathetic cardiac activity in HF. Hypothalamic oxytocin neuron activation can restore CVN activity and blunt cardiovascular dysfunction in HF.

## **M14. Cue-Triggered Food-Seeking is Modulated by the Ovarian Cycle in Obesity-Prone, but not in Obesity-Resistant Female Rats**

*Yanaira Alonso-Caraballo\*, Carrie Ferrario*

In females, naturally occurring elevations in estradiol decrease food intake and estradiol treatment in ovariectomized females is sufficient to decrease food intake and body weight. However, stimuli paired with food (food cues) also influence feeding behavior; they induce food craving, bias food choice, and increase the amount of food consumed. We have found that male rats predisposed to gain weight are more sensitive to the motivational properties of a food cue, even before the onset of obesity. However, whether a similar difference exists in females, and how cue-triggered motivation varies across the cycle are unknown. Here, we determined how conditioned approach varies between female obesity-prone and obesity-resistant rats and how this behavior changes across the cycle. Rats were trained to associate one auditory cue (CS+) with sucrose pellets, whereas a second cue (CS-) was never paired with sucrose. Rats were then tested for approach during the CS+ vs CS- in the absence of food. As expected, daily food intake and body weight were greater in obesity-prone vs. obesity-resistant rats, and food intake decreased during estrus in both groups. During conditioned approach testing, the magnitude of conditioned approach was higher in diestrus/metestrus compared to proestrus/estrus in obesity-prone rats, but remained stable across the cycle in obesity-resistant rats. Thus, although the cycle affected food intake in both groups, cue-triggered motivation was affected by the cycle only in obesity-prone rats. This pattern suggests a dissociation in the regulation of food “craving” from food consumption by naturally occurring changes in circulating hormones. We are currently assessing whether hormone replacement is sufficient to reduce conditioned approach in ovariectomized female rats. In addition, given the

role of nucleus accumbens (NAc) excitatory transmission in cue-triggered motivation, we are also assessing how estradiol affects AMPAR expression in the NAc.

## **M15. GABAA Agonist Drugs Increase Neonatal Seizure-Associated Neuronal Injury**

*Claude Wasterlain\*, Lucie Suchomelova, Jerome Niquet, Daniel Torolira, Roger Baldwin*

Status Epilepticus (SE) is common in neonates and infants, and is associated with neuronal injury and adverse developmental outcomes. GABAergic drugs, the standard treatment for neonatal seizures, can have excitatory effects in the neonatal brain, by depolarizing immature neurons with low intracellular chloride. It is not known whether this could worsen seizures and their long-term consequences. GABAergic drugs appear to stop behavioral seizures, but adverse effects might occur in a subpopulation of immature neurons which have little behavioral expression at that age. We developed a model of SE in P7 rats that resulted in high survival rates and widespread neuronal injury (Torolira et al 2016). Using this model, we studied the effect of treatment of SE with the GABAA agonists phenobarbital and midazolam. The doses used were too low to cause apoptosis by themselves (phenobarbital 10 mg/kg, midazolam 3 mg/kg). Neuronal injury was assessed with Fluoro-Jade B (FJB), 24 hours after seizure onset. We found that treatment with either phenobarbital or midazolam significantly increased status epilepticus-associated neuronal injury in many brain regions.

In thalamus, midazolam increased the number of FJB+ cells by 128% ( $p<0.01$ ), phenobarbital by 131% ( $p<0.001$ ). Both midazolam and phenobarbital treatment significantly increased neuronal injury in caudate-putamen (+279%,  $p<0.01$ ; +211%,  $p<0.01$ ), globus pallidus (+128%,  $p<0.01$ ; +150%,  $p<0.001$ ), and substantia nigra (+350%,  $p<0.001$ ; +825%,  $p<0.0001$ ) compared to untreated SE. However, only midazolam treatment increased neuronal injury in nucleus accumbens (+54%,  $p<0.05$ ). Phenobarbital treatment increased neuronal injury in hypothalamus and septal nuclei (+988%,  $p<0.0001$ ; +293%,  $p<0.001$ ), but midazolam increased it only in septal nuclei (+37%,  $p<0.001$ ). Both midazolam and phenobarbital increased neuronal injury in lateral entorhinal cortex (+171%,  $p<0.0001$ ; +114%,  $p<0.01$ ), but not in pyriform cortex. Neuronal injury in parietal cortex was significantly increased by midazolam (+54%,  $p<0.05$ ), but not phenobarbital. Hippocampus showed only mild injury, which was not altered by treatment except in ventral CA1/Subiculum after midazolam (+85%,  $p<0.05$ ). In thalamus,  $79 \pm 10\%$  (SE + midazolam group) and  $73 \pm 16\%$  (SE + phenobarbital group) of FJB+ cells expressed active caspase-3a, and many of these cells had fragmented nuclei, suggesting an active and probably irreversible form of neuronal injury. Our



results suggest that more research is needed into the possible deleterious effects of GABAergic drugs on neonatal seizures and on excitotoxic neuronal injury in the immature brain.

## **M16. Spreading Depolarization-Induced Disruption of Dendrites and Dendritic Spines in the Murine Neocortex Revealed by Two-Photon Imaging and Quantitative Serial Section Electron Microscopy**

*Sergei Kirov\*, Jeremy Sword, Ioulia Fomitcheva*

Spreading depolarization (SD) causes rapid neuronal swelling and dendritic beading with spine loss representing acute damage to synaptic circuitry. Yet, very little is known about the immediate impact of SD on synaptic circuits at the ultrastructural level. Urethane-anesthetized mice of the B6.Cg-Tg(Thy1-EGFP) MJrs/J strain expressing EGFP in a fraction of pyramidal neurons underwent a craniotomy over the sensorimotor cortex and in vivo 2-photon microscopy was used to assess dendritic integrity. Transient global cerebral ischemia was induced on the microscope stage by bilateral common carotid artery occlusion (BCCAO) achieved by tensioning sutures looped around each CCA. Controlled reperfusion was accomplished by relieving the tension of the sutures as soon as the SD was recorded with a glass microelectrode at the site of imaged dendrites. Ischemia during BCCAO and the return of blood flow during reperfusion were verified by laser speckle imaging. Somatosensory stimulus evoked intrinsic optical signal imaging (IOS) was employed to monitor loss and recovery of cortical circuit function during ischemia and reperfusion. As expected, BCCAO-induced SD invariably beaded dendrites, but dendrites recovered after reperfusion accompanied by the return of IOS maps. After confirmation of the intact dendritic structure in sham-operated mice ( $n=3$ ), or SD-induced dendritic beading after BCCAO ( $n=3$ ), or dendritic recovery after reperfusion ( $n=3$ ), mice were perfusion-fixed through the heart with mixed aldehydes, and the brain was processed for serial section electron microscopy. Three-dimensional reconstructions from sham-operated mice revealed intact dendrites with spines and healthy synapses. Dendritic cytoplasm contained intact microtubules, tubular mitochondria, and smooth endoplasmic reticulum (SER). Dendrites disrupted by SD in mice subjected to BCCAO were beaded and swollen with watery cytoplasm and disordered microtubules. Mitochondria had blebby appearance with swollen segments interconnected by thin segments indicating the beginning of fragmentation. Several dendritic beads contained swollen cisterns of SER. Most spines were collapsed on beaded dendrites but still attached to the presynaptic axonal boutons. The cytoplasm of recuperated dendrites after reperfusion contained arrays of microtubules, tubular mitochondria, and recovered cisterns of SER. All spines on recuperated dendrites had synapses. Our findings indicate that even in tissue with severe

energy deficits as during global ischemia, SD-inflicted dendritic injury is reversible if blood flow can be rapidly restored immediately after SD onset. Supported by the NIH Grant NS083858 to S.A.K.

## **M17. Lipid Peroxidative Damage is Higher in Traumatic Brain Injuries Complicated by Parenchymal Hemorrhages: Rationale for the Selective Benefit of Tirilazad in Traumatic Subarachnoid Hemorrhage Patients**

*Edward Hall\*, Jeffrey Bosken, Aaron Cook, Jimmi Hatton-Kolpek*

The purpose of this study was to characterize the concentration-time profile of lipid peroxidation LP-derived F2t isoprostanes (IsoPs) and isofurans (IsoFs) in serum and cerebrospinal fluid (CSF) during the first 7 days after adult moderate and severe traumatic brain injury (TBI) by GC/MS (UK IRB #06-0018). Inclusion criteria: were age >18yo, closed head injury, within 24hr of TBI, and Glasgow Coma Score (GCS) <10. The patients were managed according to Brain Trauma Foundation Guidelines. We enrolled 23 moderate to severe TBI (mean age 33.4 years, 70% male, median admission GCS 7) who did not receive any potentially neuroprotective agents. We collected serum samples from 15 age-matched non-TBI subjects. In CSF from TBI patients, the mean IsoP levels were as much as 6x higher than in non-TBI individuals peaking between 24 and 48 hr. The peak serum IsoP values in the 23 TBIs occurred at a mean of 35 hours with no differences between males (N=16) and females (N=7). In all the TBI patients, the total and free IsoPs peaks and the total and free IsoFs were significantly higher than non-TBI controls. Interestingly, we found that TBI patients who had either subarachnoid (SAH), subdural (SDH) and/or intraparenchymal (IPH) hemorrhages or one or more brain contusions; N=16, had significantly higher peak serum IsoP and IsoF levels compared to those patients with no hemorrhages or only epidural hemorrhages; N=7. This effect of hemorrhage is most likely the result of blood-derived free iron or hemoglobin-bound iron acting to enhance post-TBI free radical generation and to catalyze LP (Hall et al; *Neurotherapeutics* 7: 51-61, 2010). These results imply that LP and its pharmacological inhibition may be more relevant to hemorrhagic TBI pathologies. This may explain why, in a large phase III clinical trial (Marshall et al. *J. Neurosurg.* 89:519-525,1998), the potent LP inhibitor tirilazad selectively improved survival and favorable outcome in TBI patients with traumatic SAH.

## **M18. Repeat Concussion Causes Impairments in Attention and Motor Impulsivity**

*Kris Martens\*, Cole Vonder Haar*

Traumatic brain injury is a major health concern, affecting over 2.5 million individuals each year in the United States. A large portion of these injuries are mild, yet a significant number of patients go on to develop debilitating cognitive impairments. To better understand the root causes and evaluate treatments, appropriate models of mild injury and behavioral dysfunction must be developed. In the current study, we evaluated the Closed-head Impact Model of Engineered Rotational Acceleration (CHIMERA), a relatively mild nonsurgical injury model, on the five-choice serial reaction time task (SCSRT), a measure of attention and impulsivity. Rats were trained on the SCSRT to a stable baseline, and then received CHIMERA injuries either zero times per week (sham), once per week, or twice per week. The injury tip was also modified to provide either a diffuse (rubber tip) or focal (steel tip) injury. Animals that received either one or two injuries per week demonstrated substantial deficits in attention and impulsivity, but only in the case of focal injury. Animals receiving a single injury per week took longer to display deficits than their more frequent counterparts. Injuries delivered with the diffuse tip had no effect on performance. These data suggest that focal injuries have greater effects on psychiatric-like dysfunction after TBI, and that the absolute number of hits is a strong predictor of impairment. Taken together, it is clear that both the severity (focal versus diffuse) and number of injuries (earlier onset of deficits in twice per week group) are both substantial contributors to the development of injury-related symptoms and must be considered when evaluating models of injury. Furthermore, the development of pronounced symptoms, even after relatively few injuries, underscores the importance of studying mild injury.

## **M19. $\mu$ -Opioid Receptors in Nociceptive Afferents Produce a Sustained Suppression of Hyperalgesia During Chronic Pain**

*Juan Carlos Marvizon\*, Amie Severino, Wenling Chen, Wendy Walwyn*

Latent Sensitization is a rodent model of chronic pain in which recovery from the hyperalgesia produced by inflammation or nerve injury is shown to consist of pain sensitivity of indefinite duration that is suppressed by the continuous activation of analgesic receptors, including  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors and  $\alpha 2A$  adrenergic receptors. Evidence for this is that antagonists of these receptors trigger hyperalgesia in animals with latent sensitization but not in normal animals. Moreover, mice with global knock-out in the  $\mu$ -opioid receptor (MOR) are unable to recover from the hyperalgesia produced by complete Freund's adjuvant (CFA), an inflammatory agent (Walwyn et al.,

2016, J Neurosci 36: 204-221). This shows that recovery from hyperalgesia depends on the pain suppressing action of MORs. To determine whether these MORs are the ones present in nociceptive primary afferents, we bred flox-MOR mice with mice expressing Cre under the promoter for Nav1.8 sodium channels, which are selectively expressed in all nociceptive primary afferents. The resulting Nav1.8-cre/fMOR mice lack MORs in nociceptors, which was confirmed as follows. 1) RT-PCR for *opmr1* (MOR) showed decreased expression in dorsal root ganglia (DRG) but no changes in the brain. 2) In situ hybridization (RNAscope) for *opmr1* showed decreased colocalization with *scn10a* (Nav1.8). 3) Immunohistochemistry showed decreased colocalization of MOR with CGRP in primary afferent terminals in the dorsal horn. 4) MOR inhibition of substance P release was lost in spinal cord slices from these mice. Then we induced latent sensitization in Nav1.8-cre/fMOR mice and their fMOR littermates by injecting CFA in one hindpaw. Mechanical hyperalgesia, measured with von Frey filaments, returned to baseline at day 21 in the control fMOR mice, whereas in the Nav1.8-cre/fMOR mice hyperalgesia decreased somewhat but was still well below baseline 2 months after CFA. The MOR antagonist naltrexone induced strong hyperalgesia in the fMOR mice, did not produce any hyperalgesia in male Nav1.8-cre/fMOR mice, and slightly increased hyperalgesia in female Nav1.8-cre/fMOR mice. In contrast, the  $\alpha$ 2A adrenergic antagonist BRL44408 induced maximal hyperalgesia in both fMOR and Nav1.8-cre/fMOR mice. Naltrexone also produced hindpaw inflammation in the fMOR mice and female Nav1.8-cre/fMOR mice, but not in the male Nav1.8-cre/fMOR mice. These results show that during latent sensitization MORs in nociceptive primary afferents suppress hyperalgesia in male mice, whereas in female mice they play a primary but not exclusive role in suppressing hyperalgesia.

## **M20. The Parabrachial Complex: A Nexus of Ascending and Descending Pain Systems**

*Asaf Keller\*, Charles Raver, Olivia Uddin, Paige Studlack*

Chronic pain is the most common complaint of patients, affecting over 100 million Americans, and costing the nation more than \$650 billion/year in medical treatment and lost productivity. Most chronic pain patients are resistant to pharmaceutical or surgical therapies, in large part because the underlying pathophysiology of their chronic pain condition is unknown. The ultimate goal of this research program is to rectify this deficiency. Most spinal cord pain-related afferents target the parabrachial nuclear complex (PB), which then projects to multiple pain-related cortical and subcortical targets. Using a rodent neuropathic pain model—chronic constriction of the infraorbital nerve (CCI)—we test the hypothesis that chronic pain is causally related to suppressed inhibitory inputs from the central nucleus of the amygdala (CeA)

to PB. This reduced inhibition dramatically ‘amplifies’ PB neural activity. As a consequence, there is increased PB excitation of several pain-related nuclei, including the rostral ventral medulla (RVM), a key node of the descending pain modulation system. With the use of electrophysiological recordings from intact rodents and from brain slices, and taking advantage of behavioral approaches, optogenetics and pharmacogenetics, we show that: (1) CCI causes a progressive and significant reduction of inhibitory inputs to nociceptive PB neurons that project to RVM, and dramatically increases their firing; (2) Amplified PB activity is due to reduced inhibition from CeA.; (3) Reduced CeAI inhibition to PB is causally related to the development of CCI-Pain. These findings reveal novel mechanisms for the development of chronic pain, and may lead to development of novel therapies to ameliorate, and perhaps even prevent, this devastating condition.

## **M21. DLPFC Transcriptome Defines Two Molecular Subtypes of Schizophrenia**

*C. Harker Rhodes\*, Elijah F. W. Bowen, Jack L. Burgess, Richard Granger*

The Clinical Brain Disorders Branch of the Intramural Research Program at the National Institutes of Health assembled a large collection of frozen post-mortem human brains from individuals diagnosed with schizophrenia, or other psychiatric diagnoses, as well as matched control individuals. Illumina HumanHT-12 v4 expression array data was collected from dorsolateral prefrontal cortex (DLPFC) and the data deposited at dbGaP (Study ID: phs000979). We report an analysis of the data from the 189 adult schizophrenics and 206 adult controls in that cohort. Transcripts from 633 genes are differentially expressed in the DLPFC of schizophrenics as compared to the controls at levels of statistical significance which survive Bonferroni correction. Seventeen of those genes are differentially expressed at a level of statistical significance less than  $10^{-8}$  after Bonferroni correction. Weighted Gene Co-expression Network Analysis (WGCNA) of the schizophrenic subjects based on the transcripts differentially expressed in the schizophrenics as compared to controls divides them into two groups. The “type 1” schizophrenics who have a DLPFC transcriptome similar to that of controls with only 14 differentially expressed genes identified in this dataset. The “type 2” schizophrenics on the other hand, have a DLPFC transcriptome dramatically different from that of controls with 3684 expression array probes to 3221 genes detecting transcripts that are differentially expressed at a level of statistical significance which survives Bonferroni correction. This striking difference in their DLPFC transcriptomes emphasizes the fundamental biologic difference between these two groups of patients. These findings were replicated in a separate cohort using the RNAseq data from the DLPFC of schizophrenics and control subjects collected by the Common Mind Consortium.

## **M22. Increased GABA-Mediated Phasic Inhibition in the Contralateral Hippocampus 7 Days Following Middle Cerebral Artery Stroke**

*Nicole McKinnon\*, James Orfila, Christian Scroeder, Robert Dietz, Paco Herson*

Stroke survivors are at risk for impairment in cognitive functioning and memory. Increased GABA-mediated inhibition in stroke impairs functional recovery in a murine cortical stroke model, though its effect on the hippocampus, responsible for memory formation, is unknown. We hypothesized that increases in GABA-mediated inhibition occur in the hippocampus following stroke and this increase will impair long term potentiation (LTP). Adult male mice underwent transient middle cerebral artery occlusion (45 min, MCAO) or sham surgery. At post stroke day 7, LTP in hippocampal CA1 neurons was evaluated by extracellular field recordings. Additionally, GABA-mediated phasic inhibition was assessed by whole cell voltage clamp, recording amplitude and frequency of inhibitory post synaptic potentials (IPSP) in the ipsilateral (IP) and contralateral (CO) hippocampus. LTP was significantly impaired in both IP and CO hippocampus post MCAO vs sham controls ( $p < 0.05$ ). Pre-incubation with L655,708 (100nM), an inverse agonist selective for  $\alpha 5$  GABAA receptors, rescued LTP 7 days following MCAO ( $p < 0.05$ ). Increased frequency of GABA-mediated IPSP was observed in the CO hippocampus ( $p < 0.05$ ) as hypothesized. However, no difference in frequency of IPSP was observed in the IP hippocampus ( $p = 0.37$ ). The amplitude of IPSP did not differ in CO ( $p = 0.18$ ), or IP hippocampus between stroke or sham animals ( $p = 0.9$ ). Our data demonstrates that GABA-mediated inhibition contributes to the defect in the hippocampus post stroke but suggests distinct mechanisms are responsible for decreased LTP between the IP and CO hippocampi at 7 days post injury. Inhibition of specific GABA activity may provide a new therapeutic approach to improve functional recovery after stroke.

## **M23. mTORC1-Mediated Late LTP in Somatostatin Interneurons Regulates Hippocampal Network Plasticity and Memory**

*Jean-Claude Lacaille\*, Julien Artinian, Alexander Jordan, Abdessattar Khlaifia, Alexandre La Fontaine, Isabel Laplante*

Long-term synaptic plasticity is a prime candidate cellular substrate for learning and memory which is largely unexplored in inhibitory interneurons. In hippocampus, excitatory synapses onto somatostatin interneurons (SOM-INs) show cell type-specific long-term potentiation (LTP) that regulates hippocampal network plasticity, can persist 24h and requires translation via Mechanistic Target Of Rapamycin Complex 1 (mTORC1). Here we investigate the role of mTORC1-dependent LTP in SOM-INs in hippocampus by

knocking out the expression of Raptor, an essential component of mTORC1, selectively in SOM-INs (SOM-Raptor-KO mice). We first determined that SOM-INs show impairments in mTORC1 signalling and persistent synaptic plasticity in SOM-Raptor-KO mice. We next investigated the behavioral relevance of mTORC1-mediated persistent LTP. We showed with whole-cell recordings 24h after contextual fear conditioning (CFC) that training increased excitatory transmission and spine density at synapses onto SOM-INs from SOM-Raptor+/+ but not SOM-Raptor-/- mice, demonstrating that CFC induces persistent mTORC1-dependent LTP at excitatory synapses onto SOM-INs. Field recordings revealed that upregulation of pyramidal cell Schaffer collateral pathway LTP by late-LTP induction in SOM-INs was lost in SOM-Raptor-/- mice, indicating impaired SOM-IN regulation of CA1 network metaplasticity. Behaviorally, SOM-Raptor-/- mice showed impaired long-term spatial and contextual fear memories but intact long-term cued-fear memory, indicating impairments in hippocampal memory. Mice with knock-down of the upstream repressor of mTORC1, Tuberous Sclerosis Complex 1 (TSC1), in SOM-INs (SOM-TSC1+/- mice) showed increased contextual fear memory, indicating that increasing SOM-IN mTORC1 function is sufficient to modulate hippocampal memory consolidation. Our results suggest that learning-induced persistent mTORC1-mediated LTP in SOM-INs regulates CA1 network metaplasticity and hippocampal memory.

**TUESDAY, JANUARY 16 • 3:30 P.M. - 4:30 P.M. • SEA TO SKY BALLROOM B**

## **Tu1. Modulation of Kappa Opioid Receptor Activity by Nicotine and Ethanol in Adolescent and Adult Male Rats**

*Sarah Cross\*, Danny Be, Rudolph Cheong, Celie Carmona, Frances Leslie*

Concurrent use of nicotine and alcohol represents a major public health concern, and use of both substances typically begins during adolescence. Adolescence is a sensitive developmental period marked by major reorganization of brain regions involved in executive function, learning and memory, and reward processing. Previous work from our lab has demonstrated that the combination of nicotine and alcohol (Nic+EtOH) is reinforcing in adolescent, but not adult, male rats, likely due to a functionally immature kappa opioid receptor (KOR) (Larraga et al., 2017). The current study examines age differences in KOR activation and Nic+EtOH modulation of KOR activity in the midbrain and raphe nuclei, brain regions involved in reward, reinforcement, and attention. In experiment one, brain tissue from drug naïve adult and adolescent male rats was processed for U69,593-stimulated [35S]GTPgammaS binding, with or without Nic+EtOH, to determine KOR activity. Data suggest that adolescents are more sensitive to KOR stimulation than adults in the posterior ventral tegmental area (pVTA) and median raphe (MR), and that in vitro Nic+EtOH decreases agonist-stimulated KOR activity selectively in

adolescents. As neither nicotine nor ethanol interact directly with KORs but do act on alpha7 nicotinic acetylcholine receptors (nAChRs), which have recently been shown to couple to G proteins, we went on to test the hypothesis that age-dependent inhibition of KOR activity by Nic+EtOH is due to drug-induced alpha7 nAChR activity. Brain tissue from drug naïve adult and adolescent male rats was processed for U69,593-stimulated [35S]GTPgammaS binding, with or without the alpha7 nAChR antagonist methyllycaconitine (MLA). Preliminary data do not support our hypothesis, but suggest that MLA inhibits agonist-stimulated [35S]GTPgammaS binding in the pVTA and MR. These data may suggest that there are novel interactions between KORs and alpha7 nAChRs in discrete reward-related brain areas.

## **Tu2. Training Future Clinicians Through Clinical Encounters in Neuroscience**

*Bradley Tanner\*, Mary Metcalf, Brian Tanner*

For the neuroscientist or clinical faculty member in psychiatry or neurology, creating and delivering learning cases is often time-consuming and challenging. With funding from NIDA, the current project created a platform that helps faculty acquire, modify, or create neuroscience teaching cases based on their prior work, and then deliver case-based instruction to students in a variety of engaging and decision-focused formats. The platform provides a standardized and consistent neuroscience training experience for students and enhances the consistency and capability of a single university. The Unity-based Creator application enables the educator to create cases from a template or modify an existing case uploaded by a fellow neuroscientist. The application supports the inclusion of images as well as branched path dialog requiring learners to make choices and in return receive tailored feedback based their decisions. Faculty upload the resulting XML file to the case-sharing platform, similar to how developers upload phone apps to an App Store. In the Learner application, learners varying from students in early training to established residents retrieve the XML file for the neuroscience case and explore a decision focused interactive experience. They interview the simulated patient through branched path decision making, review information and images, choose among assessment, diagnostic, and treatment options, and receive feedback based on those choices. The app supports different levels of difficulty with varying feedback or support. Learners can rate the experience and read fellow student reviews and ratings. Learner apps for different delivery modalities range from a smartphone to an Oculus VR Headset. The app reads the XML file for the case and formulates an experience tailored to that platform. Using a Phone-based Learner App, students can work individually or in a group that shares the experience. In the Oculus VR Learner App, the learner interviews the patient through prompted questions and receives a spoken response from the patient



using a text-to-speech engine in the proper language. The highly immersive experience targets conversational and cultural competency-based skills. Using the Tracker App, the administrator or faculty member can track individual and group progress and identify problems and successes as learners advance in the learning activity. The app reports if the student is meeting clinical competency standards in neuroscience topics such as alcohol and substance use, psychosis, epilepsy, brain tumors, and Alzheimer's disease. Collaborative creation and sharing of cases, combined with broad dissemination to a variety of delivery platforms, provide a comprehensive solution to case-based neuroscience training. By influencing critical skills and knowledge, the solution enhances the provision of high-quality neuroscience-based healthcare to patients.

### **Tu3. Alcohol in the Central Nucleus of the Amygdala: Sex Differences, Effect of Adolescent Alcohol Consumption, and Modulation by Neuropeptides**

*Christopher Knight, Sheketha Hauser, Richard Bell, R. Aaron Waeiss, Lauren Pratt, Zachary Rodd\**

Alcohol has both stimulator and anxiolytic actions. Ethanol (EtOH) is directly self-infused to the posterior ventral tegmental area (pVTA), nucleus accumbens shell (AcbSh) and the Central Nucleus of the Amygdala (CeA). Research examining the effects of comparable experimenter microinjections of EtOH into these brain structures has indicated that EtOH is anxiolytic in only the CeA (determined by social interaction, startle response, and open field behaviors). One of the main projections of the CeA is the bed nucleus of the stria terminalis (BNST). The CeA-BNST pathway is sexually dimorphic, and is thought to be a potential biological basis for the gender differences in the rate of anxiety and PTSD disorders in humans. In addition, there is a sex difference in rats for the number of CRF+ neurons in the CeA and the effect of adolescent alcohol consumption on the expression of CRF neurons in the CeA. The current experiments were designed to determine the effect of sex on the reinforcing properties of EtOH in the CeA, the effect of adolescent alcohol consumption on the reinforcing properties of EtOH in the CeA in both males and females, and to determine the role of neuropeptides mediating EtOH reward in the CeA. Male and female Wistar rats were exposed to alcohol (intermittent exposure model; AIE) or water during adolescence (post-natal day {PND} 28-48, 4 g/kg gavage; 25% v/v EtOH, every other day). On PND 90, rats were implanted with a guide cannula aimed at the CeA. One week after surgery, rats were placed in two-lever (active and inactive) operant chambers and were able to directly self-administer 0, 75, 100, 150, 200, or 250 mg% EtOH directly into the CeA. In vitro experiments suggest that the effects of EtOH on GABAergic and glutamatergic transmission within the CeA are modulated by activity at the corticotropin releasing factor 1 receptor (CRF1) and by the neuropeptide

Nociceptin. Experiments were designed to investigate the possibility that co-infusion of either the CRF1 antagonist NBI 35965 or Nociceptin would be able to block the rewarding effects of EtOH within the CeA. For this intracranial self-administration (ICSA) experiment, adult male Wistar rats were implanted unilaterally with guide cannulas aimed at the CeA. One week after surgery, rats were able to directly self-administer 200 mg% EtOH, a dose which is readily self-administered into the CeA. All rats were allowed to self-administer EtOH for the first 4 sessions (acquisition). During sessions 5 and 6, rats were randomly assigned to groups receiving co-infusion of 200 mg% EtOH and either 5 nM, 200 nM, 25  $\mu$ M, or 50  $\mu$ M of the CRF1 antagonist NBI 35965, or 100 or 500 nM Nociceptin. The data indicated that naïve female Wistar rats will readily self-administer 75 or 100 mg% EtOH directly into the CeA, while male rats required concentrations of 200 or 250 mg% to support self-administration behaviors. Exposure to the AIE protocol results in a leftward and upward shift of the EtOH dose-response curve in both male and female Wistar rats. The pharmacological data indicated that in naïve Wistar rats, CRF antagonists did not alter EtOH self-administration into the CeA, but co-administration of Nociceptin enhanced EtOH self-administration. The current data are the first data set that indicates a major sex difference for the reinforcing properties of EtOH within a brain region. In addition, adolescent EtOH exposure enhances the rewarding properties of EtOH in the CeA during adulthood. Together, the data indicate that EtOH reward in the CeA is complex in nature and is readily influenced by sex, past alcohol history, and regulated by neuropeptides. (AA024612, AA020908, AA07462, AA012262, AA022167).

## **Tu4. Forebrain Dopamine Value Signals are Independent of Midbrain Dopamine Cell Firing**

*Jeffrey Pettibone\*, Ali Mohebi, Arif Hamid, Jenny-Marie Wong, Robert Kennedy, Joshua Berke*

Dopamine is critical for both reinforcement-driven learning and motivation. The role in learning is thought to involve reward prediction errors encoded by abrupt changes in midbrain dopamine cell firing. Motivational value has been proposed to be conveyed by slower, “tonic” changes in dopamine cell firing. Here we directly compared the firing of midbrain dopamine cells with forebrain dopamine release, in unrestrained rats performing an adaptive decision-making task. Using microdialysis we found that dopamine release scales with value in specific hotspots, including nucleus accumbens core and ventral prelimbic cortex. These subregions receive their dopamine input from the ventral tegmental area (VTA). However, the tonic firing of optogenetically-identified VTA dopamine cells showed no relationship to motivational value. Furthermore, during waiting periods firing of VTA dopamine cells progressively decreased, while accumbens dopamine release progressively increased,

consistent with error and value coding respectively. We conclude that critical motivation-related aspects of dopamine release are controlled not by dopamine cell spiking, but instead by local influences over dopamine terminals within specific target regions.

## **Tu5. Net Gains and Losses: How Daily Fluctuations in Perineuronal Net Intensity May Impact Behavior**

*John Harkness\*, Jonathan Wisor, Priyanka Bushana, Ryan Todd, Will Clegern, Nathan Allen, Monica Chang, Barbara Sorg*

Extracellular matrix aggregations called perineuronal nets (PNNs) surrounding synapses of fast-spiking, parvalbumin (PV)-containing GABAergic interneurons. PNNs are important for stabilization of synapses following learning and for limiting plasticity after the critical period. Additionally, PNNs provide oxidative buffering capacity for PV cells. Chondroitin sulfates, which make up the majority of PNNs, provide oxidation/reduction reaction potential that act as a source of protection against oxidative stress. Oxidative stress increases in the brain during periods of wakefulness, and is alleviated by sleep. PNN intensity fluctuates with age, memory, experience, and drug exposure. We investigated whether PNN intensity also fluctuated throughout sleep/wake cycles. PNNs, oxidative stress, and PV intensity were quantified in the prefrontal cortex (PFC) at four time points (ZT0, ZT6, ZT12, ZT18) during the diurnal cycle. PNNs were significantly less intense at ZT6 compared to ZT0, and significantly more intense at ZT12 and ZT18. PV intensity was also significantly increased at ZT18, compared to ZT0. Additionally, a separate group of rats was sleep deprived for up to 12 hours and the intensity of PNNs, oxidative stress, and PV were measured in the PFC. Oxidative stress was elevated in PFC neurons of sleep deprived rats compared to those allowed to spontaneously sleep, and PV intensity was increased, but PNN intensity did not differ with sleep deprivation. We determined that PNNs fluctuate throughout the sleep/wake cycle; however, this pattern was not altered by disrupting sleep. One possibility is that 12-hr sleep dep was not sufficient to disrupt the rhythm of PNN fluctuation. Alternatively, PNN intensity may correlate with cellular oxidative stress levels on a biphasic curve such that PNNs increase with cellular oxidative stress until a point when oxidative degradation of chondroitin sulfates outpaces PNN production.

## **Tu6. Sex Differences in Optogenetic Self-Stimulation of Excitatory Inputs to the Nucleus Accumbens Shell and Subsequent Locomotor Sensitization to Morphine**

*Erin Larson\*, Natalie Steenrod, Keelia Silvis, Ethan Huffington, Paul Mermelstein, Mark Thomas*

Sex differences in the vulnerability for addictive behavior are well documented, yet the circuit mechanisms mediating these differences remain unclear. Previous work in our lab has shown that cocaine-related plasticity at excitatory inputs to the nucleus accumbens shell (NAcSh) is associated with altered sensitivity to optogenetic self-stimulation behavior in a four-corner, open-field spatial task. Here, we expanded on these studies in order to identify sex differences in responding for optogenetic self-stimulation of glutamatergic inputs to the NAcSh and to examine the effects of prior exposure to optogenetic self-stimulation on the subsequent development of morphine locomotor sensitization (10 mg/kg, i.p.). To target specific NAcSh inputs, mice were injected with AAV2-CamKII-hChR2(H134R)-EYFP into either the infralimbic cortex (ILC), ventral hippocampus (vHPC), basolateral amygdala (BLA), or periventricular thalamus (PVT). Mice had optical fibers implanted over the NAcSh to allow for input-specific circuit activation (10 Hz) upon entry into one of the four corners of the spatial arena during self-stimulation testing. One week after self-stimulation testing, mice were exposed to morphine (10 mg/kg, i.p.) and the development and expression of locomotor sensitization was assessed. We found that drug-naïve females exhibited more robust self-stimulation of ILC-NAcSh projections and less self-stimulation of vHPC-NAcSh inputs compared to males (10 Hz). Females also showed estrus cycle-dependent alterations in self-stimulation behavior that differed depending on the input being stimulated. Interestingly, prior exposure to optogenetic self-stimulation also produced sex- and input-dependent effects on subsequent sensitization to chronic morphine exposure, with females being more sensitive to stimulation-related alterations in morphine sensitization. Together, these findings demonstrate NAcSh circuit-specific effects of sex and gonadal hormones on glutamate-mediated reward and addiction-relevant behaviors. Funding: This work was supported by DA041808 (MJT and PGM) and the University of Minnesota MnDRIVE Brain Conditions (MJT and EBL).

## **Tu7. Adaptive Immunity in Depressive Mood States**

*Stacey L. Kigar, Virginia H. Sun, Abdel G. Elkahoul, Miles Herkenham\**

Clinical and genome-wide association studies show a strong correlation between aberrant peripheral immunity and major depression in a subset of patients. Additionally, introducing cytokines into the body as a treatment for cancer in otherwise non-depressed patients was shown to induce depressive symptoms, suggesting that the immune system may play a role in the etiology

of depression. However, the relative impenetrability of the blood brain barrier (BBB) to immune cells and cytokines has led researchers to examine the immunogenic properties of the meninges, where lymphocytes of the adaptive branch of the immune system reside in abundance. Our laboratory recently showed that adoptive transfer of lymphocytes from chronically stressed donor mice conferred an anti-depressant effect in recipients (Brachman et al., 2015). This led us to hypothesize that (1) chronic stress alters the transcriptional profiles and signaling potential of T lymphocytes, and (2) that T cells within the meningeal compartment secrete brain-penetrant factors that modify the central milieu and thereby alter neuronal function in stress circuits controlling affective behavioral phenotypes. To investigate these hypotheses, we conducted microarray, bioinformatic, flow cytometric, and immunohistological analyses to compare two groups, chronic social defeat (CSD) and home cage (HC) mice, and characterize stress-induced alterations in T cells from spleen, lymph nodes, and meninges. Ongoing work is exploring the possibility that meningeal T cells release BBB-permeable, microRNA (miRNA)-containing extracellular vesicles, i.e., exosomes. Our preliminary data suggest that trafficking, activation status, and mRNA content of T cells is altered considerably by CSD, and we propose that these changes impinge on the brain to affect mood.

## **Tu8. Dysregulation of Non-CG Methylation by Child Abuse**

*Gustavo Turecki\**

Background: Child abuse, which includes sexual abuse, physical abuse, psychological abuse, and parental neglect, are prevalent in our society, with rates in Canada ranging from 8 to 26% depending on the specific type of abuse. Child abuse is associated with increased lifetime risk of negative mental health outcomes, including suicide. A growing number of studies suggest a relationship between child abuse and lifetime morphological and functional changes in the amygdala, a brain structure critically involved in emotional regulation, and these changes are likely mediated by epigenetic regulation. Methods: Using postmortem brain tissue from a well-characterized cohort of subjects with histories of severe child abuse (N=21) and normal controls (N= 17), we conducted whole genome bisulfite sequencing (WGBS-Seq), RNA-Seq and Chip-Seq (H3K4me1, H3K4me3, H3K27ac, H3K36me3, H3K9me9 and H3K27me3) to obtain a comprehensive map of epigenetic changes in the amygdala associated with child abuse. Results were then validated and replicated in an extended and independent cohort (N=88) Results: Recent data suggest that non-CG DNA methylation is strongly enriched in brain tissue and progressively accumulates during the first few years of life. We thus postulated that child abuse may impact on non-CG methylation. Therefore, we conducted parallel analyses of DNA methylation differences in the CG

context and in the CAC context, which exhibited the highest genome-levels of non-CG DNA methylation. Results indicated that, surprisingly, a history of child abuse associates with epigenetic adaptations that are as frequent in the CAC as in the reference CG context. By incorporating information on histone modification in the DNA methylation analysis, we observed that the cross-talk between these 2 epigenetic layers strikingly differs among CG and CAC contexts. Importantly, we also found that differentially methylated regions associated with child abuse occur in distinct chromatin states in the CG and CAC contexts, as revealed using ChromHMM. We then further investigated the most significant differentially methylated regions that showed evidence of functional impact at transcriptional level. Initially, these results were technical validated, and subsequently, replicated in an independent cohort of individuals, including individuals with histories of child abuse and controls. Conclusions: Our results unravel a previously uncharacterized source of epigenetic plasticity in the brain, which may help us explain the lifelong impact of early-life adversity on brain function, and contribute to the negative mental health outcomes that are strongly associated with child abuse.

## **Tu9. Effects of Outcome Devaluation on Sign- and Goal-Tracking**

*Cristina Maria-Rios, Christopher Fitzpatrick, Trevor Geary, Jonathan Morrow\**

When a neutral stimulus is repeatedly paired with an appetitive reward, two different types of conditioned approach responses may develop: a sign-tracking response directed toward the neutral cue, or a goal-tracking response directed toward the location of impending reward delivery. Sign-tracking responses have been postulated to result from habitual processes that are insensitive to outcome devaluation, while goal-tracking may develop from a more explicit cognitive representation of the associated outcome. However, Pavlovian responses are typically sensitive to outcome devaluation, and the published literature has been inconsistent on the sensitivity of sign-tracking to devaluation. We therefore tested sign- and goal-tracking before and after devaluation of a food reward using lithium chloride, and tested whether either response could be learned under negative contingency conditions that precluded any surreptitious reinforcement of the behavior that might support instrumental learning. We found that sign-tracking was sensitive to outcome devaluation, while goal-tracking was not. We also confirmed that both responses are Pavlovian because they can be learned under negative contingency conditions. These results indicate that sign- and goal-tracking follow different rules of reinforcement learning and suggest a need to revise current models of associative learning to account for these differences.

## **Tu10. The Contribution of Rodent Secondary Motor Cortex to Feedback Guided Actions**

*Drew Schreiner\*, Joselyn Perez, Christina Gremel*

Feedback is essential for guiding our actions, and can take several forms, from ongoing, internal representations of progress to extrinsic events like the consequences of our actions. However, the neural mechanisms responsible for integrating feedback during action selection are unclear. We developed a novel, self-initiated, self-paced, and un-cued instrumental test in mice to assess action feedback. Mice are trained to hold down a lever for at least a given duration to earn a food reward across days (i.e. >400ms to >800ms to >1600ms). We found that mice modify their lever press duration based on whether or not they successfully reached the target on the previous press. If mice meet the target, on average their next press will be of a shorter duration, whereas if they fail to meet the target they will increase the duration of their next press. We observed a role for both internal as well as external feedback, as feedback was present whether or not mice checked for a food outcome (albeit at different magnitudes). Further, in outcome devaluation studies, action feedback was present during goal-directed as well as habitual control (though with greater magnitude in the devalued state). Thus, while the action appeared to be under habitual control mice still modified the performance of that action based upon feedback. Since secondary motor cortex (M2) has been implicated in associative integration necessary for action selection, we have begun to examine its role in action feedback. Preliminary evidence suggests M2 lesion prior to acquisition impairs learning of the task while acute chemogenetic inhibition of M2 after learning similarly impairs performance and decreases feedback magnitude. Ongoing work is examining the role of M2 activity during the action and its ability to generate feedback information. Our initial results provide evidence for M2 as a key locus in utilizing internally and externally generated evidence (e.g. feedback) to select and control actions.

## **Tu11. A Prefrontal-Basal Forebrain Circuit Shapes Neuroendocrine and Behavioral Stress Responses**

*Shane Johnson\*, Rachel Anderson, Ryan Lingg, Eric Emmons, Sara Romig-Martin, Nandakumar Narayanan, Ryan Lalumiere, Jason Radley*

The prelimbic subfield (PL) of the medial prefrontal cortex has received considerable attention for its role in directing stress responses, yet the circuit basis underlying these functions has remained obscure. Our previous work has implicated the anteroventral subdivision of the bed nuclei of the stria terminalis (avBST) as a neural hub for integrating information from the limbic forebrain, and in the coordination of hypothalamo-pituitary-adrenal (HPA) and behavioral coping responses via divergent pathways. These observations raise the prospect that avBST offers a substrate for the prefrontal cortex to

coordinate neuroendocrine and behavioral responses to bias the organism toward certain response strategies. To interrogate the role of the PL–avBST pathway in stress integration, we employed an optogenetic approach to assess the effects of bidirectionally manipulating this pathway on HPA and behavioral responses in several acute challenges. In the first experiment, photoinhibition of Arch-expressing (archaerhodopsin eArch3.0) PL neuron axons in avBST during 10 min tail suspension augmented immobility ( $p < 0.05$ ) and HPA output (corticosterone [CORT], 30 min after stress onset;  $p < 0.05$ ), as compared with YFP controls. Next, we examined the role of this circuit in a behavioral paradigm that allows for the expression of a broader range of behaviors, including both active and passive coping responses. PL–avBST pathway inactivation during the shock-probe defensive burying (SPDB) test increased passive (freezing) and decreased active (burying) behaviors ( $p < 0.05$  for each) with respect to YFP control rats, without affecting general ambulatory behavior. Finally, we assessed the effects of bi-directionally modulating activity in the PL–avBST pathway on active and passive behaviors during SPDB by photostimulation of Halo (halorhodopsin eNpHR3.0) or ChR2 (channelrhodopsin ChR2[E123A]). Terminal photoinhibition via Halo produced the same effects as Arch in augmenting passive and abrogating active coping responses in SPDB, while channelrhodopsin decreased passive freezing behavior ( $p < 0.05$ ). These studies identify a novel circuit for promoting the inhibition of both HPA output and passive coping responses, and provide a novel mechanism linking a loss of top-down control with perturbations in endocrine and behavioral coping responses such as in stress-related mood disorders.

## **Tu12. Lactobacillus Reuteri Administration Alters Social Affiliation and Neurochemical Marker Expression in the Brain in Female Prairie Voles**

*Meghan Donovan\*, Yan Liu, Georgia Platt, Kathryn Jones, Zuoxin Wang*

Accruing evidence suggests a role of gut microbiota on clinically relevant behaviors including anxiety and depression. One species of bacteria in the gut, *Lactobacillus reuteri*, has been implicated in various studies for its ability to alter behaviors – including social deficits. However, we know little about how *L. reuteri* affects neurochemical systems in the brain, which may mediate the behavior. The socially monogamous prairie vole (*Microtus ochrogaster*) displays high levels of social behaviors and provides an opportunity to study those behaviors, their influences by endogenous and environmental factors, and the underlying mechanisms. Using adult female prairie voles, we tested the hypothesis that administration of *L. reuteri* may alter social behaviors and neurochemical systems in the brain. We administered *L. reuteri* into the drinking water of voles daily for 4 weeks while a control group was



administered heat-killed *L. reuteri*. Subjects then went through a series of tests for locomotion, anxiety-like, and social affiliation behaviors. Our data show that subjects which were administered live *L. reuteri* displayed decreased social affiliation compared to controls. Subject brains were collected following behavioral testing and processed for neurochemical expression in selected brain areas implicated in social affiliation and anxiety-like behaviors. Our data indicate that administration of live *L. reuteri* decreased corticotrophin releasing factor (CRF) and CRHR2 receptor levels in the nucleus accumbens, and decreased vasopressin 1a-receptor (V1aR) but increased CRF in the paraventricular nucleus compared to controls. These data demonstrate a behavior-, neurochemical-, and region-specific effect of *L. reuteri* in prairie voles. We are currently examining the composition of stool samples collected pre- and post-administration of *L. reuteri* to determine specific alterations to microbiota. (Supported by USDA-NIFA 2014-67013-21579 to KMJ and NIMH 058616-R01 and 108527-R01 to ZXW).

### **Tu13. Laminar Distribution of High Frequency Oscillations in the Epileptic Brain Induced by Focal Cortical Dysplasia in Mice**

*Qian-Quan Sun\**

The epileptic brain is often associated with the presence of high-frequency oscillations (>25 Hz) that have recently gained attention as potential biomarkers to help define the cortical seizure zone. Here we evaluate the aberrant spectral architecture and spatial distribution of high-frequency oscillations associated with spontaneous spike-wave discharges (SWDs) patterns in an experimental mouse model of focal cortical dysplasia induced by neonatal freeze lesions to the right S1 cortex. Chronic bipolar recordings from awake, behaving animals indicated a high prevalence of spontaneous spike-wave discharges SWDs in 83% (10/12) of animals exposed to the freeze lesion injury as evaluated at 5-11 months of age. Spike-wave discharges SWDs were associated with a strong increase in high-frequency oscillations locked to the spike/wave seizure pattern and largely confined to the ipsilateral S1 cortex. Acute recordings with linear micro-electrode arrays from the ipsilateral S1 cortex during periods of 'hyper-excitability' burst-suppression events indicated significant increases in spectral power across cortical lamina of freeze-lesioned animals with peak increases at 10 Hz. In addition, freeze-lesioned animals exhibited spontaneous bursts of high-frequency activity, confined predominately to granular and supragranular layers, while control animals exhibited minimal changes in 'ultra-high' frequency responses above 100 Hz (i.e. ripple waves). Spectral disruption of the freeze-lesioned brain also included a distinct pattern of altered cortical signaling as indicated by significant frequency-dependent increases in spectral coherence across the supragranular

layer (50-200 Hz) and subsequent decreases in the lower cortical layers (15-70 Hz). Spike sorting of well-isolated single-units recorded from freeze-lesioned S1 cortex indicated a differential spontaneous firing pattern of putative excitatory versus inhibitory cells. Excitatory cells were predominately observed in the outer cortical layers and showed only weak association with high-frequency activity while the deeper inhibitory units were strongly phase-locked to fast ripple oscillations (300-800 Hz). The spontaneous cyclic spiking of cortical inhibitory cells appears to be the driving substrate behind high-frequency oscillations and may prove useful in identifying regions of hyperexcitable tissue in the epileptic brain. As demonstrated in the current study, the utilization of commercially available electrode arrays offers a powerful high-resolution tool for mapping the aberrant in vivo cortical circuitry of seizurogenic tissue and identification of key cellular markers underlying brain hyperexcitability that may help guide clinical diagnosis and treatment of the epileptic brain.

## **Tu14. More Severe Clinical Deficits are Associated With Greater Disruption of the Blood Brain Barrier During the First 24 Hours After Brain Hemorrhage**

*Richard Leigh\*, Emi Hitomi, Shahram Majidi*

**Background:** Primary intracerebral hemorrhage (ICH) is thought to be associated with a diffuse inflammatory response that is likely detrimental and results in opening of the blood-brain barrier (BBB). The time course of this process is not well understood.

**Methods:** Patients with acute primary ICH who had a perfusion weighted MRI scan within the first 24 hours were identified from the NIH Natural History of Stroke study. BBB permeability images were generated from those who had adequate quality perfusion weighted source images. A whole brain permeability measure was calculated as the mean value of voxels demonstrating increased permeability due to gadolinium accumulation in the parenchymal space.

Permeability, which is expressed as a percent leakage, was compared with the admission NIH Stroke Scale (NIHSS) score and discharge modified Rankin scale (mRS) using linear regression. Poor functional outcome on discharge was defined as discharge mRS > 3. **Results:** A total of 20 patients were included in the analysis. The mean age was 63 years. The median NIHSS score and mean hematoma size was 5 and 9.6 mL, respectively. The average initial systolic blood pressure was 179 mmHg. Higher NIHSS score on admission was significantly associated with the severity of BBB disruption ( $p=0.008$ ). For the 17 patients who had mRS recorded on discharge, there was a trend to worse outcome with higher BBB disruption ( $p=0.058$ ) with twice the likelihood of a poor functional status at discharge [OR; (95%CI): 2.33; (-0.47-5.15)] for every 1 percent increase in whole brain BBB disruption. **Conclusions:** BBB disruption is higher

in ICH patients with a poor clinical status within hours of presentation. These findings suggest a rapid inflammatory response plays a role in ICH-induced brain injury.

## **Tu15. Voltammetry for Studying Neuroenergetics: A Progress Report**

*Greg McCarty\*, Leslie Sombers*

Voltammetry enables the real-time, continuous monitoring of changes in electroactive species in discrete brain nuclei. With sub-second temporal resolution, voltammetry enables changes in neurochemical concentrations, such as dopamine, to be correlated with behavioral data. To date, voltammetry has been limited to monitoring dopamine release in the striatum. Recent advances by our lab and others have enabled detection of new molecular targets with voltammetry. Of particular interest to us are voltammetric tools for studying neuroenergetics. This poster will review the progress on creating new voltammetric sensors and schemes for monitoring metabolic-related substrates, such as pH, glucose, lactate, oxygen and blood flow. For example, the modification of single carbon-fiber electrodes with a glucose oxidase (GOx) enables changes in glucose availability to be recorded within discrete locations in the brain while maintaining the beneficial properties of voltammetry. The GOx sensor has been used to simultaneously monitor dopamine release and changes in glucose availability during electrical stimulation of the mid-brain. Moreover, the hydrogel encapsulated methodology utilized for the GOx modified electrode (GOx EME) was adapted for monitoring a controversial neuroenergetic chemical, lactate. This lactate oxidase biosensor was fully characterized in vitro and combined with the GOx EME. Together, these biosensors simultaneously monitored vital neuroenergetic molecules under increased metabolic demand within the rat striatum. Similar studies for pH and oxygen sensing with voltammetry will also be reviewed. Finally, our research on microscale blood flow sensor will be described.

## **Tu16. Reelin Signal Activation is Associated With Motor Function Recovery in the Neuron Transplantation of Hemiplegic Mice**

*Nagisa Nakata-Arimitsu\*, Jun Shimizu, Kenji Takai, Chieko Hirotsu, Yoko Okada, Naruyoshi Fujiwara, Noboru Suzuki*

Neural cell transplantation is thought to be one of promising strategies for treating brain damage. The aim of this study was to investigate whether neuron transplantation and signal activation through paracrine would be associated with motor function recovery in hemiplegic mice. The mouse brain which had been cryoinjured was grafted with neuronal cells in the striatum under the

damaged motor cortex. We dissected the brains sequentially after the injury and cell transplantation and then analyzed the dissected brain. We observed strong expression of Reelin one day after the injury (day 1), mainly in the glial cells around the damaged site of the hemiplegic model mice. The level of the expression increased gradually for one week and decreased gradually until approximately day 28. We transplanted neural stem/progenitor cells obtained from wild-type B6 mice into the ipsilateral striatum of the hemiplegic mice. The grafts migrated and reached the injured cortex from the transplanted site at day 28, three weeks after the transplantation. The transplantation significantly improved the motor function of the injured mice at day 28 in beam walking and Rotarod test.

The immunohistochemistry analysis revealed that the transplanted cells at day 7 expressed ApoER, VLDLR, and phosphorylated Dab1, suggesting the involvement of Reelin signaling in the cell activity. The transplanted cells at day 28 expressed Crim1 and CTIP2, both of which are primary motoneuron markers. The grafts expressed Ncam, Ncad, and Integrin $\alpha$ 5 $\beta$ 1, which indicates that they migrated to the injured cortex through the function of such Reelin-downstream adhesion molecules. These results suggest that neurons or paracrine factor may be effective to restoring the motor functions of patients suffering from hemiplegia.

## **Tu17. Gi/o Protein-Coupled Receptors Inhibit Neurons but Activate Astrocytes and Stimulate Gliotransmission**

*Caitlin Durkee\*, Ana Covelo, Justin Lines, Alfonso Araque*

G protein-coupled receptors (GPCRs) play key roles in intercellular signaling in the brain. Their effects on cellular function have been largely studied in neurons, but their functional consequences on astrocytes are less known. Using both endogenous and chemogenic approaches with DREADDs, we have investigated the effects of Gq and Gi/o GPCR activation on astroglial Ca<sup>2+</sup>-based activity, gliotransmitter release, and the functional consequences on neuronal electrical activity. We found that while Gq activation led to cellular activation in both neurons and astrocytes, Gi/o activation led to cellular inhibition in neurons and cellular activation in astrocytes. Additionally, astroglial activation by either Gq or Gi/o protein-mediated signaling stimulated gliotransmitter release, which increased neuronal excitability. Activation of Gq and Gi/oDREADDs in vivo increased astrocyte calcium activity and modified neuronal network electrical activity. Present results reveal additional complexity of the signaling consequences of excitatory and inhibitory neurotransmitters in astroglia-neuron network operation and brain function.

## **Tu18. Homeostatic Mechanisms and the Nerve-Muscle Interaction**

*Sonsoles de Lacalle\*, Sophia Mort, Dallin Tavoian*

The long-term goal of our work is understanding neural mechanisms underlying the maintenance of homeostasis in response to fluctuations in muscle mass, and the plastic changes that are responsible for motor learning. It has been well documented that deletion of the myostatin gene results in muscle hypertrophy, and we are taking advantage of this fact to induce experimental changes in muscle size. Our first set of studies show that deleting myostatin in muscle induced substantial dysregulation of signaling pathways in the brain. Using the SuperArray Pathway Finder analysis (from SABiosciences) on brain samples (n=4 per group) taken from the hypothalamus of wild type (WT) and constitutive myostatin knock-out (KO) mice. Data is expressed as the ratio KO/WT. We found a profound effect on the mitogenic, Wnt, hedgehog, p53, stress, NFkB, NFAT, CREB, calcium/PKC, phospholipase, LDL, and retinoid pathways, and statistically significant changes in the levels of expression of a number of genes, such as Brca1 (3.1-fold decrease), Rbp1 (2.6-fold decrease), Wnt2 (2.34-fold decrease), and Jun (1.85-fold decrease). [FIGURE] To avoid potential confounding factors when a gene is knocked out throughout development, we have established a conditional gene knock-out mouse model, in which muscle-specific deletion of exon 3 of the myostatin gene results in muscle hypertrophy. Current partial analysis suggests that 14 weeks of doxycycline administration in the chow (which activates the cre/lox system and induces gene deletion) results in a decrease in plasma levels of active myostatin protein, a reduction in steroid hormones, an increase in the percent of lean mass and an increase in front limb absolute force (using a grip strength meter). Analysis of changes in signal transduction cascades in the brain of these animals is under way.

## **Tu19. The Role of Endogenous Chaperone Protein RTP4 in Opioid Receptor Heteromer Regulation**

*Wakako Fujita\**

A number of studies have revealed that MOPr and DOPr associate to form heteromers in brain regions involved in pain processing and that the levels of these heteromers (MOPr-DOPr) are upregulated following chronic morphine administration under a paradigm that leads to the development of antinociceptive tolerance. However, very little is known about the mechanism underlying MOPr-DOPr upregulation in the brain. A previous study reported that a chaperone, the receptor transporter protein 4 (RTP4), enhanced the cell surface expression of MOPr-DOPr by protecting heteromers from ubiquitination and proteosome-mediated degradation. Here we describe studies to characterize the regulation of RTP4 by opiates. We find that

treatment of cells co-expressing MOPr and DOPr with opioid receptor ligands leads to a significant increase in RTP4 mRNA expression. This effect is specific to opioid receptors since ligands targeting other G protein-coupled receptors such as serotonin or dopamine, do not lead to this increase in RTP4 expression. Moreover, chronic morphine administration to mice induces a significant increase in RTP4 expression in distinct brain regions. This effect is specific to RTP4 since chronic morphine administration does not lead to increases in other related chaperones such as other RTPs (1 to 3) or receptor expression enhancing proteins (REEPs). Interestingly, in the regions with RTP4 upregulation following chronic morphine administration we observe increases in the levels of MOPr-DOPr and of MOPr with no changes in the levels of DOPr, CB1 cannabinoid or D2 dopamine receptors. Finally, knock-down of RTP4 by intracerebroventricular injection of shRNA leads to increases in stress and body weight. Together these results suggest an important role for RTP4 in regulating MOPr-DOPr after long-term opioid treatment and in modulating stress- and reward-related behaviors. Supported by JSPS KAKENHI grants 16K19214 (to WF).

## **Tu20. Peptide Based Inhibitor of the Scaffolding Protein PICK1 Underlying Maladaptive Synaptic Plasticity**

*Marta De Luca, Nikolaj Riis Christensen, Mette Richner, Kristian Strömgaard, Ulrik Gether, Christian Bjerggaard Vægter, Kenneth Madsen\**

Background: Ionotropic glutamate receptors are responsible for the majority of the excitatory neurotransmission in both the central and peripheral nervous system. Different functional modalities of the glutamatergic synapses are encoded in a complex multiprotein machinery - including many scaffolding proteins, receptors, etc. - termed the Post Synaptic Density (PSD), that allows individual synapses to generate highly specific biological responses to differential external stimuli. Among the scaffolding ensemble involved in the synaptic plasticity of glutamatergic synapses, PICK1 is a promising pharmacological target. Aim: The pharmacological targeting of specific intracellular components of PSD enables a selective modulation of discrete responses rather than affecting general excitatory neurotransmission. In this way, serious side effects might be reduced opening new ways of treating diseases involving glutamatergic dysfunctions, such as neuropathic pain. Method: Mechanical Allodynia has been evaluated by von Frey filaments to determine the paw withdrawal threshold. Furthermore repeated administrations and dose dependence experiments have been performed. Results: We have developed a PICK1 peptide inhibitor showing a target affinity in the low nanomolar range. Intrathecal injection of the peptide in mice, hypersensitized by the spared nerve injury model of persistent peripheral neuropathic pain, reversed the mechanical allodynia for an extended period of time in a dose dependent manner.

Conclusions: The pharmacology of ionotropic glutamate receptors remains strongly underdeveloped. Although numerous diseases, including neuropathic pain, involve over-activation or sensitization of the glutamate system. We have developed a new lead compound with a great potential as a new treatment for neuropathic pain.

## **Tu21. New Insights into Mechanisms Regulating Central Release of Neuropeptides**

*Javier Stern\**

Vasopressin (VP) neurons of the hypothalamic paraventricular nucleus (PVN) release VP from their neurohypophyseal axonal terminals into the blood stream. This occurs in an activity-dependent manner, requiring the anterograde propagation of action potentials. In addition to this canonical stimulus-secretion coupling model, recent studies show that VP can also be locally released from dendrites, and that acting in a volume-transmission manner, dendritically released VP recruits and coordinate the activity of distant presympathetic PVN neurons to generate an osmotically-driven sympathoexcitatory response (Son et al Neuron 2013). Still, the fundamental mechanisms regulating neuropeptide dendritic release remain unknown. Performing simultaneous dual patch recordings from somata and dendrites, we show that in a proportion of VP neurons, somatic action potentials efficiently backpropagate to dendrites, generating a robust  $\text{Ca}^{2+}$  signal ( $3.5 \pm 0.8 \text{ F/F}_0$ ,  $p < 0.001$ ), particularly within dendritic varicosities. However, backpropagating action potentials were observed in less than 30% of recording neurons (6/30 cases). Conversely, we observed in the majority of neurons spontaneously occurring dendritic spikes, that occurred independently, or even in the absence of somatic action potentials. Dendritic spikes were completely blocked by TTX ( $n = 8$ ,  $p < 0.05$ ) and their frequencies were significantly enhanced by bath-applied NMDA ( $n = 12$ ,  $p < 0.001$ ), independently again of somatic firing discharge. Taken together, our results support the presence of a highly compartmentalized electrical activity in somatic and dendritic compartments in neurosecretory VP neurons. Based on the fact that NMDA receptors constitute a robust mechanism to evoke dendritic release of VP, we are currently testing the hypothesis that dendritic action potentials, independent from somatic firing, constitutes a key mechanism contributing to dendritic release of neuropeptides.

## **Tu22. A Mechanistic Approach to Neuroprotective Potential of Zonisamide in Seizures: Pharmacokinetic & Pharmacodynamic Link**

*Baldeep Kumar\*, Bikash Medhi, Manish Modi, Biman Saikia*

Epilepsy is a chronic neurological condition characterized by recurrent seizures, almost affects people in every country throughout the World. Recently, the neuroscientists and neurologists have investigated the use of antiepileptic drugs to prevent neuronal loss and the neurological impairment which is commonly seen with the progression of epilepsy. In this study, we evaluated the pharmacokinetics and neuroprotective effects of zonisamide in maximal electroshock (MES) induced seizures in rats. MES induced seizures lead to increased oxidative stress, activation of neuroinflammatory pathway and neuronal death. Our results indicated that treatment with zonisamide significantly protected the animals against MES induced seizure activity and reactive oxygen species production at different time intervals following drug administration. The inflammatory processes in the brain contribute to the etiopathogenesis of seizures and epilepsy and this is increasingly recognized as a result of supportive evidence in experimental models and in the clinical setting. In this study, we found a significant increase in inflammatory mediators after MES seizures. However, the administration of zonisamide abolished the activation of neuroinflammatory cytokines. Together, these findings indicated the neuroprotective potential of zonisamide by preventing oxidative neuronal damage and activation of brain inflammatory mediators in seizures. These neuro-pharmacodynamic effects of zonisamide are directly linked to its brain pharmacokinetics.

**WEDNESDAY, JANUARY 17 • 3:30 P.M. - 4:30 P.M. • SEA TO SKY BALLROOM B**

## **W1. Unbiased Profiling of the Cellular Targets of Low-Dose Ethanol**

*Daniel Bloodgood\*, Lara Hwa, Thomas Kash*

Most previous studies examining the effects of alcohol on the brain have focused on relatively high concentrations of ethanol. However, behavioral testing in humans shows that even low concentrations of ethanol resulting from only a few drinks (<10mM) can disrupt inhibitory control, motor coordination, and information processing (Hindmarch et al. 1992; Fillmore et al. 2009). By studying how low doses of alcohol affect the brain, we can better understand what brain substrates mediate the initial rewarding properties of ethanol, and how these may contribute to the development of alcohol addiction. Here we take an unbiased approach to answer this question using whole brain tissue clearing with immediate early gene mapping in response to administration with a low dose of ethanol. In this study, adult male C57BL/6J mice were



orally gavaged with 0.6 g/kg of ethanol or water, resulting in an average BEC of 30 mg/dL in ethanol treated animals. Ninety minutes following alcohol administration, animals were perfused and underwent immunolabeling for the immediate early gene c-Fos using the iDISCO+ protocol developed by Renier et al. (2016). Following sample preparation, cleared brains were imaged intact using light sheet microscopy. Automated c-Fos segmentation and alignment to a reference atlas was implemented in Python using the CLEARMAP pipeline (Renier et al. 2016). Preliminary analysis showed that low dose ethanol resulted in the greatest increase in c-fos in the central amygdala and gustatory areas, and the greatest decrease in the parabrachial nucleus and the hippocampus. Future studies will use Channelrhodopsin circuit mapping driven by immediate early gene promoters to identify outputs of activated cells in these brain regions.

## **W2. $\alpha$ -MSH-Mediated Regulation of VTA MC3R Neuron Activity**

*Katherine West\*, Aaron Roseberry*

The mesocorticolimbic dopamine system, the brain's reward system, regulates multiple behaviors including food intake, food reward, and feeding related behaviors, and there is substantial evidence that the melanocortin system of the hypothalamus, an important neural circuit regulating feeding and body weight, interacts with the mesocorticolimbic dopamine system to affect feeding and food reward. For example, melanocortin-3 (MC3R) receptors are expressed in the ventral tegmental area (VTA), and both POMC and AgRP neurons (which are the center of the melanocortin system) project to the VTA. We have also shown that injection of the MC3R agonist, MTII, directly into the VTA decreases home-cage food intake, sucrose and saccharin intake in 2-bottle choice tests, and operant responding for sucrose pellets, whereas injection of the MC3R antagonist, SHU9119, into the VTA increases home-cage food intake and operant responding for sucrose pellets. Furthermore, previous research has shown that injection of  $\alpha$ -MSH into the VTA increases dopamine turnover at downstream targets. Thus,  $\alpha$ -MSH can clearly act in the VTA to affect food intake and food reward, likely through activation of dopamine neurons, but the cellular mechanisms underlying the effects of intra-VTA  $\alpha$ -MSH on feeding and food reward are unknown. To determine how  $\alpha$ -MSH acts in the VTA to affect feeding, we performed electrophysiological recordings in acute brain slices from mice expressing EYFP in MC3R neurons to test how  $\alpha$ -MSH affects the activity of VTA MC3R neurons. Here, we show that  $\alpha$ -MSH significantly increases the firing rate of MC3R VTA neurons, and we examine the mechanisms underlying this increase in activity. Overall, these studies provide an important advancement in the understanding of how  $\alpha$ -MSH acts in the VTA to affect feeding and food reward.

### **W3. Altered Dopamine-Stimulated Reward Seeking and Endocannabinoid Activity due to Adolescent Cannabinoid Receptor Stimulation**

*Adam Manoogian\*, Mitchell Farrell, Christina Ruiz, Jeffery Huang, Jenny Cevallos, Kwang-Mook Jung, Guillermo Moreno-Sanz, Daniele Piomelli, Stephen Mahler*

Adolescence is a critical window of maturation for reward-related brain circuits, in part orchestrated by endocannabinoid (ECB) signaling. ECB signaling regulates ventral tegmental area (VTA) dopamine (DA) projections to forebrain regions like nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) in adults, and development of these circuits is altered by exogenous cannabinoid receptor stimulation during adolescence. Here, we test whether chemogenetic stimulation of VTA DA neurons in adult rats reveals altered ECB function caused by adolescent cannabinoid receptor stimulation (ACRS). Rats were treated with CB1/2R agonist, WIN 55,212-2, or vehicle during postnatal days 30-43. Cre dependent excitatory (hM3Dq) designer receptors exclusively activated by designer drugs (DREADDs) were bilaterally expressed in VTA DA neurons (or not expressed in Cre-negative littermate controls), thereby allowing excitation of DA neurons upon application of the DREADD activator, clozapine-N-oxide (CNO). ACRS and control rats were trained to self-administer palatable food pellets and a light+tone cue for 10 days, then underwent two consecutive extinction training sessions after injection of CNO (10mg/kg). Additional drug-free extinction training was then conducted until criterion was met (<25 active lever presses/day), followed by two cue-induced reinstatement tests after counterbalanced CNO and vehicle injections. Rats also underwent locomotor activity tests following CNO or vehicle, after which they were sacrificed for analysis of Fos expression in NAc and subregions of mPFC. Additional rats were used to examine DA DREADD stimulation of ECB levels in NAc and mPFC. We found that VTA DA neuron stimulation with hM3Dq DREADDs + CNO, but not CNO alone, caused distinct effects in ACRS and control rats. In ACRS rats, DA-stimulated reward seeking was potentiated, and ECB and Fos responses within mesocorticolimbic subregions were altered. This suggests that adolescent WIN exposure persistently alters ECB signaling recruited by DA, affecting circuit activity and behavior.

## **W4. Acute Chemogenetic Inhibition of Accumbal Dopamine has Sexually Dimorphic Effects in a Rat Analogue of the Iowa Gambling Task**

*Tristan Hynes\*, Jacqueline Ferland, Tanya Feng, Wendy Adams, Mason Silveira, Catherine Winstanley*

In humans, the Iowa Gambling Task (IGT) has been used to assess both risky decision-making and action impulsivity, which are key neurocognitive endophenotypes of addiction. Critically, we have developed a rodent analogue of the IGT [the rodent gambling task (rGT)] and demonstrated that risky decision-making predicts the propensity of rats to intravenously self-administer cocaine. The maintenance and development of addiction is also dependent on reward cues. Therefore, we developed a variant of the rGT, the cued rGT (crGT), where reward delivery is paired with a salient audio-visual cue. Compared to rats trained in the rGT, both males and females trained on the crGT make more risky choices at baseline and exhibit enhanced acquisition of cocaine self-administration. Previous work suggests that repeated exposure to cues which predict uncertain rewards, and repeated responding for uncertain rewards, can sensitize the dopamine (DA) system, but surprisingly, rats trained on the crGT exhibit blunted basal DA efflux within the nucleus accumbens (NAc). We therefore sought to determine how modulation of accumbal DA impacted decision-making and impulsivity. We delivered the Cre-dependent inhibitory DREADD hM4D(Gi) to the nucleus accumbens of TH: Cre+/- and TH: Cre-/- rats (n=16 per sex, per transgene), allowing us to specifically inhibit DAergic afferents to the NAc. Animals were then trained on the rGT or crGT and allowed at least 11 weeks for the DREADD to fully express. Once behaviour stabilized, rats underwent acute dosing of clozapine-n-oxide (CNO) to induce a hypo-dopaminergic state. We found that acute CNO decreased risky choice in TH: Cre+/- rats, but had no effect on risky choice in females. In female TH: Cre+/- rats, however, acute CNO reduced impulsive responding, while having no effect on the phenotype in males. These findings suggest that accumbal dopamine may modulate addiction-relevant phenotypes in a sex-specific manner.

## **W5. The Importance of Identifying the Endogenous Peptides Released and the Receptors They Act on in the VTA**

*Elyssa Margolis\**

Opioid antagonists can robustly impact specific motivated behaviors such as pain, alcohol consumption, and feeding when no exogenous opioids have been given, revealing the actions of endogenous opioid peptides. In heterologous expression systems, multiple endogenous opioid peptides (e.g. met-enkephalin,

leu-enkephalin, and b-endorphin) show little, if any, selectivity between mu and delta opioid receptors (MORs and DORs). It is also generally hypothesized that MORs and DORs signal through similar inhibitory pathways, suggesting redundancy in the system. Yet, we previously reported that MOR and DOR selective ligands can induce direct depolarizations in VTA neurons (Margolis et al., 2014; 2017), raising the possibility that different signaling pathways can be accessed by different ligands. Here we investigated MOR-DOR interactions and endogenous opioid peptide effects on midbrain VTA neurons using ex vivo whole cell recordings. We compared responses to met-enkephalin, leu-enkephalin, and b-endorphin within individual neurons (10  $\mu$ M each). While a subset showed similar hyperpolarizations to these ligands, in other cells the responses varied, including opposing responses to met-enkephalin and leu-enkephalin. Clearly, in the VTA these endogenous opioid peptides are not simply redundant. We also tested for MOR-DOR interactions using selective agonists and antagonists. Specifically, similar to observations in heterologous systems, in a subset of VTA neurons the DOR antagonist TIPP-psi (100 nM) augmented the hyperpolarization induced by the MOR agonist DAMGO (500 nM). Surprisingly, application of the MOR selective antagonist CTAP (500 nM) could either augment or switch the valence of a response to the DOR agonists DPDPE (1  $\mu$ M) and deltorphin II (1  $\mu$ M). Together, these findings demonstrate that concurrent binding of ligands to MOR and DOR in single neurons can produce unique changes in excitability that may have either synergistic or opposing effects on behavior. These observations demonstrate the critical importance of identifying the neuropeptides that are released during specific behaviors and measuring the neural responses to those peptides.

## **W6. Perineuronal Nets May Have Time Dependent Effects Following Cocaine Exposure in Modulating the Firing Properties of Fast Spiking Interneurons in the Medial Prefrontal Cortex**

*Emily Jorgensen\*, Delta Burchi, Barbara Sorg, Travis Brown*

Persistent drug-associated memories facilitate drug craving, which prompts relapse in drug addicts. Our laboratory is interested in the molecular underpinnings that are responsible for the formation of pervasive drug memories. Perineuronal nets (PNNs) are specialized extracellular matrix (ECM) structures that primarily surround inhibitory parvalbumin-containing fast-spiking interneurons, which play a role in the formation and stabilization of drug memories. Previous work by us and our colleagues showed that degradation of PNNs within the medial prefrontal cortex (mPFC) attenuates cocaine-induced reinstatement and alters firing properties of pyramidal cells. This study expands upon our previous findings and defines the changes in synaptic transmission and intrinsic excitability of PNN-expressing interneurons

following cocaine-induced conditioned place preference (CPP). To characterize these changes within the prelimbic mPFC, brain slices were prepared following cocaine-induced CPP and whole-cell electrophysiological recordings were performed. We found that there was a time-dependent attenuation in the number of current-induced action potentials after re-exposure to the CPP chamber in PNN-expressing interneurons (saline:  $93.13 \pm 3.39$ ;  $t=0$ :  $96.90 \pm 5.65$ ;  $t=30\text{min}$ :  $80.50 \pm 4.41$ ;  $t=2\text{hr}$   $76.59 \pm 4.18$ ), which returned to control levels 24hrs after CPP testing ( $t=24\text{hr}$ :  $99.88 \pm 3.57$ ). In addition, we found significant changes in both the frequency and amplitude of miniature events following re-exposure to the CPP chamber. Through this work, we aim to identify the functional consequences of cocaine-induced PNN alterations, which may impact memory formation/stability and contribute to persistent drug craving.

## **W7. Identification of Novel CACNA1C Splice Variants in Human Brain Using Nanopore Sequencing**

*Elizabeth Tunbridge\**

The voltage-gated calcium channels (VGCCs) are arguably the most tractable therapeutic targets to have emerged from recent genomic studies of psychiatric illnesses. However, much remains unknown; the molecular mechanisms linking VGCC genes and psychiatric illnesses are obscure, since none of the GWAS-significant VGCC loci are coding. The VGCC genes are large and highly-spliced; therefore, the proposal that GWAS loci might mediate their effects by specifically impacting on a subset of VGCC splice isoforms is an attractive one. Although rodent studies show that VGCC splice isoforms differ substantially from one another in their function, the profile of VGCC splice isoforms has been poorly characterised in human brain, and the full-length architecture of transcripts remains largely to be determined. We amplified the coding exon chain of CACNA1C (the strongest GWAS psychiatric VGCC target) from healthy, human post-mortem brain tissue. We used nanopore sequencing to characterise and disambiguate full-length CACNA1C isoforms. Using this approach, we found multiple novel exons in human CACNA1C, including 5 that have, to date, been validated using Sanger sequencing, as well as numerous novel transcripts. Our findings demonstrate that the isoform profile of human brain CACNA1C is considerably more complex than currently appreciated. They also demonstrate, for the first time, the utility of using nanopore amplicon sequencing to characterise full-length isoforms of genes of interest in human post-mortem brain. Ongoing studies will further characterise the functional significance of these isoforms and identify those most relevant for psychiatric illnesses.

## **W8. Orbitofrontal Cortex Controls State-Dependent Value Updating for Action Control**

*Emily Baltz\*, Ege Yalcinbas, Rafael Renteria, Christina Gremel*

Orbitofrontal cortex (OFC) is thought to be important for inferring current state and value information necessary to guide goal-directed decision-making. However, changes in motivational state alone are often insufficient to alter action control. Overlooked is the necessity for incentive learning, or the need to experience the outcome value in the new motivational state, in order to produce a corresponding change in action control. The role OFC plays in state-dependent incentive learning is unknown. Here we develop a mouse model of incentive learning and show that mice undergo incentive learning following positive and negative shifts in motivational state. Mice were trained to lever press for sucrose under light or extensive food restriction. We then shifted the motivational state by changing the food restriction positively (from light to extensive) or negatively (from extensive to light) and then mice experienced the new sucrose value in a revaluation session. We assessed whether mice updated value through a non-reinforced lever press test session the subsequent day. By doing this, we were able to isolate the ability to update value from the ability to control actions using value changes. We found that chemogenetic attenuation of OFC excitatory neuron activity during sucrose revaluation did not influence value per se, as the macro- and-micro-structure of consummatory licking and palatability behaviors remained intact. However, OFC attenuation during revaluation following either positive or negative shifts in motivation prevented the ability to update value as assessed during the lever press test session where OFC was intact. Preliminary optogenetic experiments suggest OFC activity is only necessary during sucrose revaluation suggesting a role for OFC directly encoding value change, but not value itself. Our findings provide experimental evidence for a pivotal role of OFC in state-dependent incentive learning that is independent of value computation.

## **W9. Time-of-Day and Time Spent Awake Affect Alertness and Performance Levels of Ship Pilots on Irregular Schedule**

*Philippe Boudreau\*, Sylvain Lafrance, Diane Boivin*

Ship pilots of the St-Lawrence River operate under a “first-in, first-out system”, which can lead to fatigue, and impaired alertness and performance. In this observational field study, our goal was to investigate how circadian and sleep-wake dependent factors influence pilots’ sleep/wake cycle, and their alertness and psychomotor performance levels at work. During the summer of 2014, a total of 18 male St-Lawrence River ship pilots were recruited for a 16-21 day field study. Pilots’ chronotype, sleepiness and insomnia levels were documented

using standardized questionnaires before the start of the study. During the study, their sleep/wake cycle was documented daily by a sleep-wake log and wrist-worn activity monitoring. Alertness were subjectively assessed ~5x/day by a 100-mm visual analogue scale. Psychomotor performance was objectively assessed by a 5-min psychomotor vigilance task (PVT) at the start and end of each shift and rest day. Pilots were of intermediate (50%) or morning (50%) chronotype. Excessive sleepiness and clinical insomnia of moderate severity was present in 33.3% and 20.0% of pilots, respectively. Ship transits were distributed around the clock, and lasted on average  $\pm$  SEM  $5:56 \pm 0:22$  h. Before work days, main sleep periods generally occurred at night, and objectively lasted  $6:02 \pm 1:01$  h. At the end of work days, pilots subjectively reported sleeping  $7:38 \pm 1:38$  h in the prior 24 h. Significant circadian and time-spent-awake effects were observed on subjective alertness and objective psychomotor performance, with minimum levels observed between 09:00 and 10:00. Individual earlier phases in psychomotor performance were correlated earlier with chronotype. Pilots' rhythms of alertness and performance levels were suggestive of a day-oriented circadian system, despite their irregular work schedule. When combined, both circadian and time-of-day effects produce worst alertness and psychomotor performance levels when long shifts ended in the morning.

## **W10. Is Netrin-1 a Long-Range Chemoattractant?**

*Celina Cheung\*, Karen Lai Wing Sun, Stephanie Harris, Timothy Kennedy*

Gradients of secreted long-range attractant and repellent proteins are thought to guide growing axons during neural development. In the embryonic spinal cord, commissural axons pioneer a circumferential trajectory to the floor plate at the ventral midline in response to multiple extracellular cues. These include dorsally secreted repellent BMPs and ventrally derived attractants, such as netrin-1 and sonic hedgehog. Netrin-1 is expressed by cells in the ventricular zone and floor plate, and is essential for commissural axon guidance in vivo. Recent findings have demonstrated that netrin-1 made by ventricular zone progenitor cells is essential for commissural axon extension to the midline. These studies also purport to rule out a role for netrin-1 secreted by floor plate cells as a long-range cue that directs axon extension, instead arguing that netrin-1 functions as a short-range cue that promotes axon extension along a permissive corridor. Here, we examined the localization of netrin-1 protein in the embryonic spinal cord. We detect a graded distribution of floor plate derived netrin-1 protein that is distributed many cell diameters, hundreds of microns, away from netrin-1 expressing cells, the defining characteristic of a long-range cue. Further, we show that manipulating the distribution of netrin-1 within the embryonic spinal cord severely disrupts commissural axon guidance, providing evidence that the precise distribution of netrin-1 protein is critical to its guidance function. Our findings support the operation of netrin-1 as long-range chemoattractant that directs axons to the ventral midline of the embryonic spinal cord.

## **W11. Effects of Prostacyclin Signaling on Alzheimer's Disease Associated-Pathologies**

*Jason Eriksen\*, Tasha Womack, Craig Vollert, Christina Beckett, Michael Murphy*

Vascular pathologies are associated with accelerated neuronal damage and cognitive decline in Alzheimer's disease (AD). We have conducted studies to address the effect of prostacyclin, a protective vasodilatory prostanoid, on the development of neurodegenerative pathologies in a mouse model of AD. The central hypothesis is that prostacyclin signaling may be protective at the site of the neurovasculature by influencing integral components of the blood brain barrier (BBB). Using behavioral studies, immunohistochemistry and biochemical assays, we are currently characterizing prostacyclin-mediated changes in behavior, amyloid deposition, and vascularization. Altered prostacyclin expression appears to protect against amyloid-associated declines in cognitive function, but also appear to alter neurovascular function.

## **W12. Loss of Neuronal Chaperone 7B2 Reduces A $\beta$ Plaque Burden in APP/PS1 Alzheimer's Model Mice**

*Timothy Jarvela\*, Tasha Womack, Polymnia Georgiou, Todd Gould, Jason Eriksen, Iris Lindberg*

Reduction of neuronal proteostasis is a hallmark of Alzheimer's and other neurodegenerative diseases. Underlying molecular mechanisms which lead to plaque formation are poorly understood. Protein chaperones play an important role in maintaining proteostasis and preventing aggregation. We have shown that the neuronally-expressed secretory chaperone 7B2 can block in vitro fibrillation of the A $\beta$ 1-42 peptide. To determine whether 7B2 functions as a chaperone in vivo in beta amyloid plaque formation, we measured the learning capacity of 7B2 knockout mice versus wild-type mice in an Alzheimer's model mouse using the Morris water maze. Mice were divided into two cohorts and subjected to 9 days of training and one day of testing. While APP/PS1DeltaE9 mice fared significantly worse than mice not expressing the transgene, there was no statistically significant change in the learning capacity of 7B2 knockout mice compared to 7B2-expressing mice. After training, brains were subjected to post mortem analysis by immunofluorescence to determine the levels of A $\beta$  in the cortex. We found that mice with partial or complete lack of 7B2 expression showed a significantly lower number and total size of Thioflavin S plaques compared to 7B2-wildtype mice. However, this unexpected decrease in amyloid burden did not correlate with overall learning ability. We conclude that while the loss of 7B2 results in a reduction in the number of Thioflavin S plaques and in total plaque burden, this effect is not correlated with overall memory deficits in the Alzheimer's model mouse. We are currently investigating the effect of 7B2 loss on APP oligomer production in brain homogenates.



## **W13. Small Molecule Modulation of Nerve Growth Factor Receptor in the Brain Using MRI-Guided Focused Ultrasound**

*Kelly Markham-Coultes\*, Kristiana Xhima, H. Uri Saragovi, Kullervo Hynynen, Isabelle Aubert*

A reduction in neurotrophin receptor (NTR) signaling is thought to contribute to the cognitive decline in Alzheimer's disease (AD), alongside other pathological hallmarks. Decreased nerve growth factor (NGF) levels, as well as receptor levels and downstream NGF signaling components are associated with the degeneration of basal forebrain cholinergic neurons and correlated with decreased cognitive function in AD. Therapies using NGF have shown promise in rescuing cholinergic neurotransmission, however efficacy of NGF is limited by its bioavailability, short half-life and adverse consequences of p75NTR activation. In this study, MRI-guided focused ultrasound (MRIfFUS) was used to transiently and non-invasively increase the permeability of the blood-brain barrier (BBB). A systemically administered tropomyosin receptor kinase A (TrkA) ligand crossed the BBB where MRIfFUS was applied. A transgenic mouse model of amyloidosis with cholinergic deficits was used for these studies. Briefly, intravenously administered TrkA agonist was delivered to basal forebrain cholinergic neurons using MRIfFUS in transgenic and non-transgenic littermates. Protein phosphorylation of downstream signaling effectors implicated in neuronal growth, survival and plasticity were quantified. An increase in TrkA, MAPK, Akt and CREB phosphorylation were observed after treatment. This proof-of-concept study demonstrates the feasibility of this therapeutic approach. These results suggest that we can deliver a TrkA-specific agonist using MRIfFUS to modify signaling cascades implicated in neuronal survival and plasticity in a mouse model of AD.

## **W14. Shifting Patterns of Synaptic and Extrasynaptic GABA-A Receptor Activation Explain the Loss of Inhibition and Emergence of Synchrony During Seizure Evolution.**

*David Naylor\**

Seizure onset is marked by fast-rhythmic activity associated with a rapid and enduring loss of synaptic inhibition as measured by paired-pulse inhibition. After several seconds, slow synchronous 3 – 6 Hz activity emerges with an action-potential 'spike' followed by a slower synaptic potential 'wave', and this persists for approximately one minute before seizures are terminated with a prolonged inhibitory post-ictal state. Postsynaptic GABA-ARs containing gamma2 subunits mediate phasic inhibitory currents in hippocampal granule cells in response to brief high concentration transmitter release and rapidly

desensitize to low-level tonic or brief hi-frequency pulsatile GABA exposure. Conversely, extrasynaptic GABA-ARs containing delta subunits are largely non-desensitizing, have greater GABA affinity, and are responsible for tonic inhibitory currents in response to mostly stable low concentrations of extracellular GABA. It is uncertain how conditions can influence GABA spillover to extrasynaptic sites that impacts the spatio-temporal profile of GABAergic inhibition and influences circuit behavior. To probe this, computational models were developed and optimized to fit phasic/IPSC, tonic, and multi-synaptic evoked currents and showed that high-frequency activity rapidly desensitizes postsynaptic receptors in a frequency-duration dependent manner that, along with estimated 1-3 micromolar activity-induced increases in GABA, contributes to persistent losses of paired-pulse inhibition. In addition, prolonged hi-frequency stimulation promotes GABA spillover to a relatively few extrasynaptic receptors (~ 4 per every synapse) that prolongs and stretches the spatial extent of synaptically-released GABA and restricts inhibition to slower more synchronized patterns of activation. In summary, evidence is provided for the evolution of seizures from a phase of fast-rhythmic activity that progresses to a phase of slowing synchrony that depends on a dynamic shift of activation from synaptic to extrasynaptic GABA-A receptors.

## **W15. Verbal Learning and Memory Outcome in Selective Amygdalohippocampectomy Versus Temporal Lobe Resection in Patients With Hippocampal Sclerosis**

*Olaf Paulson\*, Mette Thrane Foged, Kirsten Vinter, Louise Kristensen, Troels W. Kjær, Brice Ozenne, Sándor Beniczky, Flemming Find Madsen, Lars H. Pinborg*

**Purpose:** To investigate the influence of the epilepsy surgery approach on cognition and seizure outcome in patients with temporal lobe epilepsy and histopathological verified hippocampal sclerosis (HS). It is controversial whether selective amygdalohippocampectomy (SAH) has a better neuropsychological outcome compared to nonselective temporal lobe resection (TLR). **Methods:** We identified 108 adults (>16 years) with HS, operated between 1995-2009 in Denmark. Exclusion criteria: Intelligence below normal range, right hemisphere dominance, other native language, dual pathology, missing follow-up data. Among the patients 56 fulfill these criteria and were analyzed. The patients were allocated to SAH (n=22) or TLR (n=34) based on intraoperative electrocorticography. Verbal learning, verbal memory and semantic fluency were tested pre- and post- surgery. **Results:** Altogether 73% were seizure-free one-year and 64% seven-years after surgery. Seizure outcome did not differ between patients operated using the SAH versus the TLR at one-year ( $p=0.951$ ). At seven-years, in patients operated on the same side, an unadjusted model showed no difference ( $p=0.177$ ) while adjusting for age and duration of epilepsy revealed that right-sided TLR were more likely

to be seizure-free than right-sided SAH patients ( $p=0.048$ ). Verbal learning was more affected in patients resected in the left hemisphere than in the right ( $p=0.002$ ). In patients with left-sided TLR, a worsening in verbal memory performance was found ( $p=0.011$ ). Conclusion: There was no difference in seizure outcome between the TLR and SAH approaches after one year. At seven year follow up we would consider the slightly better result for right sided operations to be a coincidence. Verbal learning was worse in patients operated in the left hemisphere. TLR in the left hemisphere was associated with a worse outcome in verbal memory.

## **W16. Analysis of Brainstem-Derived Neural Stem Cell Populations in Adult Zebrafish After Spinal Cord Injury**

*Jeffery Plunkett\*, Angelo Milli, Raul Banos, Michael Fernando, Martin Oudega*

Post-embryonic neurogenesis is limited in the mammalian brain. On the other hand, in zebrafish (*Danio rerio*) multiple proliferative neurogenic and stem cell niches remain active throughout adult life. It has been well documented that, in contrast to mammals, adult zebrafish recover functionally from an anatomically complete spinal cord injury (SCI). Damaged axons deriving from specific neuronal populations within the brainstem are able to regenerate across and beyond the injury and integrate into axon circuits. The focus of our research is to study whether SCI affects the fate of neurogenic progenitor cells in the adult zebrafish brain. We predicted that SCI will induce endogenous, quiescent brainstem progenitor cells to differentiate and become involved in the overall regenerative response. Our data demonstrate that the neural stem progenitor cell markers nestin, sox2, and neuroD1 are expressed in specific “regenerative” brainstem nuclei in adult zebrafish with SCI. Furthermore, using retrograde tracing we found that the expression of neural stem progenitor markers correlated with the nuclei of brainstem neurons that project into the spinal cord. We are examining specific gene targets within the stem/neural progenitor pathway at various time-points to gain a better understanding of the role of stem/progenitor cells in axon regeneration in the zebrafish CNS.

## **W17. Progressive Multifocal Leukoencephalopathy in the Absence of Immunosuppression**

*Sybil Stacpoole\*, Benjamin Zucker*

A 69-year-old woman presented with a cortical hand syndrome progressing over several weeks. MRI brain showed characteristic appearances of progressive multifocal leukoencephalopathy (PML), confirmed by detection of the JC virus in CSF, despite the absence of any evidence of immunosuppression. Treatment with mirtazapine, mefloquine and cidofovir did not affect the progression of the

disease, which was fatal within 7 months of presentation. This report adds to the small case literature that suggests that PML can occur in immunocompetent people, albeit extremely rarely.

## **W18. Three GRIPs 1 Spot: Critical Determinants for the Binding of Three GPCR-Interacting Proteins Within the Same Six-Residue Region of the Dopamine D2 Receptor**

*Kim Neve\*, Hun-Joo Lee, Cecilea Clayton, Hongxiang Lan, Yong Liu*

In my laboratory, the same 6-residue region on the D2 receptor has been implicated in separate investigations of determinants of the binding of three GPCR-interacting proteins (GRIPs): arrestin, calmodulin, and S100B. Using a combination of in vitro co-immunoprecipitation and cellular assays, we have reported that D2 receptor residues 210IKI212 are required for the binding of calmodulin, and that residues 212IYIV215 are required for the binding of arrestin. We now report that the calcium-binding protein S100B requires 211KI212 to bind to the D2 receptor third intracellular loop, rather than a putative S100B-binding motif that is ~20 residues away (233RANLKTP240). Furthermore, the D2 receptor mutant 211KI212→AA that we predict is unable to bind S100B also exhibits almost complete loss of ability to recruit arrestin. Strategies for assessing how the binding of multiple GRIPs is choreographed are discussed, as well as the implications. For example, a considerable amount of elegant work suggests that GPCRs function as part of a stable signalplex with other GPCRs and many GRIPs, and that the proteins within this signalplex shift their relative positions depending on the activation states of the receptors and other proteins without fully dissociating, but it is difficult to reconcile our finding of at least three proteins binding to the same small region with the model of a stable signalplex. Furthermore, an increasingly common research tool is to use mutated receptors deficient in binding an interacting protein (biased receptors) as tools for determining the effect of the protein on receptor function in vivo, but this type of study relies on the assumption that only one pathway (e.g., arrestin recruitment) is altered. If multiple independent pathways are altered by a mutation, then interpretation of the results is greatly complicated. (VA Merit Review)

## **W19. Effect of Hormonal Contraceptive Phase on Default Mode Network Activity During Working Memory Under Stress**

*Alexandra Ycaza Herrera\*, Ricardo Velasco, Sophia Faude, Jessica White, Philipp Opitz, Ringo Huang, Kristie Tu, Mara Mather*

Hormonal contraception (HC) can modify the stress response and memory processes. Both processes have been shown to influence brain activation measured using functional magnetic resonance imaging. Moreover, stress can modify brain activation during cognitive tasks, such as working memory. However, few studies have examined how the ability of HC to modify the stress response might subsequently alter the effects of stress on working memory related brain activation. To examine if HC influences stress effects on brain activation during a working memory task, we tested 20 women using monophasic 28-day HC containing 7 inactive days. Women were seen twice, once during days 8 to 21, when HC hormones are present (active phase) and once during days 24 to 28, when no HC hormones are present (inactive phase). Women completed a stressor (cold pressor test) followed by an n-back task in the scanner. Women completed 0-back and 2-back blocks of the n-back task. Default Mode Network (DMN) activity was greater during the 0-back than 2-back blocks of the task. Furthermore, we found that women showed greater DMN activation in these blocks during the active phase of their HC cycle than during the inactive phase, particularly, in the posterior cingulate. The greater difference in DMN activity between 0- and 2-back blocks during the active phase of the HC cycle suggest that women experience more efficient switching between DMN and working-memory networks during the active than inactive phase of HC.

## **W20. Potassium Channel Inactivation Drives Nonlinear Acceleration of Motoneuron Activity**

*Ronald Harris-Warrick\*, Remi Bos, Frederic Brocard, Cecile Brocard*

Spinal motoneurons are nonlinear integrators of the locomotor network. The most distinctive nonlinear firing property consists of a self-sustained firing evoked by a brief excitation. This all-or-none bistable behavior arises from a prolonged depolarization known as a “plateau potential” which is mediated by persistent inward currents. From extensive in vitro recordings, the plateau potential appears to be preceded by a slow subthreshold membrane depolarization, then manifested by a spike frequency acceleration before reaching a steady state firing rate. Analogous firing-frequency acceleration, seen in motor units from in vivo recordings, provides evidence that the slow voltage transition to plateau is part of the physiological repertoire of motoneurons. The other striking manifestation of the slow voltage transition

to the plateau potential is the cumulative depolarization of the membrane potential with repetitive excitations at short intervals, known as a “windup” phenomenon. The slow voltage transition to the plateau has been assumed to rely on progressive recruitment of L-type  $\text{Ca}^{2+}$  channels, since both spike-frequency acceleration and windup are blocked by nifedipine in motoneurons. Instead, the present study demonstrates in rats and mice that the slow voltage transition to plateaus is mediated by slow inactivation of a nifedipine-sensitive  $\text{K}^{+}$ -current mediated by  $\text{Kv}1.2$  channels. The current underlying a slow voltage-dependent depolarization is accompanied by a voltage-dependent conductance decrease and is eliminated by potassium channel blockers and selective  $\text{Kv}1.2$  antagonists. The depolarization in turn activates slow inward currents that sustain the plateau state.

## **W21. The Effects of Real-Time Biofeedback Integrated Into Neuromuscular Training on Knee Motor Resting-State Connectivity**

*Jed Diekfuss\*, Dustin Grooms, Adam Kiefer, Scott Bonnette, Ryan MacPherson, Christopher DiCesare, Staci Thomas, Michael Riley, Gregory Myer*

Functional brain connectivity can be altered by neuromuscular training. However, these training paradigms are typically generic and are not designed for specific motor deficits. We have developed an augmented neuromuscular training (aNMT) program that utilizes interactive real-time biofeedback to improve landing biomechanics for the reduction of anterior cruciate ligament (ACL) injury risk. aNMT utilizes kinematic and kinetic analysis to map key biomechanical parameters to an interactive shape viewed by participants in real-time. Participants are instructed to perform exercises to achieve a goal shape, which equates to producing target biomechanical parameters, while deviations from the targets result in specific shape distortions. Over six weeks of training, participants ( $n = 18$ ) performed a series of aNMT-based progressive exercises (e.g., squat, overhead squat, squat jump, tuck jump, single leg Romanian dead lift, pistol squat). Resting-state connectivity fMRI scans were collected pre and post training. Twenty-eight motor-related regions of interest (ROIs) were created based on previously published data. Paired-samples  $t$  tests with a false discovery rate correction for multiple comparisons determined differences in connectivity using 12 pre-selected motor-related ROIs as seeds (post > pre). There was significantly greater connectivity between the right supplementary motor area and left thalamus,  $t(17) = 3.92$ ,  $p = .03$ . The right supplementary motor area is responsible for the planning and coordination of movement and the left thalamus is associated with neuromotor control. The increased connectivity between these regions suggest a possible neural mechanism for improved motor adaption associated with aNMT. These findings have implications for ACL injury prevention as interventions can be developed to facilitate efficient adaptation via the promotion of additional neuroplasticity.

## W22. Reliability of Functional Neuroimaging for Lower Extremity Motor Control

*Dustin Grooms\*, Jed Diekfuss, Lacy Haas, Brynne Williams, John Lanier, Kayle Bridgewater, Weihong Yuan, Jonathan Dudley, Jonathan Ellis, Kim Barber-Foss, Staci Thomas, Mekibib Altaye, Myer Gregory*

Advances in human neuroimaging techniques support the capture of highly accurate spatial images of neural function during rest, cognitive tasks, and more recently with complex motor tasks. However, technical challenges regarding head motion limit capability to capture neural activity during lower limb movements. Without overcoming the issues of head motion artifact, we will continue to have an incomplete understanding of supraspinal control of locomotion for tasks associated with physical activity (e.g., kicking a soccer ball) and daily life (e.g., walking, rising from a chair). To address this gap in knowledge, we have developed novel lower extremity motor neuroimaging paradigms that minimize absolute, relative, and task-correlated head motion. Specifically, we have developed a unilateral leg kicking task involving primarily quadriceps contraction, a customizable resisted single-leg press task engaging the quadriceps and hip extensors, and a bilateral leg press that requires coordinated hip and knee flexion and extension. Thirteen healthy females participated in the reliability experiment across two sessions six weeks apart ( $16.2 \pm 0.7$  yrs,  $163.8 \pm 4.7$  cm,  $59.6 \pm 8.7$  kg). Head motion was limited to .23-.43 mm of absolute motion and .06-.11 mm of relative head motion across all tasks. Intraclass correlation coefficients have demonstrated high between session reliability (ICC: .82-.94) for primary motor cortex mean for all tasks. The established reliability of these novel paradigms will allow the future study of the neural control of human locomotion and a better understanding of the neural consequences of disorders that affect motor control and help improve interventions aimed at restoring locomotion capability after neurologic or orthopedic insult.

THURSDAY, JANUARY 18 • 3:30 P.M. - 4:30 P.M. • SEA TO SKY BALLROOM B

## Th1. Phasic Dopamine Release in the Nucleus Accumbens Core Differentially Alters Drug-Taking and Drug-Seeking

*Ryan Farero\*, Lauren Burgeno, Jennifer Steger, Marta Soden, Nicole Murray, Larry Zweifel, Paul Phillips*

Altered dopamine (DA) transmission is implicated in most contemporary theories of drug abuse. However, the direction, timing and context in which alterations of DA transmission occur remain a matter of debate. Both drugs themselves, and the cues that are repeatedly paired with drugs are capable of driving dopamine release in the nucleus accumbens core (NAcc). Recent work from our lab implicates diametric changes in drug-cue elicited NAcc

DA transmission in mediating escalation of drug intake and resumption of drug-seeking after abstinence. Within the NAcc an attenuation of phasic DA transmission to response-contingent drug cues was observed in animals that escalated their daily drug consumption. Additionally, increasing dopamine release by administering L-DOPA, a dopamine precursor, prevents and reverses escalation of drug-intake. In diametric opposition, phasic DA transmission increased within the NAcc in response to non-contingent drug-cues, which coincided with increases of drug-seeking behaviors. Furthermore, the increase in phasic DA transmission to non-contingent drug-cues was enhanced during withdrawal periods. Due to this divergence of phasic DA transmission observed in response to drug-related cues, we hypothesize that NAcc phasic DA transmission is mediating escalation of drug-taking, and drug-seeking in a divergent manner. To investigate this, we injected an AAV ChR2 containing viral vector with a CaMKII-delta promoter (AAV1-CaMKII $\delta$ -ChR2-mCherry) bilaterally in the VTA of male Wistar rats. Our initial results indicate photostimulation paired with response-contingent drug-cues decreases drug-intake in escalated animals, whereas photostimulation paired with non-contingent drug-cues increase drug-seeking behavior. Moreover, we found that photostimulation unpaired to drug-cues increases animals' drug-seeking ( $p < .05$ ). These direct manipulations will elucidate the role that NAcc phasic dopamine transmission has in both drug-taking and drug-seeking contexts.

## **Th2. Diet-Induced Obesity Impairs Outcome Devaluation and Alters Excitability of the OFC**

*Lauren Seabrook\*, Lindsey Naef, Corey Baimel, Madelyn Ellis, Stephanie Borgland*

To make an appropriate decision one must evaluate the appropriate value of the outcome based on current information. This goal directed behavior, updating the action based on the value of the outcome is mediated via the orbital frontal cortex (OFC). The OFC has previously been shown to be important in outcome guided behaviours and is essential for selecting goals based on current, updated values of expected reward outcomes. Little is understood on how this neural circuit is impeded in diet-induced obesity. We tested the hypothesis that obese mice have impaired ability to devalue rewards and this may be due to alterations in the OFC. We found that unlike lean mice, obese mice had impaired outcome devaluation when pre-fed with the sucrose reward. This was not due to altered motivation for the sucrose reward as obese and normal weight animals performed similarly on a progressive ratio for sucrose. Using in-vitro whole cell patch clamp electrophysiology we show that diet induced obesity reduces inhibitory tone onto OFC pyramidal neurons. To determine if decreased inhibitory input to pyramidal neurons leads to impairment in reward devaluation in normal weight animals, we expressed an inhibitory DREADDs in VGAT ires cre mice. Reducing inhibitory tone onto pyramidal neurons in



normal weight animals induced deficits in selective satiety reward devaluation. Together we find that diet-induced obesity decreases inhibitory tone onto pyramidal neurons in the OFC and this is associated with deficits in outcome devaluation.

### **Th3. Neural Circuit Mechanisms Underlying Drug-Induced Changes in Motivated Behaviors**

*Johannes de Jong\*, S. Atiyeh Afeji, Iskra Pollak Dorocic, James Peck, Vivian Han, Christina Kim, Karl Deisseroth, Stephan Lammel*

The mesocorticolimbic dopamine (DA) system, which is comprised of DA neurons in the ventral tegmental area (VTA) and their projections to different forebrain regions, has been fundamental in the formulation of most models of drug use, abuse, and addiction. Recently, we demonstrated that different afferent inputs to the VTA mediate reward- and aversion-related behaviors in profoundly different ways. Because drugs of abuse (e.g., cocaine, morphine) modify the function of excitatory inputs to the VTA, we hypothesized that drug-evoked synaptic adaptations in specific VTA afferent pathways may underlie some of the maladaptive behaviors of individuals with substance use disorder (SUD). The lateral hypothalamus (LH) represents a major afferent pathway of the VTA, which has been previously implicated in both positive and negative motivational states. Using a multidisciplinary approach combining in vivo optogenetics, fiber photometry, synaptic electrophysiology, rabies virus-based tracing and in situ hybridization, we studied a) function, b) circuit architecture and c) drug-evoked synaptic plasticity of the LH→VTA pathway. We first established a critical role of the glutamatergic component of the LH→VTA pathway for mediating aversion-related behaviors by performing optogenetic stimulation and silencing experiments as well as fiber photometry in freely moving mice. Next, we elucidated the complete circuit architecture of the LH→VTA pathway by combining anatomical and functional neural circuit mapping. We found that, qualitatively, LH neurons target all VTA DA and non-DA subpopulations. Quantitatively, however, we discovered a highly-biased input scheme, which reveals that DA neurons projecting to nucleus accumbens (NAc) medial shell represent a dominant downstream effector of glutamatergic LH neurons. Remarkably, 24 hours after a single injection of cocaine (15 mg/kg, intraperitoneal), the synaptic strength of excitatory LH inputs onto VTA DA neurons projecting to NAc medial shell was significantly reduced compared to saline-treated animals. In contrast, a single injection of cocaine had no effect on the synaptic strength of excitatory LH inputs onto VTA DA neurons projecting to NAc lateral shell. Taken together, our results suggest that cocaine exposure induces synaptic depression in a brain pathway that

encodes aversion-related behaviors, which may explain some of the maladaptive behaviors of individuals with SUD in which they continue drug-seeking/drug-taking behavior in the face of negative consequences.

## **Th4. Optogenetic Activation of the Central Amygdala Generates Addiction-Like Preference for Reward Despite Adverse Consequences**

*Mike Robinson\*, Charlotte Freeland, Rebecca Tom, Aarit Ahuja, Hannah Maniates, Olivia Lofaro, Carli Poisson, Anna Knes, Ariel Ben-Ezra*

Drug and behavioral addictions are characterized by focused pursuit of a single reward above all others. Excessive motivation to pursue reward leads to persistent addictive-like decisions that often undermine an individual's best interests, and prevail despite adverse consequences. The amygdala plays a key role in reward processing and generating motivation. In the following studies, we explored how optogenetic stimulation of the central amygdala (CeA) modulates decision-making and reward choice, causing specific rewards to be almost compulsively preferred in manners that model many of the DSM criteria for addiction. Rats were trained to choose between a reward paired with CeA laser stimulation or an otherwise unpaired identical or alternative reward. Rats developed a nearly exclusive preference for the CeA laser-paired reward over the unpaired reward. This was true whether the reward was a sucrose pellet or an infusion of cocaine. For sucrose, this preference persisted even when a much larger sucrose reward was offered as an alternative, or when the preferred reward was paired with an electric footshock. CeA laser stimulation also produced persistent pursuit of a flavored reward paired with conditioned taste aversion. For cocaine, CeA laser stimulation produced an escalation of cocaine intake, and compulsive nibbling of the nose port paired with laser-associated cocaine, as though seeking more. For both cocaine and sucrose, CeA stimulation dramatically increased an animal's motivation for the laser-paired reward over an otherwise identical unpaired reward. In each case, these effects were not the consequence of any independently rewarding properties of optogenetic activation of the CeA alone. These findings suggest that the CeA is involved with assigning increasing value to reward and directing decision-making by generating narrowly focused motivation to seek out reward that may persist in the face of more rewarding alternatives and adverse consequences.

## **Th5. Divergent Behavioral and Synaptic Changes Caused by Different Patterns of Morphine Exposure in Mice**

*Emilia Lefevre\*, Kerry Trotter, Patrick Rothwell*

In the treatment of chronic pain, the gold standard is prescription of opiate based analgesics. This often leads to negative consequences such as analgesic tolerance and addiction. Reducing the dramatic fluctuations of plasma opioid drug levels is thought to minimize their abuse liability, hence the pharmaceutical development of extended-release opioids. Despite this, the opioid abuse epidemic continues to rise, indicative of the need for improved pharmacokinetic strategies. Our central hypothesis is that even minor lapses in opioid plasma levels leads to maladaptive changes in brain function that promote abuse liability and addiction. To investigate this hypothesis, mice were implanted with osmotic minipumps to continuously deliver morphine (63mg/kg/day for 6 days), and administered twice-daily naloxone injections (10mg/kg s.c.) to interrupt opioid receptor stimulation. Continuous morphine exposure over 6 days lead to tolerance of the psychomotor inducing effects of morphine. In contrast, mice whose morphine exposure was interrupted by naloxone developed psychomotor sensitization; the basic assay for studying addiction behavior in rodent models. Using ex-vivo slice electrophysiology, spontaneous Inhibitory Post-Synaptic Currents (sIPSC) were measured from the D1 and D2 subtype medium spiny neurons (MSNs) of the nucleus accumbens. I discovered that continuous morphine exposure led to an increased amplitude of sIPSCs on D1 MSNs and decreased frequency of sIPSCs on D2 MSNs. This is interpreted as a shift in the balance of inhibition; with more inhibition of the functionally drug-reward promoting D1 MSNs and less inhibition of the D2-MSNs. I am currently examining whether interrupted morphine exposure evokes the opposite effect on inhibitory synaptic function, similar to the opposing behavioral effects. Our work may have significant clinical implications, highlighting the dangers of prescription opioids that cause even minor fluctuations in opioid receptor occupancy.

## **Th6. Sweet Tooth or Neophile? Evaluating Developmental Risk Factors for Cocaine Seeking in Male and Female Rat**

*Chloe Jordan\*, Susan Andersen*

Drug abuse during adolescence substantially increases the risk of substance use disorder (SUD). Although many teens experiment with drugs, only a small percentage become dependent. Early identification of high-risk individuals is critical for targeted interventions to reduce SUD rates. Reward-related traits, such as sugar preferences and novelty responses, are linked to drug-taking in adults, but few studies have examined the predictive utility of these traits before the vulnerable adolescent period. We hypothesized that strong sucrose

preferences and novelty responses early in development (post-natal days [P]19-23) can predict cocaine seeking in adolescence and adulthood. Male and female rats (n=8-12/sex) were screened for sucrose preferences using 2bottle choice procedures; novelty responses were evaluated in a 2-sided chamber where exploration of the 2nd side was allowed after 3 days' habituation to the 1st. Adolescents (P42) received i.v. catheters and self-administered cocaine (0.5 mg/kg) under a variable interval schedule, to support high levels of cocaine seeking. Stepwise regression revealed that high sucrose preferences were associated with elevated cocaine seeking in males ( $R^2=0.54$ ,  $p<0.01$ ), but not females. Novelty preferences were not significant. However, novelty-induced locomotion was associated with cocaine seeking in females ( $R^2=0.48$ ,  $p<0.02$ ), but not males. In a separate group of rats (n=12-13/sex), novelty-induced locomotion also predicted adolescent motivation to earn cocaine (progressive ratio breakpoints;  $R^2=0.58$ ) and relapse in adulthood following early initiation of cocaine use (P28-60;  $R^2=0.73$ ,  $p<0.05$ ), independent of plasma estradiol levels. These findings reveal hitherto unreported sex differences in risk factors for cocaine abuse. While early sucrose preferences may predict risk in males, novelty responses may be more efficacious predictors for females. Future research will characterize the neural substrates of these traits during early development.

## **Th7. Effects of Genetic Deletion of Mu Opioid Receptors From Kölliker-Fuse and Prebötzing Complex Neurons on Morphine-Induced Respiratory Depression**

*Adrienn Varga\*, Erica Levitt*

Activation of mu opioid receptors in respiratory centers, such as the pontine Kölliker-Fuse (KF) and the preBötzing complex (preBotC), causes a reduction in respiratory rate. The goal of this study was to examine and compare the relative contribution of opioid-sensitive neurons in the KF and preBotC to the reduction in respiratory rate caused by the opioid agonist morphine. Mice with floxed mu opioid receptors were injected with AAV2-Cre-GFP virus into either the KF, or preBotC, bilaterally to locally delete mu opioid receptors. After viral expression (4-5 weeks) head-out plethysmography was used to measure respiratory rate in unanesthetized mice at baseline and following systemic administration of morphine (10 mg/kg, i.p.). Mu opioid receptor deletion both in the KF and preBotC led to a significantly smaller reduction in respiratory rate compared to uninjected or GFP injected controls. Additionally, in whole-cell recordings from KF neurons in brain slices, opioid agonist-mediated currents were abolished, confirming successful deletion of mu opioid receptors. Together these data indicate that opioid sensitive neurons in the KF, as well as the preBotC, contribute to morphine-induced respiratory depression.

## **Th8. Generality and Mechanism of RMTg Responses to Aversive Stimuli**

*Hao Li\*, Peter Vento, Maya Eid, Dominika Pullmann, Thomas Jhou*

The rostromedial tegmental nucleus (RMTg) is a GABAergic nucleus that sends strong inhibitory projections to DA neurons, thus acting as a “braking” system for DA neurons. RMTg neurons encode negative reward prediction errors (RPEs), i.e. they are activated by aversive stimuli and by cues that predict aversive outcomes, and inactivation or lesions of the RMTg greatly reduce many behavioral responses to these stimuli. Because RPE signals in the RMTg strongly resemble responses of the lateral habenula (LHb), it had been assumed that the LHb drives most of these responses, but using *in vivo* electrophysiology recording and Ca<sup>2+</sup> imaging, we found that these RPEs (preferentially found in VTA-projecting neurons) are not the only types of aversion-related signals encoded by the RMTg, and that overall RMTg responses to aversive stimuli and cues are driven by a variety of different afferents. Temporal inactivation of the LHb with GABA agonists eliminated surprise-driven activations of RMTg responses to aversive stimuli, while temporal inactivation of the mPFC reduced the RMTg responses to shock-predictive cues. Additionally, optogenetic inhibition of PBN terminals in the RMTg attenuated shock-induced responses of RMTg neurons. In ongoing studies, we will evaluate the contribution of these distinct RMTg afferents to punishment resistance and the effects of the RMTg lesion on DA firing patterns in responses to reward and aversion.

## **Th9. Using the Intermittent Access Self-Administration Procedure to Assess Sex Differences in the Motivation for Cocaine**

*Alex Kawa\*, Terry Robinson*

Studies assessing addiction-like behaviors in rats using the Intermittent Access (IntA) cocaine self-administration procedure have produced findings suggesting that the temporal pattern of cocaine consumption (in the case of IntA, characterized by intermittent spiking of brain cocaine concentrations) is a critical factor for addiction-like behavior. This pattern of intermittency more closely resembles the temporal pattern of cocaine consumption in humans suffering from addiction and thus can serve as an asset in animal models of addiction-like behavior. To this point, studies using the IntA procedure have involved male rats, exclusively. However, work in humans and in animals using the “Long Access” (LgA) model, has shown that females may be more susceptible to develop addiction-like behavior. For example, female rats are more likely to acquire self-administration and do so more rapidly than males, and escalate their cocaine intake to a greater degree than male rats. In humans, females more rapidly progress from casual cocaine use to cocaine addiction,

suggesting some sex difference that predisposes them to suffer from addiction. Previous work has shown that IntA cocaine experience produces robust incentive-sensitization in male rats, but this remains to be tested in female rats. In this study, we directly compared the effects of IntA self-administration on the motivation to self-administer cocaine in male and female rats measured using behavioral economic metrics. Our results reinforce previous findings regarding addiction-like behavior in males, as males exhibited an escalation in drug consumption, as well as an increase in motivation to self-administer cocaine over the course of the 30 day IntA procedure. In female rats, we observed an even greater escalation in drug consumption as well as stronger motivation to consume cocaine throughout IntA experience. Finally, a 14-day abstinence period led to greater incentive-sensitization in female rats than male rats.

## **Th10. Role of Anterior Dorsal Lateral Hypothalamic Area Perineuronal Nets in Cue-Induced Reinstatement of Cocaine-Seeking Behavior**

*Jordan Blacktop\*, Barbara Sorg*

Addiction involves drug-induced neuroplasticity of the circuitry of motivated behavior, which includes the medial forebrain bundle and the lateral hypothalamic area. Emerging at the forefront of neuroplasticity regulation are specialized extracellular matrix structures that form perineuronal nets (PNNs) around certain neurons, mainly parvalbumin positive (PV+) fast-spiking interneurons (FSINs), making them a promising target for the regulation of drug-induced neuroplasticity. Brain regions within the circuitry of motivated behavior with comparatively high PNN expression may provide neurobiological insight into maladaptive drug-induced neuroplasticity and subsequent drug seeking. Very little is known about how PNN-expressing neurons in the LHA control drug-seeking behavior. We previously reported that the dorsal and intermediate zones of the anterior lateral hypothalamic area (LHAad) exhibited robust PNN expression using the PNN marker *Wisteria floribunda* agglutinin (WFA), and that approximately two-thirds of WFA positive neurons co-expressed PV. Removal of PNNs with the enzyme chondroitinase ABC (Ch-ABC) expression blocked the acquisition of cocaine- but not sucrose-induced CPP and self-administration. Here we focused on the rodent model of relapse (reinstatement). The goals of this set of experiments were to: 1) determine whether PNN expression within the LHAad is necessary for cue-induced reinstatement 2) characterize the phenotype of LHAad PNN-surrounded neurons, and 3) determine mesocorticolimbic inputs to and projections from the LHAad. Here we report that LHAad PNNs are necessary for the expression of cue-induced reinstatement of cocaine-seeking behavior. Furthermore, the phenotype of LHAad PNN-surrounded neurons was determined using the excitatory markers VGLUT2 and glutamate and the

inhibitory markers GAD65/67 and GABA. Predominant co-localization of WFA with VGLUT2 and GABA over GAD65/67 and glutamate suggests that the PNN-rich LHAad receives dense glutamatergic input (VGLUT2) and is predominantly GABAergic. Moreover, retrobead injection into the LHAad, NAc, and VTA demonstrates that the LHAad receives robust prefrontal cortex input while providing moderate input into the VTA and minimal input into the NAc. In summary, these data indicate that PNN expression in the LHAad: 1) is necessary for expression of cue-induced reinstatement of cocaine-seeking behavior 2) is predominantly co-localized with PV+ GABAergic neurons that receives robust glutamatergic inputs, and 3) receives input from layer V of the prefrontal cortex and provides input into the VTA.

## **Th11. Understanding the Neural Mechanisms of Enhanced Incentive Motivation in Obesity Prone Rats**

*Rifka Derman\*, Carrie Ferrario*

Studies in humans and rodents suggest that stronger incentive-motivational responses to food cues drive over-consumption that leads to and maintains obesity, particularly in susceptible individuals. Excitatory transmission in the Nucleus Accumbens (NAc) mediates both food- and drug-seeking behaviors that are initiated and maintained by cues associated with these rewards and consumption of palatable foods enhances NAc AMPAR transmission. However, whether cue-triggered food-seeking differs in obesity-prone vs -resistant rats, and the potential role of NAc AMPARs in this behavior is unknown. Here, we use single-outcome Pavlovian-to-instrumental transfer (SO-PIT) to test whether cue-triggered food-seeking differs in obesity-prone vs -resistant rats prior to the development of obesity. Next, we examined whether the training leading up to PIT testing was sufficient to alter NAc AMPAR surface expression. Lastly, we determined the effect of intra-NAc AMPAR blockade on the expression of SO-PIT. We found that obesity-prone rats exhibit stronger SO-PIT than -resistant rats, that training selectively increases NAc CP-AMPA surface expression only in obesity-prone rats, and that NAc CP-AMPA blockade is sufficient to prevent the expression of SO-PIT in obesity-prone rats. Furthermore, additional behavioral studies show that obesity-prone rats exhibit stronger sensory-specific PIT (SS-PIT), a unique form of PIT that relies on both the basolateral amygdala (BLA) and the NAc shell. Ongoing studies using chemogenetic expression of DREADDs are underway to determine the involvement of the BLA-NAc shell pathway in the enhanced SS-PIT in obesity-prone rats. In sum, our data strengthen the idea that the food cues exert stronger and more selective motivational influence on food-seeking in obesity susceptible vs. resistant populations, and reveal novel roles for NAc CP-AMPA surface expression in this behavior.

## Th12. Effect of Oxytocin on Stress-Induced Reinstatement of Alcohol-Seeking Behavior in Male and Female Mice

*Courtney King\*, Howard Becker*

Alcoholism is a chronic relapsing disease characterized by periods of abstinence followed by return to heavy use. While many factors contribute to increased relapse vulnerability, stress is considered to play a prominent role in triggering relapse. A growing body of literature suggests that the oxytocin (OT) system plays a role in a number of stress-related psychiatric disorders including alcohol addiction. Work from our lab has demonstrated that systemic administration of OT reduced binge-like alcohol drinking and operant oral self-administration in male C57BL/6J mice. The present study was designed to extend these findings by examining the effects of OT treatment on alcohol relapse-like behavior.

Further, there is evidence to suggest that females may be more responsive to stress and are at greater risk for return to heavy drinking following abstinence. Thus, the present study also aimed to investigate potential sex differences in the ability of stress to trigger alcohol relapse-like behavior as well as the ability of OT to attenuate this effect. Adult male and female C57BL/6J mice ( $n=12$ /group) were trained to acquire stable rates of lever responding under a fixed-ratio (FR)-4 schedule for 12% ethanol in daily 20 min sessions. Once lever responding and alcohol intake stabilized ( $<15\%$  variability over 3 consecutive days) mice entered into the extinction phase of the study (responding yields no alcohol delivery) for 14 days before reinstatement testing. All mice underwent stress-induced reinstatement testing using either predator odor (2,3,5-Trimethyl-3-thiazoline; TMT) or the  $\alpha$ -2 adrenergic receptor agonist yohimbine. For TMT-induced reinstatement, mice were exposed to TMT for 15 min and then immediately placed into operant self-administration chambers to examine alcohol-seeking behavior under extinction conditions. At 30 min prior to the reinstatement test session (15 min prior to TMT exposure), separate groups of mice were injected (ip.) with vehicle (saline) or OT (0.1, 0.5, 1 mg/kg). Systemic OT administration attenuated stress (TMT)-induced reinstatement of alcohol seeking behavior in a dose-related manner in male and female mice. Further, female mice showed greater sensitivity to OT treatment compared to males (leftward shift in dose-response function). For yohimbine-induced reinstatement, mice were injected (ip.) with yohimbine (0, 0.3, 0.625 mg/kg) 1 hr prior to reinstatement testing. At 15 min post-yohimbine injection, mice are injected (ip.) with vehicle (saline) or OT (1 mg/kg). Male mice showed a dose-related increase in stress-induced alcohol seeking behavior that was attenuated by OT. Females are currently being tested - we hypothesize that females will exhibit stress-induced alcohol relapse-like behavior at lower doses of yohimbine compared to males (leftward shift in yohimbine dose-response) and OT will attenuate this effect. Taken together, these data highlight potential sex differences in stress-induced reinstatement of alcohol seeking behavior in mice and add to accumulating evidence that the OT system may represent



a promising target for the treatment of alcohol use disorders. Supported by NIAAA grants P50 AA10761, U01 AA014095, U24 AA020929, T32 AA007474 & VA Medical Research.

### **Th13. Chronic Ethanol Exposure Alters Dorsomedial Striatal D1 Receptor Function Disrupting Goal-Directed Actions**

*Rafael Renteria\*, Christina Gremel*

A significant component of ethanol dependence is the disruption to decision-making processes. We have recently shown that ethanol dependence leads to dysfunction in goal-directed control, resulting in a reliance on habitual circuits. The disruption in goal-directed control was found to involve a decrease in transmission from the orbital frontal cortex (OFC) to the dorsomedial striatum (DMS). Interestingly, we found that OFC-DMS transmission was selectively attenuated to D1 MSNs of the direct pathway with no change in OFC transmission to D2 MSNs of the indirect pathway. It is unclear how the disruption in OFC transmission is cell-type specific given that OFC projection neurons have been shown to project to both D1 and D2 MSNs equally. One possibility is a postsynaptic mechanism in which endocannabinoids (eCB) released from D1 MSNs act as a retrograde signal to reduce OFC transmission. We used a well-validated model of ethanol dependence, chronic intermittent ethanol (CIE) vapor exposure and performed whole-cell patch clamp recordings of D1 MSNs in the DMS 3-21 days in withdrawal. In both Air control and CIE exposed mice, eCB-mediated LTD was reliably induced by (S)-3,5-dihydroxyphenylglycine (DHPG). However, the cell-type specificity of reduced OFC-DMS transmission could be induced by an alteration in dopamine receptor function as D1 receptor activity has also been shown to regulate eCB signaling. In Air control mice, we found that DHPG-LTD was blocked by D1 agonist, SKF 81297. In contrast, SKF 81297 had no effect on DHPG-LTD in CIE mice. In addition, SKF 81297 was found to increase excitability of D1 MSNs in Air controls but had no effect on D1 MSNs of CIE exposed mice. These findings suggest that ethanol dependence leads to a disruption of D1 receptor function that may result in unregulated endocannabinoid plasticity at OFC terminals to D1 MSNs.

## **Th14. Modulation of Endocannabinoid-Mediated Synaptic Plasticity Within the Orbitofrontal Cortex by a Palatable Diet**

*Benjamin Lau\*, Stephanie Borgland*

The orbitofrontal cortex (OFC) plays a key role in the cognitive and emotional processing of decision-making. Dysfunction of the OFC is thought to underlie compulsive behaviours, including obsessive-compulsive disorder, drug and behavioural addictions. It is well established that the endogenous cannabinoid (endocannabinoid) system is important for appetite regulation. However, its precise role within the OFC in modulating eating has yet to be elucidated. Using in-vitro patch clamp electrophysiology, we show that CCK-expressing GABAergic synaptic inputs onto pyramidal neurons within layer II/III of the OFC are sensitive to endocannabinoids. Specifically, they exhibit endocannabinoid-mediated short-term depression (depolarization-induced suppression of inhibition, DSI) and long-term depression (iLTD, via theta-burst stimulation). Since obesity is typically associated with an overactive endocannabinoid system, we examined whether consumption of a palatable, high-fat and energy-dense cafeteria diet altered endocannabinoid signaling within the OFC. We found there was a reduction in inhibitory GABAergic synaptic transmission onto OFC pyramidal neurons following extended access (24 hr), but not restricted access (1 hr) to a cafeteria diet. This suppression of inhibition was partly reversed by the neutral CB1 receptor antagonist, NESS-0327 (0.5  $\mu$ M), indicating the presence of tonic levels of endocannabinoids in obese animals. Associated with this endocannabinoid tone, we observed an enhancement of DSI and an impairment of iLTD. Furthermore, we showed that the upstream mechanism underlying these palatable diet-induced changes was activation of Group 1 metabotropic glutamate receptors (mGluRs). Specifically, mGluR-iLTD induced by the Group 1 mGluR agonist, DHPG (50  $\mu$ M) was impaired in obese animals, and endocannabinoid tone was blocked in the presence of the mGluR5 antagonist, MTEP. In addition, we further show that iLTD is rescued in obese animals via restoration of glutamate homeostasis by N-acetylcysteine. Together, our findings suggest that long-term exposure to a palatable diet alters glutamatergic synaptic transmission within the OFC, resulting in enhanced endocannabinoid signaling and tone mediated by Group 1 mGluR activation, which leads to a decrease in GABAergic synaptic transmission. This endocannabinoid-mediated disinhibition is thought to result in hyperexcitation of OFC pyramidal neuron output, which may be a cellular mechanism for overeating. The rescue of palatable diet-induced changes in synaptic plasticity by restoring glutamate homeostasis may be a potential therapeutic strategy for treating obesity.

## Th15. AMPA Receptor Translation is Altered Following the Incubation of Cocaine Craving

*Michael Stefanik\*, Mike Milovanovic, Marina Wolf*

Long-lasting synaptic modifications rely on the synthesis of new proteins. Protein synthesis-mediated changes in synaptic connections are believed to underlie long-term alterations in neural circuits involved in a variety of behaviors. We recently identified a novel linkage between protein translation and adaptations in medium spiny neurons of the NAc that leads to enhanced drug seeking. Incubation of craving depends on the time-dependent strengthening of AMPA receptor (AMPA) transmission onto medium spiny neurons in the nucleus accumbens (NAc) through the accumulation of high-conductance, GluA2-lacking, Ca<sup>2+</sup>-permeable AMPARs (CP-AMPA). NAc slices from "incubated" rats exposed for 1hr to protein synthesis inhibitors showed signs of a normalized state of synaptic transmission, including the reduction in the elevated levels of CP-AMPA. We first sought to investigate the mechanisms that regulate translation in the NAc in the drug-naïve state, and then determine whether translation is dysregulated after a period of prolonged withdrawal (>40 days) from extended-access cocaine self-administration. Further, we wanted to examine whether the translation of specific key proteins was altered following incubation. Male Sprague Dawley rats underwent 10 days of extended-access cocaine self-administration (6hr/day, 0.5mg/kg/infusion) followed by >40 days of withdrawal. SUNSET labeling with the antibiotic puromycin (+/- drugs) was used to measure protein translation in freshly dissected NAc tissue. Results show that overall translation was unaltered by mGlu1 blockade (LY367385) but increased by mGlu5 blockade (MTEP). NMDAR blockade (APV) increased overall translation in naïve and saline, but not cocaine, rats. Then, to test the hypothesis that AMPAR translation was altered after incubation, we immunoprecipitated puromycin-labeled proteins and immunoblotted for key proteins like GluA1 and GluA2. Results demonstrated that GluA1, but not GluA2, translation is increased in the NAc of incubated rats, and that this is independent of the loss of NMDAR regulation of translation seen after incubation. This increase GluA1 synthesis may account for the upregulation of homomeric GluA1 receptors in the NAc of "incubated" rats. This suggests that ongoing protein translation maintains synaptic adaptations in MSNs that are directly linked to incubation of craving.

## **Th16. Selective Manipulation of Inhibitory Signaling in Dopamine Neurons of the Ventral Tegmental Area Alters Drug-Related Behavior**

*Nora McCall\*, Ezequiel Marron Fernandez de Velasco, Kevin Wickman*

Dopamine (DA) neurons of the ventral tegmental area (VTA) are an important component of reward circuitry and have been widely implicated in cellular and behavioral responses to drugs of abuse. Inhibitory G protein signaling mediated by GABAB receptors (GABABRs) and dopamine 2 receptors (D2Rs) regulate the excitability of VTA DA neurons, DA neurotransmission, and behaviors modulated by DA. G protein-gated inwardly rectifying K<sup>+</sup> (GIRK) channels are a major downstream effector of GABABR and D2R, and the selective ablation of GIRK channels from DA neurons increases behavioral sensitivity to cocaine and morphine. Additionally, exposure to cocaine decreases the strength of GABABR and D2R signaling in VTA DA neurons via the internalization of GIRK channels. The hypothesis of the present study is that the strength of GIRK channel-mediated inhibitory signaling in VTA DA neurons is inversely proportional behavioral sensitivity to drugs of abuse. A key prediction of this hypothesis is that enhancing GIRK channel signaling in VTA DA neurons will decrease behavioral sensitivity to drugs of abuse. To increase GIRK channel-dependent signaling in VTA DA neurons, we employed a Cre-dependent viral approach to over-express GIRK channels or Gi/o-linked inhibitory designer receptors exclusively activated by designer drugs (DREADDs) specifically within DA neurons of the VTA of DATCre (+) mice prior to behavioral and electrophysiological evaluation. Our preliminary results show over-expressing GIRK channels increases inhibition mediated by GABABR and D2R, and decreases behavioral sensitivity to cocaine. Similarly, inhibition of VTA DA neurons with inhibitory DREADD, which is partially mediated by GIRK channels, decreases the behavioral effect of cocaine and morphine. Together, this data suggests VTA DA neuron GIRK channels contribute to behavioral sensitivity to drugs of abuse, and are a promising target for therapeutic intervention in disease states with altered DA neuron excitability.

## **Th17. Cocaine Alters Circuit-Specific Synaptic Connectivity in the Nucleus Accumbens**

*Corey Baimel\*, Laura McGarry, Adam Carter*

Repeated exposure to drugs of abuse alters the neural circuits of the nucleus accumbens (NAc). NAc medium spiny neurons (MSNs) are the principle cell type in the NAc, and can be divided into two broad subpopulations based on their expression of dopamine 1 or 2 receptors, with drugs strongly rewiring inputs at D1+ MSNs. Glutamatergic inputs from the ventral hippocampus (vHPC) are prominent in the NAc medial shell and repeated cocaine alters

synaptic transmission of vHPC input onto D1+ MSNs. However, D1+ MSNs are not a homogenous cell population, and can be further subdivided by their downstream projection targets, including the ventral pallidum and the ventral tegmental area. The basal synaptic connectivity and the impact of repeated drug exposure on these output-specific circuits is unknown. Here we use anatomical tools, whole-cell electrophysiology, two-photon microscopy and optogenetics to examine how repeated cocaine exposure alters the connectivity of vHPC inputs in the mouse NAc medial shell. We find that in drug-naïve mice, vHPC inputs are strongest in the NAc medial shell, and have a synaptic bias onto a subpopulation of MSNs. We then show how repeated cocaine exposure alters vHPC input at these cell types following acute or prolonged withdrawal from cocaine. This work reveals how repeated cocaine reorganizes cell-type and output-specific connectivity in the NAc.

## **Th18. The Influence of the Mediodorsal Thalamus on Orbitofrontal Cortex Processing**

*Ege Yalcinbas\*, Christina Gremel*

Goal-directed decision-making involves using changes in sensory and motivational information to control behavior. Historically, research has explored the role of the thalamus in passing such information to cortex, with recent interest in the mediodorsal thalamic nucleus' (MD) role in decision-making processes. The MD is reciprocally connected with the orbitofrontal frontal cortex (OFC), a subregion that has been shown to be important for adaptive decision-making and goal-directed behavior. We have recently found that the OFC is necessary for updating outcome value following shifts in motivational state. Here, we assessed the contribution of MD in supporting OFC processing during value updating in a shifted motivational state. After mice were trained on an incentive learning paradigm, their motivational state was shifted by manipulating food restriction state. Mice were then given the opportunity to update value through re-exposure to the outcome in their shifted motivational state. The activity of MD neurons that project specifically onto the OFC (MD-OFC) was chemogenetically attenuated during this period of value updating, and whether OFC processing was disrupted was tested via a 5-minute extinction test in the same operant context on the following day. Attenuating MD-OFC activity impaired the ability to update outcome value in comparison to agonist treated controls. Our findings suggest that MD modulation of OFC is necessary for OFC to update value. Further work is needed to elucidate the precise manner in which MD projection neurons modulate the activity of OFC neurons and to identify whether MD is passing specific information to OFC.

## **Th19. Parvalbumin-Positive Interneurons in the Nucleus Accumbens Inhibit Impulsive Behavior**

*Marc Pisansky\*, Patrick Rothwell*

Impulsive behavior characterizes various psychiatric disorders, including drug addiction. The nucleus accumbens (NAc), a forebrain region classically implicated in reward, is central to the neural circuitry mediating impulsivity. Within the NAc, primary projecting medium spiny neurons (MSNs) receive feed-forward inhibition from parvalbumin-positive (PV+) interneurons. In this study, we investigated the role of PV+ interneurons within the NAc core on impulsive behavior using the five-choice serial reaction time (5-CSRT) task in mice. The 5-CSRT task requires an operant response to be withheld until it can be directed to a location indicated by a brief visual cue. Premature responses, defined as those occurring prior to the onset of the visual cue, are an index of impulsivity. Prior to training mice in this task, we virally expressed the Gi-coupled hM4D DREADD receptor within PV+ interneurons and systemically administered the ligand CNO prior to the final stage of testing. Chemogenetically inhibiting PV+ interneurons increased premature responses without altering response latencies or open field locomotor activity. Our current efforts involve using fiber photometry to measure in vivo activity of PV+ interneurons during the 5-CSRT task. These experiments indicate that PV+ interneuron activity shapes the selection and timing of behavioral responses, most likely through feed-forward inhibition of MSN activity and striatal output.

## **Th20. Noradrenergic Transmission in the Ventral Periaqueductal Gray Modulates Arousal**

*Kirsten Porter-Stransky\*, Samuel Centanni, Canaan Jerome, Saumya Karne, Jennifer Wong, Andrew Escayg, Danny Winder, Darlene Mitrano, David Weinshenker*

The activity of dopamine (DA) neurons in the ventral periaqueductal gray (vPAG) tracks with arousal state, and lesions of vPAGDA cells increase sleep; however, the circuitry controlling these wake-promoting DA neurons is unknown. The present study combined electrophysiology, immunoelectron microscopy, and behavioral pharmacology in mice to elucidate a novel local circuit in the vPAG that promotes arousal. Direct activation of vPAGDA neurons using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) or agonist stimulation of local  $\alpha 1$ -adrenergic receptors ( $\alpha 1$ ARs) promotes arousal, while  $\alpha 1$ AR blockade reduces wakefulness.  $\alpha 1$ ARs drive vPAGDA activity in a glutamate-dependent, action potential-independent manner, consistent with a non-neuronal source of the glutamate. Compared to other dopaminergic brain regions,  $\alpha 1$ ARs in the vPAG are enriched on astrocytes. Mimicking  $\alpha 1$ AR transmission, Gq-DREADD activation of vPAG

astrocytes is sufficient to increase wakefulness. Together, these experiments indicate a novel arousal circuit and mechanism whereby astrocytic  $\alpha 1$ ARs activate vPAGDA neurons via glutamate transmission.

## **Th21. Bound and GAGed: Molecular Mechanisms Localizing Netrin-1 in Neural ECM**

*Stephanie Harris\*, Heleen van't-Spijker, Celina Cheung, K. Adam Baker, Simon Moore, James Fawcett, Jessica Kwok, Timothy Kennedy*

Axons often travel long distances to reach their targets during development. Netrin-1 is a bi-functional axon guidance protein that can attract or repel extending axons and is crucial for proper spinal cord development. Commissural neurons, born in the dorsal embryonic spinal cord, extend axons to the ventral midline where the concentration of netrin-1 is high. The netrin-1 receptor Deleted in Colorectal Cancer (DCC) is expressed by commissural neurons and required for the chemoattractant response to netrin-1. Netrin-1 protein is comprised of three major domains; the laminin related domains VI and V, and an NTR-like C domain. Domains VI and V contain sequences that bind DCC while the functional significance of the C domain is not known. We are investigating the possibility that netrin-1 may be localized and anchored in the extracellular matrix (ECM) through specific interactions of the C-domain with ECM Glycosaminoglycans (GAGs). GAGs are expressed in both developing and adult CNS, and composed of a core protein decorated with multiple unbranched sugar side chains. Our findings indicate that netrin-1 binds Heperan Sulfate Proteoglycans (HSPG) and Chondroitin Sulfate Proteoglycans (CSPG) isolated from developing and adult rat CNS, and that HSPGs increase axon outgrowth in response to netrin-1. We are currently investigating possible interactions between netrin-1 and GAG protein rich perineuronal nets (PNN) that regulate synapse function in the adult brain.

## **Th22. The Filum Terminale of the Spinal Cord is a Source of Autologous Neural Progenitor Cells**

*Ryan Chrenek, Laura Magnotti, Ruchira Jha, David Cardozo\**

Neural stem cells (NSCs) are undifferentiated cells in the central nervous system (CNS) that are capable of self-renewal and can be induced to differentiate into neurons and glia. Current sources of mammalian NSCs are confined to regions of the CNS that are critical to normal function and surgically difficult to access, which limits their therapeutic potential in human disease. We have found that the filum terminale (FT), a previously unexplored, expendable, and easily accessible tissue at the caudal end of the spinal cord, is a source of multipotent cells in postnatal rats and humans. Cells were isolated from the FT rats, from terminated fetuses, and from children

and adolescents who had undergone surgical resections for tethered spinal cords. These cells gave rise to neurospheres which proliferated over extended periods of time in culture. The neurospheres were induced to differentiate in vitro into neurons and glial cells. Through directed differentiation using sonic hedgehog and retinoic acid in combination with various neurotrophic factors, FT-derived neurospheres generated motor neurons that were capable of forming neuromuscular junctions in vitro. To understand the source of these cells, we conducted a histological analysis of the FT NSC niche in postnatal rats and humans. Immunohistochemical characterization reveals that the FT is mitotically active and its cells express similar markers to those in other CNS niches. In addition, the organization of the FT mostly closely resembles that of the adult spinal cord stem cell niche. More recently, we have studied the ability of FT-derived progenitors to survive and differentiate in vivo. These cells survived when injected into chick embryos and initial studies of in utero injections into E15 mouse embryos suggest that they are capable of differentiating into CNS neurons which engraft into the brain tissue.

## **Th23. Identification of Novel Targets for Parkinson's Disease Levodopa-Induced Dyskinesia**

*Roberta Marongiu\*, Leandra Velazquez, Jillian Joyce, Michael Kaplitt*

The gold standard for treatment of Parkinson's disease (PD) is the pharmacological restoration of dopamine transmission with administration of the dopamine precursor levodopa. This dramatically improves motor symptoms; however, over time about 80% of patients develop abnormal involuntary movements, or levodopa-induced dyskinesia, which constitute a major cause of disability and can limit therapeutic efficacy. We have identified the p11 (S100A10) and LRRK2 proteins as novel targets for treatment of levodopa-induced dyskinesia. To investigate the influence of striatal p11 on dopamine signaling, we generated an AAV vectors to block production of murine p11 (AAV-sh.p11) and stereotactically injected it into the dorsal striatum of 6OHDA lesioned mice. We first found that inhibition of striatal p11 significantly decreased rotational behavior in response to acute treatment with D1 and D2 receptor agonists, apomorphine, and levodopa. Furthermore, we observed that inhibition of striatal p11 significantly decreases abnormal involuntary movements due to levodopa chronic treatment by roughly 50% when compared to control mice. This indicates that normal p11 levels are necessary for striatal dopamine responsiveness. Recently, clinical and experimental data have suggested that the PD-related leucine-rich repeat kinase 2 (LRRK2) may be important for striatal neuronal function. Specifically, LRRK2 is particularly enriched in striatal medium spiny neurons and has been associated with several key regulators of striatal function, including PKA and pERK1/2. To test the hypothesis that LRRK2 may influence striatal responses to dopamine replacement therapy and the development of dyskinesia in PD,



we generated AAV vectors to inhibit mouse LRRK2 (AAV-sh.LRRK2) and, as for the experiments reported above, we injected it into the dorsal striatum of 6OHDA lesioned mice. Interestingly, mice that received striatal AAV-sh.LRRK2 showed a significant 40-50% increase in dyskinesia scores and an increased percentage of mice with limb and orolingual dyskinesia by about 40% respect to control group. Our preliminary results suggest that endogenous levels of LRRK2 are important for dorsal striatum response to dopamine. Taken together our data suggest that optimal levels of p11 and LRRK2 are necessary for proper response of the dorsal striatum to dopamine replacement therapy in PD mice.

## **Th24. Dominant Negative Variant of the Dopamine Transporter Associate With Early-Onset Parkinsonism and Psychiatric Disease**

*Freja Hansen\*, Natascha Arends, Sasha Tolstoy, Kathrine Jensen, Aparna Shekar, Jenny Aguilar, Matthew Lycas, Troels Rahbek-Clemmensen, Tina Skjærringe, Lars Friberg, Lisbeth Møller, Aurelio Galli, Lena Hjermand, Ulrik Gether*

The dopamine transporter (DAT) exerts a critical function in dopamine homeostasis by mediating reuptake of dopamine. Complete 'loss of function' mutations in DAT have been identified as a rare cause of autosomal recessive parkinsonism-dystonia with infantile/childhood onset. We recently described the first patient, carrying DAT missense mutations, who suffered from both adult early-onset parkinsonism and ADHD. Here, we further expand the clinical spectrum of DAT associated disease with an additional patient that present with the unique combination of early-onset parkinsonism and concurrent psychiatric disorder. This patient is heterozygote for a missense mutation, DAT-K619N, located in the C-terminal of DAT. Two SPECT scans of the patient, performed seven years apart, show reduced DAT binding along with mild progressive dopaminergic neurodegeneration. In heterologous cells, DAT-K619N demonstrates reduced dopamine uptake capacity, attenuated amphetamine induced efflux, and reduced expression. Using fluorescent timers and Stochastic optical reconstruction microscopy (STORM), we demonstrate that the sequestration of DAT-K619N into nanodomains is impaired, and that the DAT-K619N is subject to accelerated turnover. Importantly, DAT-K619N exerts a dominant negative effect on WT DAT function in vitro as well as in vivo upon viral expression in WT mice. *Drosophila Melanogaster* expressing the hDAT-K619N mutant further substantiated a pronounced phenotype in vivo, as the flies show clear hyperactivity along with impaired dopamine uptake and a dramatic (90%) reduction in amphetamine induced dopamine efflux, compared to flies expressing WT hDAT. Our results provide additional support for the pathological outcome of abnormal DAT function, and suggests that heterozygosity for a 'gain of disruptive function' DAT variant potentially have more devastating effects than heterozygosity for loss of function variants.

## **Th25. Investigation Into Presymptomatic Huntington's Disease Patients' Views on Preventative Drugs**

*Marcus Parrish\*, Andrea Hanson-Kahn, Kevin Grimes*

Huntington's Disease (HD), a progressive, genetic, fatal, neurodegenerative disease, affects 2.7 out of 100,000 people in the world. Symptoms of HD, which often begin during middle age and worsen over 10-25 years, include involuntary movements, psychiatric disturbances, reduced functional capacity, and cognitive impairment. Individuals at risk due to a family history of HD can be genetically tested before symptom onset to determine their gene status. If identified as gene positive early, individuals may have an extended window between genetic diagnosis and onset of overt symptoms for intervention with therapeutic treatments. However, regulatory agencies have yet to approve any drug that inhibits the progression of HD in the presymptomatic population. One reason for the lack of preventative drugs is that regulatory agencies require the alteration of patients' symptoms to demonstrate therapeutic efficacy. Requiring development of symptomatic endpoints would lead to decades-long trials that would be unlikely to get funded. The use of biomarkers as primary endpoints for clinical trials may expedite development of preventative HD drugs. Studies have shown that inflammatory markers and structural brain volumes change during the decade before symptom onset and correlate with motor issues in HD patients. In this poster, we investigate the views of individuals at-risk for developing HD on preventative drugs. Through focus groups and surveys, we determine whether the at-risk HD population would be willing to take preventative drugs that have been shown to inhibit brain shrinkage and neuroinflammation, but have yet to show a change in symptom onset. From this investigation, we will propose a new regulatory paradigm for preventative therapeutics to the FDA that will be guided by the preferences of at-risk HD individuals and centered on proof of safety and disease progression markers. It is our hope that this study facilitates the development of preventative treatments for HD.

## **Th26. Predicting the Valence of Active and Passive Affective States Using FNIRS**

*Lucas Trambaiolli\*, Claudinei Biazoli Jr, André Cravo, João Sato*

The ability to ascribe pleasant or unpleasant values to stimuli or mental states is considered a fundamental and universal property of human affective experiences. However, the neural mechanisms underlying this ability have been largely discussed. Recent neuroimaging meta-analyses of fMRI and PET data favor the affective workspace model, in which positive and negative emotions rely on similar networks with varied activity patterns. In this context, we aimed to further test this model using functional near-infrared spectroscopy (fNIRS).

Forty-nine subjects had their cortical hemodynamic activity monitored by fNIRS during both passive affective pictures viewing and active eliciting of affective states. We applied multivariate brain decoding techniques to test how positive and negative valences are encoded in cortical areas. Our results corroborate the affective workspace hypothesis with high accuracies for the discrimination of positive or negative valences from neutral ones, but not for the discrimination between positive and negative valences, in both experimental conditions. Predictions accuracy of  $89.90 \pm 13.84\%$  /  $85.41 \pm 14.43\%$  were observed for positive versus neutral discrimination and of  $91.53 \pm 13.04\%$  /  $81.54 \pm 16.05\%$  for negative versus neutral (passive/active conditions, respectively). Moreover, sensors close to the dorsomedial prefrontal, right lateral and medial orbitofrontal cortices and left and right occipital cortices had the highest relevance assigned by the classifier. Our results support the notion that positive and negative valences share traditional areas related to emotions as well as visceromotor and sensory integration networks.

## **Th27. Testing the Transition From Positive to Negative Reinforcement in Alcoholism: Application of a Novel Experimental Paradigm in a Clinical Sample**

*Spencer Bujarski\*, J. David Jentsch, Daniel Roche, Vijay Ramchandani, Karen Miotto, Lara Ray*

The Allostatic Model, proposes that alcoholism is characterized by a transition from positive reinforcement in early drinking to abstinence-related dysphoria and negative reinforcement in late-stage dependence, however the concordance between this preclinical model and human psychopathology is unknown. The aim of this study is to test this proposed transition in humans. Heavy drinking participants ranging in alcohol use disorder (AUD) severity completed a novel intravenous alcohol administration paradigm combining an alcohol challenge (target BrAC = 60mg%), with progressive ratio self-administration. Subjective responses to alcohol (SR) comprised stimulation/hedonia, negative affect, sedation, and craving domains. Analyses tested whether AUD severity predicted SR and/or self-administration, and whether AUD severity moderated the associations between SR and self-administration. AUD severity predicted greater alcohol craving and greater self-administration BrAC curves. Craving during the challenge strongly predicted self-administration. Sedative responses predicted lower levels of self-administration. AUD severity was associated with greater basal negative affect, but not alcohol-related alleviation thereof and negative affect did not predict self-administration. AUD severity did not predict stimulation, nor did stimulation predict self-administration regardless of AUD severity. This study represents a novel approach to translating preclinical neuroscientific theories to the human laboratory. As hypothesized, craving was a robust predictor of self-administration and a strong sedative response

was protective. Contrary to our allostatic hypotheses, we observed neither a transition from positively reinforced alcohol consumption, nor a transition to negative reinforcement. Future studies with more severe AUD samples and acute stressors are warranted to more fully test allostatic processes.

## **Th28. Global and Cell-Type Specific Disruptions of Psychiatric Risk Gene CACNA1C Alter Ascending Serotonin System Activity**

*Daniel Ehlinger\*, Richard Tenpenny, Kathryn Commons*

Human genetic variation in the gene CACNA1C alters expression of the Cav1.2 L-type calcium channel (LTCC) and has been strongly associated with enhanced risk for a broad range of neuropsychiatric disorders including major depression, bipolar and schizophrenia. Furthermore, a gain of function missense mutation (G406R) in Cav1.2 LTCCs produces the severe neurodevelopmental condition Timothy Syndrome that presents with autism spectrum disorder. Here, we use several mouse models to explore how altered *Cacna1c* function and expression influences ascending serotonin (5-HT) neuron activity: a clinically relevant neural circuit implicated in the etiology or treatment for each of these disorders. First, we assessed 5-HT system abnormalities in the TS2-neo mouse that contains the global gain of function Timothy Syndrome mutation in *Cacna1c*. Following acute stress exposure (forced-swim), behavioral analyses and immunofluorescent labeling of Tph2 and Fos reveals enhanced active coping behavior, enhanced 5-HT neuron activity in dorsal raphe (DR), and excessive feedback-inhibition of the rostral DR in TS2-neo mice. These alterations are accompanied by elevated 5-HT content in the dorsal striatum and decreased 5-HT turnover in the amygdala regions. Next, we asked whether *Cacna1c* expression within 5-HT neurons directly influences ascending 5-HT neuron activity. To this end, we crossed Tph2-*icre*/ERT2 mice with Cav1.2-*loxP*/Ai14-TdTomato mice to produce a temporally controlled and 5HT neuron specific knock out of Cav1.2 LTCCs. Results suggest that 5-HT neuron Cav1.2 LTCCs directly influence coping behavior, DR 5-HT neuron activity, and feedback-inhibition of the ascending 5-HT system. Collectively, these data reveal a potential neurological mechanism through which alterations in the CACNA1C may enhance risk to develop a broad range of neuropsychiatric disorders and suggest the ascending 5-HT system as a therapeutic target for individuals with risk-associated genetic variation in CACNA1C.

## **Th29. An Early-Life Traumatic Event Alters Hippocampal Theta, Low Gamma, and High Gamma Power and Theta-Gamma Comodulation During an Episodic Memory Task in Adulthood**

*Sarine Janetsian-Fritz\*, Christopher Lapish*

Episodic memory is one of the most prevalent cognitive deficits observed in schizophrenia (SZ). Theta (6-10 Hz), low gamma (30-50 Hz), and high gamma (50-100 Hz) frequencies in the hippocampus (HC) are critical for encoding and retrieval of episodic memories. In addition, theta-gamma comodulation (TGC), defined as correlated fluctuations in power between these frequencies, may provide a mechanism for coding episodic sequences by coordinating neuronal activity at timescales required for memory encoding and retrieval. Since patients with SZ have impaired episodic memory, the overall objectives of these experiments were to assess local field potential (LFP) recordings in the theta and gamma range from the dorsal HC during an episodic memory task in an animal model that exhibits a subclass of symptoms that resemble SZ. LFPs were recorded from the HC to assess theta and gamma power to determine whether early life trauma (maternal deprivation (MD) for 24-hrs on postnatal day (PND 9)), which is thought to increase the risk for psychopathology, altered theta and high/low gamma power compared to sham rats during novel object recognition (NOR). Brain activity was recorded while animals underwent NOR on PND 70, 74, and 78. Furthermore, the effects of TGC in the HC were assessed during NOR between groups. MD animals were impaired on the NOR task and had no change in theta or low/high gamma power or TGC when interacting with the novel or familiar object during trials where they performed unsuccessfully or successfully. However, higher theta and gamma power and TGC was observed in sham animals depending on the object they were exploring or whether it was a successful or unsuccessful trial. These data indicate altered functioning of the HC following MD and a dissociation between brain activity and behavior in this group, providing support that early life trauma can induce cognitive and physiological impairments that are long lasting. In conclusion, these data identify a model of early life stress with a translational potential, given that there are points of contact between human studies and the MD model. Furthermore, these data provide a set of tools that could be used to further explore how these altered neural mechanisms may influence cognition and behavior.

## **Th30. A Prospective Study of Brain Functional Connectivity in Females With Anterior Cruciate Ligament Rupture**

*Jed Diekfuss\*, Dustin Grooms, Weihong Yuan, Jonathan Dudley, Kim Barber-Foss, Staci Thomas, Jonathan Ellis, Daniel Schneider, James Leach, Myer Gregory*

Anterior cruciate ligament (ACL) injuries are thought to result in the remodeling of the central nervous system. However, the reported neurologic differences post-ACL injury may be present prior to the injury, as the primary mechanism of injury is non-contact and attributed to motor coordination errors. The purpose of this study is to present a unique dataset originally captured for a concussion intervention, but which also provided prospective neurological data for participants who experienced an ACL injury. High school female athletes received resting-state connectivity scans using fMRI prior to their competitive soccer season. Two of these athletes later experienced an ACL injury (ACLI). We matched these ACLI participants to eight teammates who did not go on to sustain an ACL injury (Controls, C) based on age, grade, gender, height, and weight (ACLI:  $n = 2$ ,  $16.0 \pm 0\text{yrs}$ ,  $169.0 \pm 2.8\text{cm}$ ,  $60.1 \pm 8.3\text{kg}$ ; C:  $n = 8$ ,  $15.9 \pm 0.8\text{yrs}$ ,  $164.0 \pm 4.9\text{cm}$ ,  $58.3 \pm 7.6\text{kg}$ ) to examine differences in preseason connectivity. Twenty-five knee-motor regions of interest (ROIs) were created based on previously published data. Mann-Whitney U tests were conducted due to the small and uneven sample sizes to determine group differences in connectivity using five of the pre-selected ACL-related ROIs as seeds. Results revealed significantly greater connectivity between the left primary sensory cortex and the right posterior lobe of the cerebellum for the C ( $Mdn = .40$ ) relative to the ACLI ( $Mdn = -.09$ ),  $U = 0.0$ ,  $p = .04$ . ACL injuries often occur during attention-demanding, highly complex environments, and our preliminary data suggest that those who do not later sustain an ACL injury exhibit a stronger functional connection between a sensory-motor region and a region responsible for balance and coordination. These findings have distinct implications for ACL injury prevention as prospective pre-screening may permit more effective training development that promotes adaptive neuroplasticity.

## **Th31. The Effects of Insulin Excitatory Transmission in the Nucleus Accumbens of Lean and Obese Rats**

*Max Oginsky\*, Zuleirys Santana Rodriguez, Carrie Ferrario*

Studies of brain reward and motivation systems show that insulin enhances dopamine release in the nucleus accumbens (NAc) and produces LTD in the VTA. The NAc plays critical roles in motivation for food, however how insulin affects NAc excitatory transmission in the lean or obese state is unknown. Here we used electrophysiological approaches to examine the effects of insulin

on NAc excitatory transmission in non-obese and obese adult rats. We found that activation of insulin receptors enhances pre-synaptic glutamate release, whereas activation of insulin like growth factor receptors (IGFRs), which are also sensitive to insulin, reduces it. Furthermore, insulin induced increases in excitatory transmission were lost following high-fat diet-induced obesity. This may be due in part to a down-regulation of insulin receptor expression, as surface expression of IR $\beta$ , the obligatory subunit of the insulin receptor, was reduced in the NAc of high-fat vs. chow fed groups. High-fat diet resulted in obesity and elevations in fasted insulin levels. Thus, these data suggest that physiological manipulation of insulin is sufficient to alter the NAc response to insulin. Recordings were made in medium spiny neurons within the dorsomedial region of the NAc core, which receives strong input from the prelimbic medial prefrontal cortex (PrL). Interestingly, when we recorded from more lateral and ventral regions of the core that are less densely innervated by PrL, the response to insulin was absent. This suggests that effects of insulin may vary across synaptic inputs. This possibility is currently under investigation. Finally, preliminary results in females suggest that they may be more sensitive to insulin-receptor mediated effects on excitatory transmission than males. Together, our studies reveal novel roles for the regulation of NAc excitatory transmission by insulin and add to our understanding of how peripheral and central hormones interact to influence brain motivational systems.

## **Th32. Localization of Dopamine D2 Autoreceptors on Dopamine Neurons**

*Brooks Robinson\*, James Bunzow, John Williams*

Dopamine D2 autoreceptors are G protein-coupled receptors (GPCRs) that regulate the excitability of dopamine neurons. In the midbrain, D2 receptors are activated by the somatodendritic release of dopamine from neighboring neurons. Using GFP-tagged receptors, the distribution and signaling of D2 receptors on dopamine neurons in the substantia nigra pars compacta (SNc) were investigated. Using two-photon and confocal imaging, D2 receptors were found to be clustered on the somata, dendrites, and spines of dopamine neurons. Quantification of receptor frequency and clustering using IMARIS software was done on reconstructions of dendritic segments that were initially imaged with confocal microscopy. Additionally, using simultaneous electrophysiology and two-photon imaging, the functional consequence of this distribution of D2 receptors was studied. Localized theta electrode stimulation indicated that dopamine release sites were near the receptors and spatially restricted. The photo-uncaging of exogenous dopamine also indicated that D2 receptors experience a high and localized concentration of dopamine. Together, the distribution and localized activation of receptor clusters indicate a purposeful placement within dopamine synapses of midbrain D2 autoreceptors.

### **Th33. Novel LTP at an Opioid-Sensitive GABAergic Synapse in the VTA**

*Robyn St. Laurent\*, Julie Kauer*

Persistent opioid-induced changes in the reward pathway, such as the dopamine-rich ventral tegmental area (VTA), may precede the transition to addiction. Opioids decrease inhibition onto VTA dopamine cells, increasing excitability. Spontaneous activity of dopamine cells in the VTA is tightly regulated by inhibitory inputs, and morphine exposure has been demonstrated to affect synaptic plasticity at inhibitory synapses. However, the VTA is a heterogeneous region with different subsets of neurons having distinct functional effects on behavior, and therefore, opioid-induced adaptations may also depend on the precise circuit involved. Recently, we discovered a novel form of long-term potentiation at opioid-sensitive inhibitory synapses in the VTA using a low frequency stimulation (LFS) pairing protocol (LFS-LTPGABA). We observed LFS-LTPGABA in dopamine cells recorded in the lateral VTA (LTP in 13/25 Ih+ cells) when inhibitory postsynaptic currents (IPSCs) were evoked by electrically stimulating caudal to the VTA in a horizontal midbrain slice. The location of the stimulating electrode differs from other reports examining inhibitory synaptic plasticity in the VTA, including one finding that IPSCs exhibit LTD with LFS. These differences can most likely be attributed to stimulating different inputs onto dopamine cells. Using optogenetics, we are currently investigating possible input regions located caudal to the VTA that have GABAergic projections, including the rostromedial tegmental nucleus and the dorsal raphe. We are also looking at the locus of this plasticity because the LTP was accompanied by a decrease in paired pulse ratio, suggesting an increase in presynaptic release probability. Interestingly, this LTP may be NMDAR-independent (LTP in 5/7 Ih+ cells in the presence of d-AP5; IPSC amplitude normalized to baseline =  $146 \pm 17\%$ , paired t test  $p = 0.029$ ,  $n = 7$  cells). Supported by DA011289 (JAK) and T32 NS 62443-8 (RS).

### **Th34. Pharmacotherapeutic Potential of NDGA Against 6-OHDA Induced Parkinson's Disease in Mice**

*Baldeep Kumar\*, Rupinder Kaur Sodhi, Raghunath Singh, Anurag Kuhad*

Parkinson's disease (PD) is debilitating, chronic, a neurodegenerative motor disorder which occurs due to decrease in dopamine levels neurons of the substantia nigra. Oxidative stress and health of striatal dopaminergic neurons are one of the most important etiopathological aspects of PD. With this background present study has been designed to explore the neuroprotective potential of Nordihydroguaiaretic acid (NDGA) in 6-OHDA-induced Parkinson's disease in mice. Male BALB/c mice ( $25 \pm 2$ gm) were administered 6-OHDA unilaterally to striatum following defined coordinates in stereotaxic



apparatus. The behavioral assessment was done on 14-15, 21-22, 29-30th day for locomotion and motor deficits. The effects of NDGA (at varying doses) on oxidative stress, neuroinflammation, apoptosis, mitochondrial dysfunction, neurotransmitters and biochemical alterations were assessed. NDGA significantly alleviates the neuro-motor deficits produced by 6-OHDA in rota-rod and open field test. Further NDGA has been found to be neuroprotective by increasing the levels of antioxidant enzymes (SOD, Catalase, and GSH) and heme-oxygenase-1 (HO-1) levels in brain and reduces plasma nitrite and lipid peroxidation. It has also found to protect against neuroinflammation, mitochondrial complexes-I and IV were found to be increased whereas reduced levels of caspase-3. NDGA found to increase levels of dopamine, homovanillic acid, Kynurenic acid whereas levels of Quinolinic acid which is neurotoxic was found to be decreased. NDGA also increased brain BDNF levels which is a neurotrophic factor. It is evident from current results that with a virtue of a potent antioxidant, NDGA could be an adjunct in the pharmacotherapy of PD.



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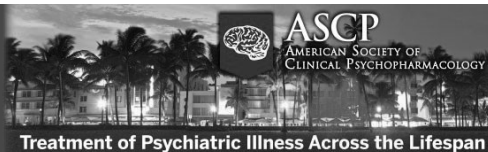
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Treatment of Psychiatric Illness Across the Lifespan

## CALL FOR SUBMISSIONS

You are invited to participate in the Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP) to be held at the Loews Miami Beach, May 29—June 1, 2018 by submitting a proposal and attending the meeting. The committee welcomes submissions from the U.S. as well as international proposals.

The theme of this year's meeting is "Treatment of Psychiatric Illness Across the Lifespan."

### The Program Committee is especially interested in proposals on the topics of:

- |   |   |
|---|---|
| a. Treatment of psychiatric disorders across the lifespan, including youth, adolescents, young adult, and geriatric | f. Opiate abuse across the lifespan, including in youth and elderly |
| b. Primary prevention of psychiatric disorders  | g. Suicide risk and prevention across the lifespan                  |
| c. Drug/Substance Abuse   | h. Career development across the lifespan                           |
| d. Medical marijuana  |   |

Detailed instructions to submit your abstracts and to register are available at [www.ASCPMeeting.org](http://www.ASCPMeeting.org).

### 2018 Submission Categories and Deadlines:

New Investigator Awards, Posters, and Individual Research Reports:	January 30, 2018
Pharmaceutical Pipeline Presentations:	February 13, 2018

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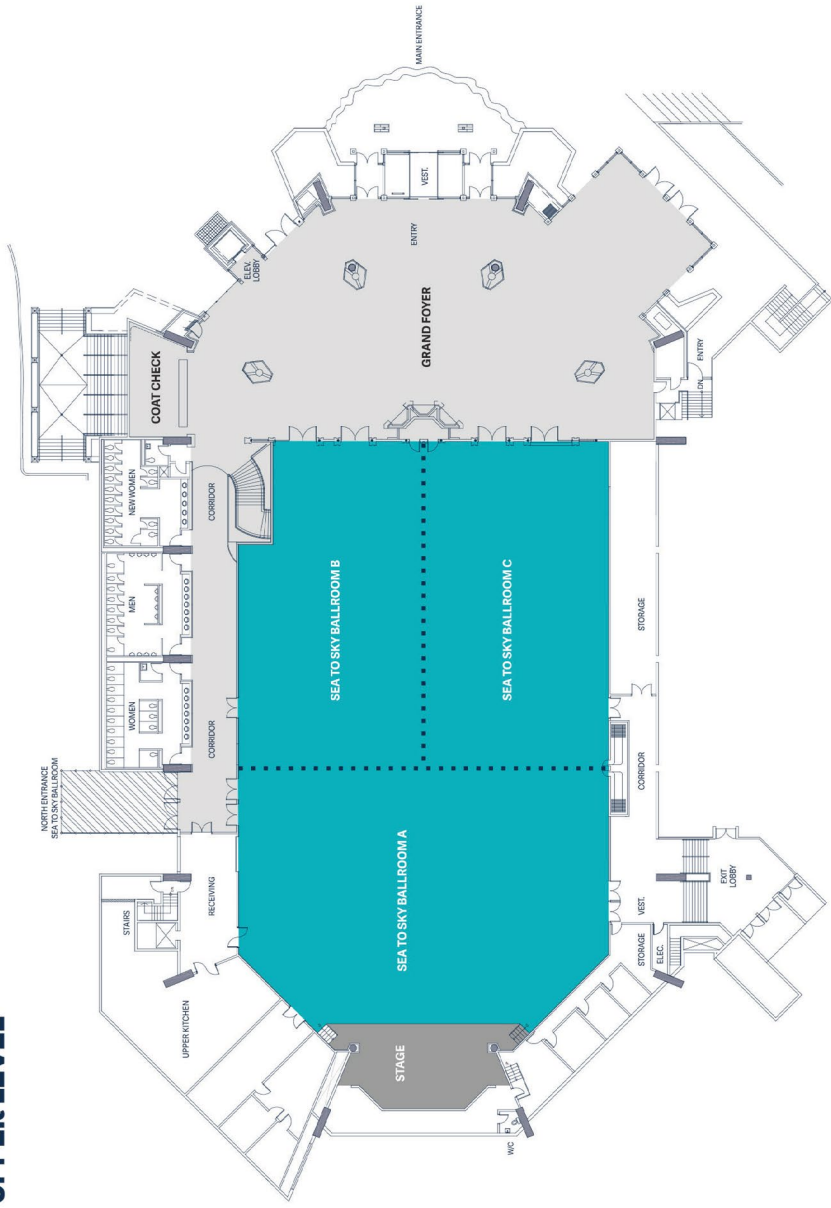




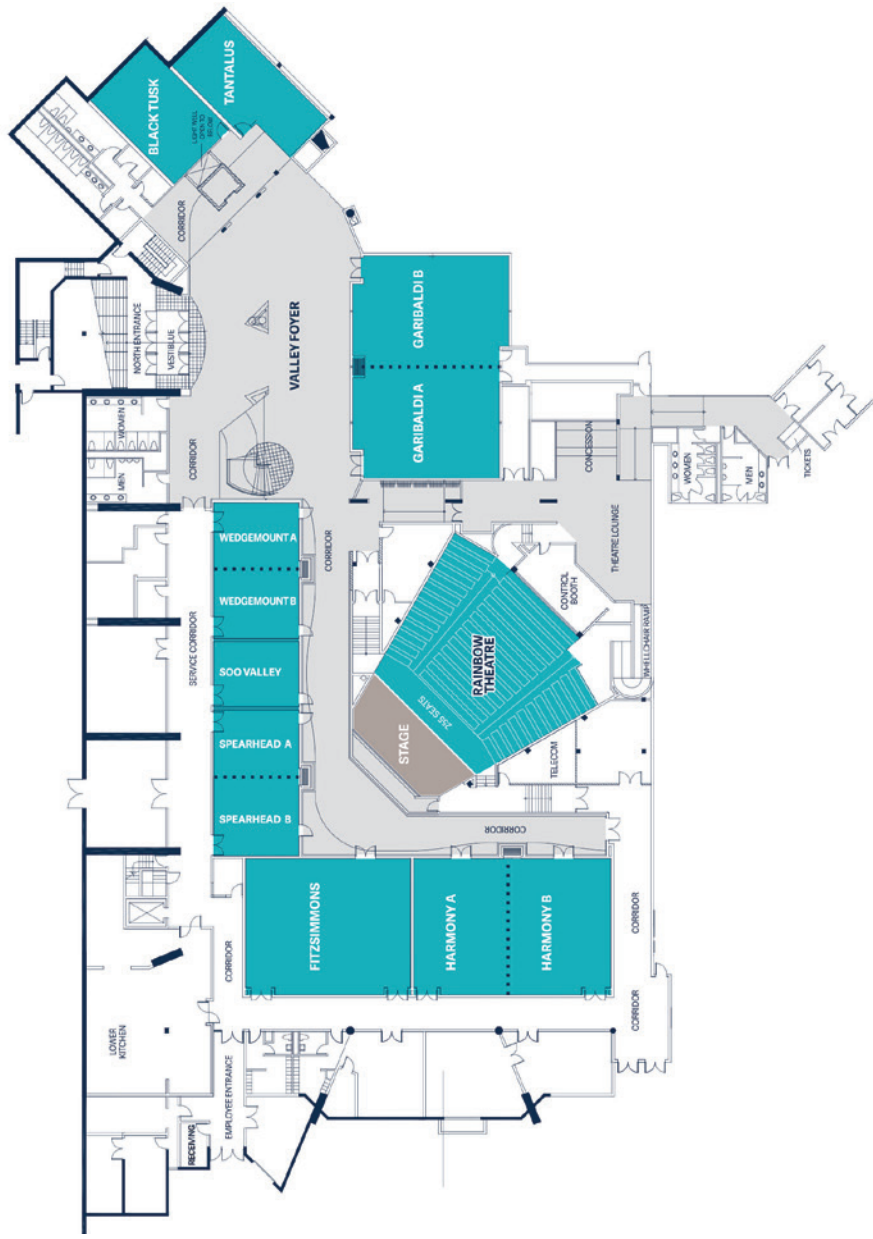




## UPPER LEVEL



# LOWER LEVEL



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