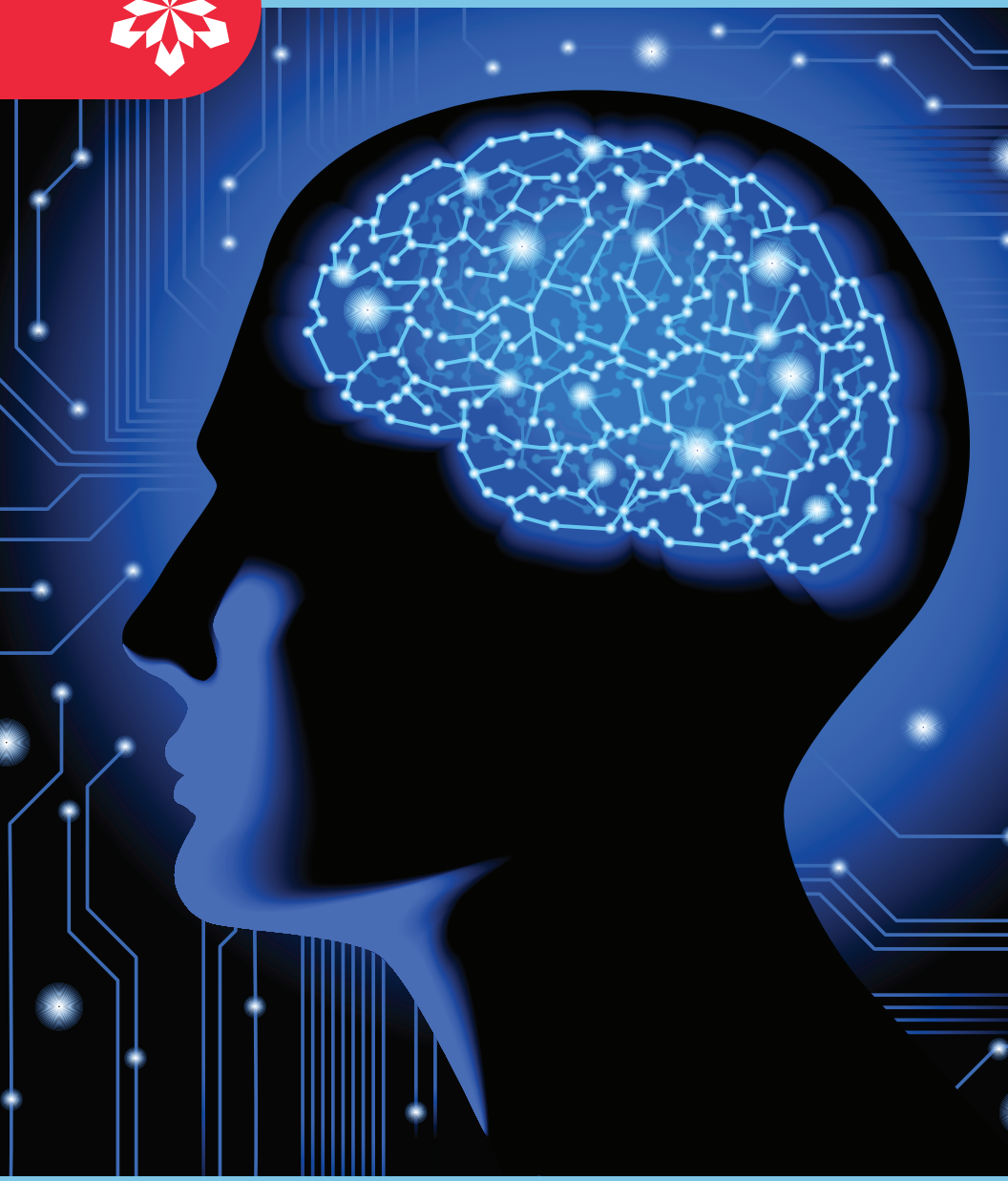
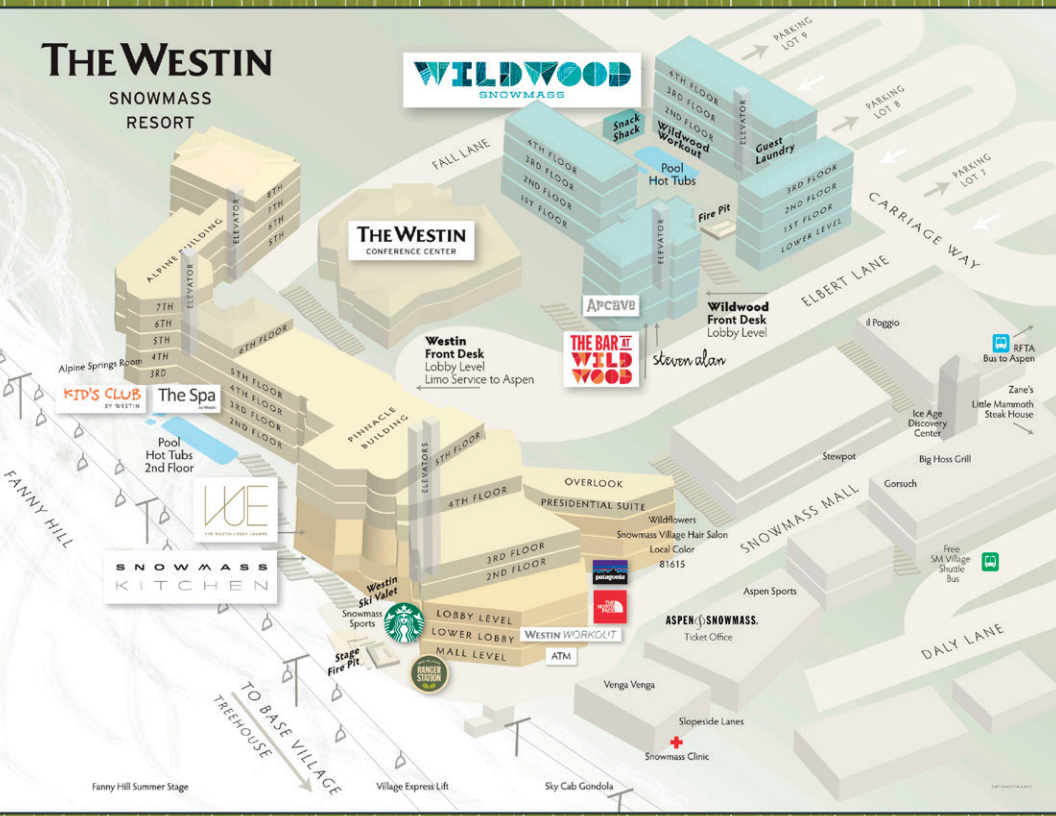
52ND ANNUAL WCBR

JAN. 28–FEB. 2, 2019

SNOWMASS, CO

WINTER CONFERENCE ON BRAIN RESEARCH





LEGEND

DINING

- Snowmass Kitchen
- Vue Westin Lobby Lounge
- Ranger Station
- Starbucks
- Bar at Wildwood
- Snack Shack

- Big Hoss Grill
- Il Poggio
- Little Mammoth Steakhouse
- Stewpot
- Venga Venga
- Zane's Tavern

AMENITIES

- The Spa by Westin
- Westin Workout
- Kid's Club
- Ski Valet
- Westin Conference Center
- Westin Stage & Firepit
- Westin Limo Service
- Wildwood Workout
- Wildwood Guest Laundry
- Wildwood Firepit
- Arcave

- ATM
- Aspen/Snowmass Ticket Office
- Fanny Hill Summer Stage
- Ice Age Discovery Center
- RFTA Bus Service
- Slopeside Lanes
- Snowmass Clinic
- Snowmass Village Free Shuttle

SHOPPING/RETAIL

- Steven Alan at Wildwood
- North Face
- Patagonia
- Snowmass Sports

- 81615
- Aspen Sports
- Gorsuch
- Local Color
- Snowmass Village Hair Salon
- Wildflowers

WELCOME TO THE 2019 WINTER CONFERENCE ON BRAIN RESEARCH (WCBR)!

Welcome to the 2019 Winter Conference on Brain Research (WCBR). This year is our 52nd annual meeting, and we are pleased to return to Aspen Snowmass for the first time in a number of years. We are excited about the lineup of scientific and networking activities that will be offered during the conference, as well as the new and updated facilities. Please note that the conference runs from Monday evening through Saturday evening, a slight shift in our usual schedule.

The opening scientific presentation of the conference will be a plenary lecture during breakfast on Tuesday, January 29th. Our speaker is Tracy L. Bale, PhD from the Departments of Pharmacology and Psychiatry at the University of Maryland School of Medicine, and Director of the Center for Epigenetic Research in Child Health and Brain Development. Dr. Bale is an internationally recognized scientist who focuses on the connection between environmental stress and fetal development. Her research has provided novel insight into the increased neurodevelopmental risk to males following prenatal insults, such as maternal stress, and the role of placental sex (XX vs. XY) in buffering effects of gestational insult. Her lab identified OGT expression in the placenta as critical in providing protection to female offspring. Her lab is also making important discoveries linking paternal stress experience to offspring dysregulation through novel epigenetic markers in the sperm. Recently, Dr. Bale has focused on bridging basic and clinical research, translating her work on epigenetic markers in the sperm, and collaborating with Dr. Neill Epperson to mechanistically examine the impact of early life adversity on neuropsychiatric disease in women. Dr. Bale's lecture connects developmental neuroscience to cognition and neuropsychiatric disease, and as such should be informative and enjoyable for all of our attendees.

Throughout the conference, parallel panel presentations and daily poster sessions will span the breadth of neuroscience. Additional elements of the program warrant your attention. There will be two special workshops on scientific-career pathways and alternative funding mechanisms for basic

science and clinical research. On Friday evening, a special poster session will showcase the highest ranked posters from junior investigators. Please note that the Mountain Lunch will be Friday, February 1st and the closing banquet is Saturday, February 2nd.

Two WCBR "Pioneer" panels will take place during the meeting, honoring the work of some of the most accomplished scientists who have been regular attendees and leaders of WCBR. 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 more-junior speakers from the same field. The 2019 Pioneers are Drs. Barry Levin and Oswald Steward. Barry E. Levin, MD is Professor Emeritus in the Department of Neurology at Rutgers, New Jersey Medical School. He is best known for his basic research in the neural regulation of energy and glucose homeostasis in animal models of obesity and diabetes. Oswald (Os) Steward, PhD is Distinguished Professor of Anatomy & Neurobiology and Director of the Reeve-Irvine Research Center (RIRC) at the University of California, Irvine. His research has focused on neuronal growth and plasticity in the mature nervous system. Please join us in honoring these two Pioneers in neuroscience and active participation in WCBR.

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 Town Hall will be a joint presentation from former WCBR chair Dr. Barbara Lipska and her co-author Elaine McArdle, who will be discussing Barbara's recent memoir *The Neuroscientist Who Lost Her Mind: My Tale of Madness and Recovery*. The talk will be held on Wednesday, January 30th at 7:00pm and will be followed by a book signing.

An important aspect of WCBR is the abundant opportunity for networking, from the opening reception on Monday night through the banquet on Saturday night. Snowmass has amazing skiing, along with world class dining, shopping, and other off-slope entertainment. It has extensive slopes for all levels, and plenty of activities for non-skiers. We are certain you will enjoy it.

Thomas M. Hyde, Conference Chair
52nd Winter Conference on Brain Research
Aspen Snowmass, January 28-February 2, 2019

Contents

General Information

WCBR INFORMATION DESK AND MESSAGE CENTER are at the 1st Floor Registration in the Conference Center at The Westin Snowmass Resort.

The Information Desk hours are as follows:

Monday, January 28, 2019	12:00 p.m. – 7:00 p.m.
Tuesday, January 29, 2019	7:00 a.m. – 7:30 p.m.
Wednesday, January 30, 2019	7:00 a.m. – 7:30 p.m.
Thursday, January 31, 2019	7:00 a.m. – 7:30 p.m.
Friday, February 1, 2019	7:00 a.m. – 6:00 p.m.
Saturday, February 2, 2019	7:00 a.m. – 6:00 p.m.

Pick up your badge at the WCBR Information Desk at the 1st Floor Registration Desk in the Conference Center at The Westin Snowmass Resort. If you have purchased guest meal tickets, these will also be available at registration.

EXHIBITS AND POSTER SESSIONS are in Salon A. Light refreshments are provided from 3:30 p.m. – 4:30 p.m., Tuesday, January 29th through Friday, February 1st. Exhibitor setup is Tuesday, January 29th, from 12:00 p.m. – 3:00 p.m. All exhibitors should have their materials removed by 10:00 p.m. on Friday, February 1st.

POSTER SESSION 1, TUESDAY, JANUARY 29th
Posters can be set up after 11:30 a.m. on Monday.

Posters will be available for viewing from 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 must be removed by 8:30 p.m. on Tuesday.

POSTER SESSION 2, WEDNESDAY, JANUARY 30th
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Wednesday.

Posters will be available for viewing from 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 must be removed by 8:30 p.m. on Wednesday.

POSTER SESSION 3, THURSDAY, JANUARY 31st
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Thursday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Thursday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Thursday.

POSTER SESSION 4, FRIDAY, FEBRUARY 1st
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Friday.

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 Friday.

Please refer to pages 27–35 for a listing of poster sessions.

BREAKFAST is served to all conference delegates during the keynote presentation on Tuesday, January 29th from 7:00 a.m. – 8:30 a.m. in Salon A & B. Tickets are not required for the Tuesday breakfast.

Wednesday through Saturday breakfast will be available from 6:30 a.m. – 8:30 a.m., in the Snowmass Kitchen and the Wildwood. ***Guest breakfast vouchers will be required for admission and will be distributed at registration.***

Don't forget to visit the posters & exhibits

Continuing Medical Education (CME)

SATISFACTORY COMPLETION

Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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In support of improving patient care, this activity has been planned and implemented by Amedco LLC and the Winter Conference on Brain Research (WCBR). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement – Amedco LLC designates this live activity for a maximum of 29.0 *AMA PRA Category 1 Credits™* for physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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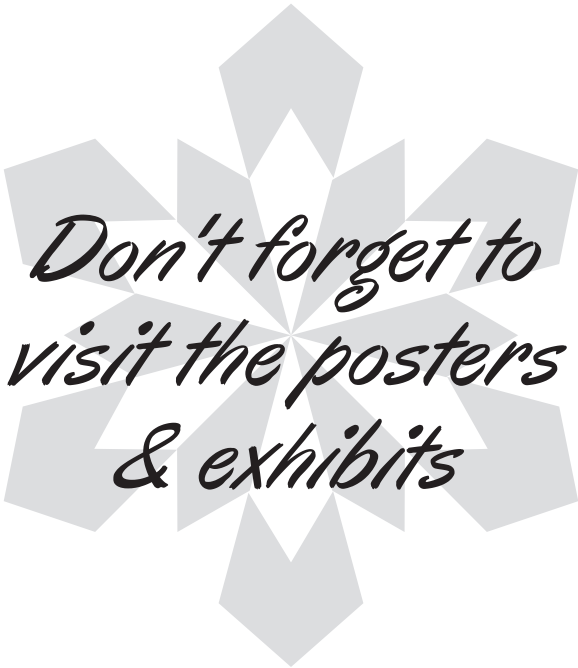

Conference Support

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.

Supernus Pharmaceuticals

The National Institute on Drug Abuse and the National Institute on Alcohol and Alcoholism of the National Institutes of Health under Award Number R13 DA047792 .
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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

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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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Pioneer Awardees

For the 52nd 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 Tuesday, January 29th and Thursday, January 31st.

BARRY LEVIN, MD

Barry E. Levin, MD, is Professor Emeritus in the Department of Neurology at Rutgers, New Jersey Medical School. He is best known for his basic research in the neural regulation of energy and glucose homeostasis in animal models of obesity and diabetes. His research has focused on the physiological, neuroanatomical, biochemical, hormonal, cellular and molecular factors that underlie individual variability in the propensity to develop diet-induce obesity and diabetes. Barry has attended WCBR for more than 40 years and has served as Conference Chair and on the Board of Directors. He continues to attend WCBR following his official retirement as a means of keeping up with new developments in neuroscience, the excellent skiing and fellowship that this very special meeting affords him.

OSWALD STEWARD, PHD

Oswald (Os) Steward, PhD, is Distinguished Professor of Anatomy & Neurobiology and Director of the Reeve-Irvine Research Center (RIRC) at the University of California, Irvine. His research has focused on neuronal growth and plasticity in the mature nervous system. His foundational discovery was the discovery of local protein synthesis at synapses, which revealed a previously unknown aspect of neuronal cell biology. This has led to our current understanding that local protein synthesis plays a pivotal role in normal synaptic function, and that disorders of synaptic protein synthesis underlie neurodevelopmental disorders such as Fragile-X Mental Retardation Syndrome. Os has attended WCBR for over 35 years, organizing workshops and panels and competing in the snowboard category in the Smitty Stevens race.

Featured Presenters

KEYNOTE ADDRESS

Tuesday, January 29, 2019 from 8:30 a.m. – 9:30 a.m.
Parental Delivery: Somatic Signals Impacting Neurodevelopment
Salon A & B

TRACY L. BALE, PHD

Tracy L. Bale, PhD, is a Professor of Pharmacology and Psychiatry, and Director of the Center for Epigenetic Research in Child Health and Brain Development at the University of Maryland School of Medicine. She is a member of the Society for Neuroscience and the American College of Neuropsychopharmacology. Dr. Bale completed her PhD at the University of Washington and her postdoctoral work at the Salk Institute with Dr. Wylie Vale. She was previously a Professor of Neuroscience at the University of Pennsylvania for 15 years. Dr. Bale was recruited to the University of Maryland School of Medicine as a STRAP recruit and the Director of the Center for Epigenetic Research in Child Health and Brain Development. Dr. Bale's research focuses on understanding the role of stress dysregulation in neurodevelopmental and neuropsychiatric diseases, and the sex differences that underlie disease vulnerability. Her groundbreaking work has uncovered the molecular mechanisms by which the environment influences parental germ cell signals and placental trophoblast development, altering fetal brain development and maturation.

BRAIN TALK TOWN MEETING

Wednesday, January 30, 2019 from 7:00 p.m. – 8:30 p.m.
The Neuroscientist Who Lost Her Mind
Salon B

BARBARA LIPSKA, PHD

Barbara K. Lipska was born, raised and educated in Warsaw, in Communist Poland. She received her MSci. degree in organic chemistry from the University of Warsaw, and Ph.D. in medical sciences in 1988 from the Medical Academy of Warsaw. In 1989 she immigrated with her family (husband Mirek Gorski and two children Kasia Lipska and Witek Lipski) to the U.S. She started a postdoctoral fellowship at the National Institute of Mental Health (NIMH) in Bethesda, MD. During her career at the NIMH, she became an internationally recognized leader in animal modeling of schizophrenia, and in postmortem human brain research. In 2013 she became Director of the Human Brain Collection Core at the NIMH. She published ~150 papers in peer-reviewed journals. She is a marathon runner and a triathlete. In 1999, she finished the NYC marathon in 3:45 (8:30 min/mile), her personal record.

ELAINE MCARDLE

A journalist for 30 years, Elaine McArdle has written extensively for the *Boston Globe, Boston Globe Magazine, Boston Magazine, Harvard Law Bulletin, Harvard Ed. Magazine, Northeastern Law Magazine*, and many more. A graduate of Centenary College of Louisiana and Vanderbilt University Law School, she has taught media law to law students and practicing lawyers, with a focus on landmark legal decisions upholding the critical role of a free press in a democratic society. She has taught memoir, narrative non-fiction, and investigative interviewing skills to reporters, writers, and criminal defense lawyers and investigators. She is co-author, with Dr. Carolyn Bernstein, of *The Migraine Brain* (Simon & Schuster, 2008). A senior editor at *UU World* magazine, she lives in Portland, Oregon with her husband Jack McGrail. As co-author with Dr. Barbara K. Lipska of *The Neuroscientist Who Lost Her Mind,* it is the authors' hope that Dr. Lipska's remarkable story will expand compassion for, and understanding of, people who suffer from mental illness.

Program

MONDAY, JANUARY 28, 2019

6:00 P.M. – 6:30 P.M.

Welcome Reception for Newcomers, Travel Fellows, and Mentors • Salon C, D, & E

6:30 P.M. – 7:30 P.M.

Welcome Reception • Salon A & B

TUESDAY, JANUARY 29, 2019

7:00 A.M. – 8:30 A.M.

Breakfast • Salon A & B

8:30 A.M. – 9:30 A.M.

Keynote Address • Salon A & B

Parental Delivery: Somatic Signals Impacting Neurodevelopment

Presenter: Tracy Bale

9:45 A.M. – 11:00 A.M.

Pioneer Session #1: Barry Levin • Cathedral Peak

Individual Differences Make the Experimental World Go Round

Pioneer: Barry Levin
Chair: Lloyd Fricker
Investigators: Carrie Ferrario, Jessica Barson

2:00 P.M. – 3:30 P.M.

Career Development Session # 1 • Castle Peak Auditorium

New Funding Approaches in Biomedical Research and Development

Kari Stoever (Chair), James Kelly, LaTese Briggs

3:30 P.M. – 4:30 P.M.

Exhibit and Poster Session 1 • Salon A

4:30 P.M. – 6:30 P.M.

Panel • Alpine Springs

The Opioid Epidemic: Unraveling Opioid-Induced Respiratory Depression

Erica Levitt (Chair), Gaspard Montandon, James Zadina, Andrea Kliewer

4:30 P.M. – 6:30 P.M.

Panel • Castle Peak Auditorium

Beyond Inflammation: Neuroimmune Pathways in Alcohol Use Disorders

Sean Farris, Florence Varodayan (Chair), S. Alex Marshall, Angela Ozburn (Co-Chair)

Panel • Cathedral Peak

Novel Approaches to Studying CNS Nutrient-Sensing

Karen Ryan, Susanne La Fleur, Carrie Ferrario (Chair), Darleen Sandoval (Co-Chair)

Panel • Overlook

Plasticity and Homeostasis in Cortical Circuits During Sleep/Wake Cycles

Alfredo Kirkwood (Chair), Kaiwen He, Michelle Bridi, Sara Aton, Keith Hengen

Panel • Salon B

Decoding Value and Motivation in the Ventral Pallidum

Thomas Hnasko (Chair), Meaghan Creed (Co-Chair), Lauren Faget, Bo Li, Jocelyn Richard, Ilya Monosov

Panel • Salon C

Ventral Hippocampal Circuits in Addiction-Related Behaviors

Rutsuko Ito, William Griffin (Chair), Jacqueline Barker (Co-Chair), Jeffrey Weiner

Panel • Salon D

Understanding and Correcting Excitability Defects in Fragile X Syndrome

Leonard Kaczmarek, Vitaly Klyachko, Anis Contractor, Hye Young Lee (Chair)

Panel • Salon E

Treating Neurodevelopmental Disorders in the Post-Genomic Era: From Animal Models to Clinical Trials Using Artificial Intelligence

Francois Bolduc (Chair), Sean McBride (Co-Chair), Sarah Lippe, David Hessl

6:30 P.M. – 7:00 P.M.

Refreshment Break • Conference Center Lobby

7:00 P.M. – 8:30 P.M.

Panel • Alpine Springs

Advanced Whole-Brain Imaging Methods in Awake or Freely-Moving Animals

Hanbing Lu, Zsolt Lenkei (Chair)

Panel • Castle Peak Auditorium

Developing and Investigating Animal Models of Compulsive Drug Taking

Mark Ferris (Co-Chair), Olivier George, Lindsay Halladay, Cody Siciliano (Chair)

Panel • Cathedral Peak

Neural Activity in Cognition and Disease

Erin Hascup (Chair), Heather Boger, Kevin Hascup, Jesse Jackson

Workshop • Overlook

So, You Want to Be a Billionaire. Is Entrepreneurial Neuroscience in Your Future?

John Mendelson, David Devilbiss (Chair)

Panel • Salon B

Voltage-Gated Ion Channels in the Pathophysiology and Treatment of Brain Disorders

Elizabeth Tunbridge (Chair), Jeremy Hall, Brady Maher

Panel • Salon C

What do the PFC and the Hippocampus Tell the Nucleus Accumbens? Implications for Addiction and Depression

Scott Thompson (Chair), Lucas Sjulson, Tara LeGates, Matthew Hearing

Panel • Salon D

Biological Predictors of PTSD Development in the Aftermath of Trauma

Vasiliki Michopoulos (Chair), Felicia Gould, Rebecca Hinrichs

Panel • Salon E

Subclinical MRI Biomarkers of Cerebral Small Vessel Disease in the Pathogenesis of Vascular Cognitive Impairment and Dementia

Clinton Wright (Chair), Richard Leigh, Michelle Caunca

WEDNESDAY, JANUARY 30, 2019

6:30 A.M. – 8:30 A.M.

Breakfast • Snowmass Kitchen and Wildwood

7:30 A.M. – 9:30 A.M.

Panel • Alpine Springs

Ski Knees? Altered Cyclic Nucleotide Signaling May Be to Blame

Michy Kelly (Chair), Annemieke Kavelaars, Carmen Dessauer, Hanting Zhang

Panel • Castle Peak Auditorium

Effects of Exercise on Alcohol and Drug Addiction: Mechanisms and Clinical Implications

Howard Becker (Chair), Matthew Solomon, Marissa Ehringer, Jean Abel, Mark Smith

Panel • Cathedral Peak

Novel Molecular Substrates and Circuits in the Epigenetic Regulation of Reward Learning

Rianne Campbell, Mary Kay Lobo, Jeremy Day (Chair), Farah Lubin

Panel • Overlook

Vulnerabilities to Disorders of Motivation and Reward

Elizabeth Pitts (Co-Chair), Mark Ferris (Chair), Joshua Beckmann, Amy Johnson, Daniel Covey

Panel • Salon B

Trafficking Events That Underlie Synaptic Plasticity and Memory

Kristen Harris, Jason Shepherd (Chair), Matthew Kennedy, Don Arnold

Panel • Salon C

Thalamus: Cell Type, Function and Plasticity

Xiaoke Chen (Chair), Huizhong Tao (Co-Chair), Anton Schulmann, Antoine Adamantidis, Carey Y. L. Huh, Stanislav Zakharenko

Panel • Salon D

Neuroplasticity Factors Contributing to Opioid Use, Escalation, and Relapse Vulnerability

Nicholas Graziane, Emilia Lefevre, Christopher Olsen, Aric Madayag (Chair)

Panel • Salon E

Neuroimaging Biomarkers of Treatment Response

Anil Malhotra (Chair), Stephanie Winkelbeiner, Miklos Argyelan, Melanie Blair, Philipp Homan

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session II • Salon A

3:30 P.M. – 4:30 P.M.

Biotech Entrepreneurs Networking Coffee Break • Wildwood

This coffee break is designated for members of the pharmaceutical and biotech communities to interface with one another and with scientists who are developing commercialization of byproducts of their research.

4:30 P.M. – 6:30 P.M.

Panel • Alpine Springs

Circuit-Specific Synaptic and Structural Plasticity in Addiction

Jacqueline McGinty (Chair), Michael Scofield, Kathryn Reissner, Matthew Hearing

Panel • Castle Peak Auditorium

Novel Mechanisms for the Regulation of CRF Signaling in Stress and Alcohol Drinking

Melissa Herman (Chair), Carolina Haass-Koffler, A. Leslie Morrow, Marcus Weera, Candice Contet (Co-Chair)

Panel • Cathedral Peak

Preclinical and Clinical Gene Therapies for Neurodegenerative Diseases: Carving Opportunities and the 'off-Piste' Challenges of an Emerging Platform

Warren Hirst (Chair), Isabelle Aubert, Anurag Tandon, Kathrin Meyer

Panel • Overlook

But Can I Still Ski? Effects of Traumatic Brain Injury on Emotion and Motivated Behavior

Jessica Barson (Chair), Alana Conti, Ramesh Raghupathi, Servio Ramirez, Patricia Molina

Panel • Salon B

Lifting Dopamine Into a New Era: Illuminating the Slopes With New Fluorescent Tools

Amy Newman (Chair), Lin Tian, Claire Deo, Ulrik Gether (Co-Chair), Kenneth Madsen

Short Course • Salon C

The Epilepsies: Current Trends in Diagnosis, Treatment, and Research

Thomas Swanson (Chair), Ian Miller, Amy Brooks-Kayal, Thomas Swanson

Panel • Salon D

Learning Structure in the World: The Computational and Neural Basis of Bayesian Models of Reinforcement Learning

Frederike Petzschner, Angela Langdon, Michael Frank (Co-Chair), Bruno Averbeck (Chair)

Panel • Salon E

The Function and Role of AMPA Receptors in Human Disease

Ingo Greger, Michael Maher, Linda Nowak, Stephen Traynelis (Chair)

7:00 P.M. – 8:30 P.M.

Brain Talk Town Meeting • Salon B

The Neuroscientist who Lost Her Mind

Barbara Lipska, Elaine McArdle

9:00 P.M. – 11:45 P.M.

Karaoke Night • Base Camp Bar & Grill

THURSDAY, JANUARY 31, 2019

6:30 A.M. – 8:30 A.M.

Travel Fellow/Mentor Breakfast • Salon A

6:30 A.M. – 8:30 A.M.

Breakfast • Snowmass Kitchen and Wildwood

7:30 A.M. – 9:30 A.M.

Panel • Alpine Springs

Diverse Roles of the Hypothalamus and Hypothalamic Circuits in Motivation and Psychopathology

Marisela Morales (Chair), David Barker (Co-Chair), Adam Gordon, Alexander Johnson, Richard O'Connor

Panel • Castle Peak Auditorium

Embracing the Diversity of Self-Administration Protocols in Drug Addiction Research

Sara Jones, Matthew Wanat (Chair), Rachel Smith, Yavin Shaham

Panel • Cathedral Peak

New Insights Into the Workings of Synapses

David Bredt, Katherine Roche, Roger Nicoll, Andres Maricq (Chair)

Panel • Overlook

Psychiatric Risk Factors in the Development of Non-Combat Related PTSD

Felicia Gould (Chair), Mackenzie Jones, Vasiliki Michopoulos

Panel • Salon B

When the Terrain Goes From Exhilarating to Aversive: Expression and Function of the Kappa Opioid Receptor

Lee-Yuan Liu-Chen, Charles Chavkin, Elyssa Margolis (Chair), Anushree Karkhanis

Panel • Salon C

Functional and Molecular Heterogeneity of CNS Stem and Progenitor Populations

Francis Szele (Chair), Steven Levison, Teresa Wood, Wendy Macklin

Panel • Salon D

Structure and Function of Glutamate Receptors

Johannes Hell (Chair), Bernd Fakler, Elva Diaz, Terunaga Nakagawa, R. Suzanne Zukin (Co-Chair)

Panel • Salon E

Ski-Atal Processing in Decision Making and Maladaptive Choice

Jennifer Wenzel (Co-Chair), Natalie Zlebnik (Chair), Barry Setlow, Erik Oleson, Catharine Winstanley

9:45 A.M. – 11:00 A.M.

Pioneer Session #2: Oswald Steward • Cathedral Peak

Getting the Message From Genes to Synapses

Pioneer: Oswald Steward
Chair: R. Suzanne Zukin
Investigators: Shannon Farris, Patricia Pirbhoy

2:00 P.M. – 3:30 P.M.

Career Development Session # 2 • Castle Peak Auditorium

Career Development Workshop: Skills for the New Investigator

Lakshmi Devi (Chair), Carrie Ferrario, Travis Brown, Lique Coolen, George Wilcox

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session III • Salon A

4:30 P.M. – 6:30 P.M.

Panel • Alpine Springs

From Molecules to Mind: Genetic Defects in Cell-Cell Signaling That Cause Neurological Disorders

Cedric Asensio (Chair), Lakshmi Devi, Lloyd Fricker, Iris Lindberg

Panel • Castle Peak Auditorium

Parabrachial Nucleus: A Nexus of Affective Pain

Asaf Keller (Chair), Sarah Ross, Yarimar Carrasquillo, Marisela Morales

Panel • Cathedral Peak

Dysregulation of Abused-Substance Intake by Kappa-Opioid Signaling

Paul Phillips (Chair), Sara Jones, Lara Hwa, Ryan Farero, George Koob

Panel • Overlook

Epigenetic Substrates of Experience-Dependent Plasticity and Their Dysregulation in Psychiatric Disease

Mary Kay Lobo, Philipp Mews (Chair), Erin Calipari, Christoph Anacker

Panel • Salon B

Ch-Ch-Changes: Redefining the Role of the Basolateral Amygdala and Orbitofrontal Cortex in Tracking Value

Kurt Fraser (Chair), Melissa Malvaez, Caitlin Orsini, Vincent Costa

Panel • Salon C

New Circuit and Synaptic Mechanisms of Dopamine Function

Paul Kramer, Brooks Robinson, Talia Lerner, Chris Ford (Chair)

Panel • Salon D

Pursuing Reward Cues: Sign-Tracking in Models of Learning, Addiction and Risky-Decision Making

Jonathan Morrow (Chair), Sam Bacharach, Nadia Chaudhri, Mariya Cherkasova

Panel • Salon E

Treatment for Traumatic Brain Injury: One-Size Doesn't Fit All

Cole Vonder Haar (Chair), Edward Hall, Olga Kokiko-Cochran, Akiva Cohen, Kris Martens

6:30 P.M. – 7:00 P.M.

Refreshment Break • Conference Center Lobby

7:00 P.M. – 8:30 P.M.

Panel • Alpine Springs

The Importance of Choice Procedures in Addiction Neuroscience

Marco Venniro (Chair), Matthew Banks, Margaret Haney

THURSDAY, JANUARY 31, CONTINUED

Panel • Castle Peak Auditorium

Synaptic Pathologies in Schizophrenia, Autism and Alzheimer Disease

Zachary Wills (Chair), Bruce Herring, Robert Sweet

Panel • Cathedral Peak

New Trends in Advancing Clinical Imaging of Neurological Disorders

Xiaoping P. Hu, Darren Kadis, Olaf Paulson (Chair)

Panel • Overlook

Understanding and Improving Concussion Self-Report: An Interdisciplinary and Multi-Method Perspective on Military Academy Cadets

Christopher D'Lauro (Chair), Michelle Weber, Karin De Angelis, Julianne Schmidt

Panel • Salon B

Calcium Channel Regulation and Synaptic Plasticity: Pre and Post

William Catterall (Chair), Ivan Kadurin, Johannes Hell, Mark Dell'Acqua

Panel • Salon C

Chaos at the Controls: Recent Avenues in Examining Cognitive Dysfunction in Addiction

Marek Schwendt, M. Foster Olive, Justin Gass (Chair)

Panel • Salon D

Reactive Astrocytes as a Target in Neuropathologies - Context-Dependent Responses and Treatment Opportunities

Milos Pekny (Chair), Elly Hol, Kristian Franze

Panel • Salon E

Improving the Therapeutic Index of NMDAR/nNOS Signaling Cascade Inhibitors (HINT: Delve B-Low the Surface)

Andrea Hohmann, Carston Wagner, Carolyn Fairbanks (Chair)

Save the Date!

WINTER CONFERENCE ON BRAIN RESEARCH

JANUARY 25–30, 2020
BIG SKY, MONTANA

FRIDAY, FEBRUARY 1, 2019

6:30 A.M. – 8:30 A.M.

Breakfast • Snowmass Kitchen and Wildwood

7:30 A.M. – 9:30 A.M.

Panel • Alpine Springs

Modulation of Signaling and Plasticity Induced by Cannabinoids

Shane Hentges (Chair), Alex Straiker, Sade Spencer, Henrietta Szutorisz, Olivier Manzoni

Panel • Castle Peak Auditorium

Restoring Cellular and Circuit Function to Prevent Epilepsy and Its Co-Morbidities

John Huguenard (Chair), Chris Dulla, Amy Brooks-Kayal, Mark Beenhakker, Anne Anderson

Panel • Cathedral Peak

BNST or B-Friendly: The Bed Nuclei of Stria Terminalis as an Integrative Control Center for Adaptive and Maladaptive Behaviors

Lara Hwa (Co-Chair), Lindsay Halladay, William Giardino (Chair), Travis Goode

Panel • Overlook

History Matters: How Drug Type and Use Pattern Influences Addiction Vulnerability and Treatment

Mary Torregrossa (Chair), Jacqueline Barker, Jamie Peters, Timothy O'Neal

Panel • Salon B

A New Age of Monoamine Detection Following Synaptic Stimulation

John Williams (Chair), Tommaso Patriarchi, Aya Matsui, Armando Salinas, Haining Zhong

Panel • Salon C

The Use of In Vivo Imaging Techniques to Link Neural Function and Behavior

Erin Calipari, Samuel Centanni (Chair), Alexander Smith (Co-Chair), Jenna McHenry

Panel • Salon D

It's All Down Hill From Here, or is it? How Life Experiences Can Alter the Hormonal Trajectory for Risk and Resilience

Gretchen Neigh (Chair), Deena Walker, Liisa Galea, C. Neill Epperson

Panel • Salon E

Mechanisms of Chronic Pain in Primary Afferents and the Spinal Cord

Juan Carlos Marvizon (Chair), Annemieke Kavelaars, James Zadina, George Wilcox

10:30 A.M. – 12:00 P.M.

Smitty Stevens Ski Race • Spider Sabich Race Arena

12:00 P.M. – 2:30 P.M.

Mountain Lunch • Base Camp Bar & Grill

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session IV • Salon A

4:30 P.M. – 6:30 P.M.

Panel • Alpine Springs

Behavioral and Computational Properties of the Anterior Cingulate Cortex

Alicia Izquierdo (Chair), Aaron Gruber, Ilya Monosov, Sarah Heilbronner

Panel • Castle Peak Auditorium

Astrocyte Regulation of Reward Circuit Function and Behavior

Aric Madayag, Xinzhu Yu, Wendy Xin, Carlos Paladini (Chair)

Panel • Cathedral Peak

Fetal Origins of Adult Disease (FOAD)-Relevance in Psychiatry

Daniel Weinberger, Amanda Law (Chair), C. Neill Epperson, Thomas Hyde

Panel • Overlook

Ketamine, Psilocybin and Psychedelics in Psychiatry: Data, Mechanisms and Trends

David Pickar (Chair), Gerard Sanacora, Carla Canuso, David Erritzoe, Alan Schatzberg

Panel • Salon B

Advances in Understanding Dopamine Dynamics and Contribution to Decision-Making

Geoffrey Schoenbaum, Claire Stelly, Ali Mohebi, Arif Hamid (Chair)

Panel • Salon C

Excite Me or Excite Me Not: Homeostatic Plasticity in Health and Disease

Hey-Kyoung Lee (Chair), Patrick Kanold, Elizabeth Quinlan, Hee Jung Chung

Panel • Salon D

The Role of Catecholamines in Mild Traumatic Brain Injury

David Devilbiss (Chair), C. Edward Dixon, Floyd Thompson, Ramesh Raghupathi

Panel • Salon E

Translational Studies on the Impacts of Developmental Nicotine Exposure on Adolescent and Adult Learning, Memory and Addiction

Shahrdad Lotfipour (Chair), Kay Linker, Thomas Gould, Alexey Ostroumov

6:30 P.M. – 7:30 P.M.

WCBR Business Meeting • Salon B

All are invited and encouraged to attend.

7:30 P.M. – 9:30 P.M.

Special Poster Session and Reception • Salon A & C

SATURDAY, FEBRUARY 2, 2019

6:30 A.M. – 8:30 A.M.

Breakfast • Snowmass Kitchen and Wildwood

7:30 A.M. – 9:30 A.M.

Panel • Alpine Springs

Guidance of Reward Seeking Through Dynamic Neural Circuits

Lauren Dobbs, Vijay Mohan K Namboodiri (Co-Chair), James Otis (Chair), Meaghan Creed

Panel • Castle Peak Auditorium

Collusion Between Dopamine and its Collaborators in Motivated Behavior

Margaret Rice, Kate Wassum (Chair), Benjamin Saunders, Jennifer Wenzel

Panel • Cathedral Peak

Skiing With Friends and Avoiding Collisions With Others: Organization of Intracellular Signaling

Kim Neve (Chair), Eric Janezic, Michel Bouvier, Roshanak Irannejad, Angela Wild

Panel • Overlook

The Inhibitory 'Edge' - GABAergic Circuit Control in Fear, Anxiety and Reward

Katharine Smith, Ethan Guthman, Melissa Herman, Molly Huntsman (Chair)

Panel • Salon C

Seizures, Cannabidiol and the Developing Brain

Angus Wilfong, Anne Anderson, David Naylor (Co-Chair), Claude Wasterlain (Chair)

Panel • Salon D

Auditory Pathway: From Circuits to Behavior

Alfonso Junior Apicella (Chair), Li Zhang (Co-Chair), Shaowen Bao, Maria Geffen, Daniel Llano, Matthew McGinley

Panel • Salon E

Glutamate Transporter -1 (GLT-1) Regulation in Health and Disease

Lori Knackstedt (Chair), Kathryn Reissner, Michelle Olsen, Paul Rosenberg

4:00 P.M. – 4:30 P.M.

Coffee Break • Conference Center Lobby

4:30 P.M. – 6:30 P.M.

Panel • Alpine Springs

The Intestinal Microbiota: Our Best Frenemy in Neurological Disorder and Disease

Kyle Frantz (Chair), Claire de La Serre, Laura Cox, Benoit Chassaing

Panel • Cathedral Peak

Circuit and Synaptic Mechanisms of Compulsive Drug Seeking

Christina Gremel (Chair), Carl Lupica, Frederic Hopf, Rafael Renteria (Co-Chair), Lauren Dobbs

SATURDAY, FEBRUARY 2, CONTINUED

Panel • Overlook

Less is More: The Intermittent Access Model as an Alternative to Long/ Continuous Access Models for Promoting Addiction-Like Behavior in Laboratory Animals?

Florence Allain, Susan Ferguson, Alex Kawa, Morgan James (Chair)

Panel • Salon C

What's Love Got to Do with It? Oxytocin Treatment for Stress and Addiction

Brian Trainor, Jill Becker (Co-Chair), Tiffany Love (Chair), Harriet de Wit

Panel • Salon D

Mechanisms by Which the Prefrontal Cortex Mediates Maladaptive Behaviors

Devin Mueller (Co-Chair), James Otis, Jason Radley, Lique Coolen (Chair)

Panel • Salon E

Understanding Others: Neural Circuits for Social Behavior and Autism-Associated Dysfunction

Ofer Yizhar (Chair), Eunee Lee, Francesco Papaleo, Jaideep Bains

6:45 P.M. – 7:30 P.M.

Cocktail Hour • Conference Center Lobby

7:30 P.M. – 11:45 P.M.

Awards Banquet and Dance • Salon A & B

Save the Date!

WINTER CONFERENCE ON BRAIN RESEARCH

JANUARY 25–30, 2020
BIG SKY, MONTANA

POSTER SESSION I

TUESDAY, JANUARY 29, 2019 • SALON A

Posters will be available for viewing from 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. Real-Time High-Precision Pharmacokinetic Measurements of Cocaine in the Brain

Tod Kippin

TU2. Effect of Drug History on Motivation and Craving in a Rat Model of Polydrug Abuse

Elizabeth Crummy

TU3. Psychomotor Sensitization Following an Intermittent Access Schedule of Cocaine Self-Administration

Crystal Carr

TU4. Divergent Expression of Methylated DNA Cytosine Dioxygenases in the Nucleus Accumbens of Mice Exhibiting Variable Ethanol Behavioral Sensitization

Graham Kaplan

TU5. Controllability of Stressors Differentially Alters the Severity of Cocaine-Induced Encoding Deficits of Associative Cues Within the Nucleus Accumbens

Kayla Siletti

TU6. Examining Neuroadaptations Following Oxycodone Self-Administration and Prolonged Forced Abstinence

Michael Stefanik

TU7. Investigation of the Role of Neuroimmune Signaling in Oxycodone Seeking

Kyle Brown

TU8. Modulating Cue-Reactivity With Theta-Burst Stimulation to the Frontal Pole: A Novel Target With Transdiagnostic Relevance

Colleen Hanlon

TU9. Nicotine Gateway Effects Enhance Adolescent Alcohol Intake and Age-Independent Alcohol Preference in Male Mice

Shahrdad Lotfipour

TU10. Optogenetic Inactivation of Orbitofrontal Cortex Abolishes Devaluation-Sensitive Aspects of Behavior During Economic Choice

Matthew Gardner

TU11. Representation of Environmental Structure by the Orbitofrontal Cortex and Hippocampus Within an Odor Sequence Task

Jingfeng Zhou

TU12. Modeling Motivational Influences on Sustained Attention

Harrison Ritz

TU13. A Toolbox for Modeling Instrumental Learning With the Reinforcement Learning Drift Diffusion Model
Mads Pedersen

TU14. White Matter Connectivity Supports Brain State Transitions Underlying Working Memory
Eli Cornblath

TU15. Simulating the Benefits of Motivational Dopamine States in the OpAL Model
Alana Jaskir

TU16. Microbes & Monoamines: Stepping Stones from Dysbiosis to Neuropsychiatric Disease
Stephen Skolnick

TU17. Milling With Ultraviolet Excitation (MUVE) for Brain Phenotyping
Jason Eriksen

TU18. Regulation of 5-HT1B Serotonin Receptor Expression in the Striatum by Dopamine Depletion and L-DOPA Treatment
Heinz Steiner

TU19. Chemogenetic Activation of Paraventricular Nucleus of the Hypothalamus Oxytocin Neurons Restores Oxytocin Release and Reduces Mortality, Cardiac Inflammation and Fibrosis, as Well as Improves Autonomic Balance and Cardiac Function in an Animal Model of Heart Failure
David Mendelowitz

TU20. The Necroptotic Pathway is Involved in Seizure-Induced Neuronal Necrosis
Denson Fujikawa

TU21. Is TBI Susceptibility Related to Subject-Specific Brain Morphology and Biomechanics?
Francis Loth

TU22. Protection From TBI-Induced Vision Loss by the N-Acetylserotonin Derivative HIOC Through a BDNF/TrkB Receptor Mechanism
P. Michael Iuvone

TU23. Temporal Characterization of Neuroinflammation After Cranial Irradiation in the Mouse
Fredrik Kamme

TU24. Ahnak Scaffolds L-Type Voltage-Gated Calcium Channel and Modulates Depressive Behavior
Junghee Jin

TU25. Elucidating Neural Circuits That Transmit Affective-Motivational Pain Signals to the Amygdala
Sung Han

TU26. CB2 Agonists Increase Ectopic Ovarian Tumor Growth Independent of Their Peripheral Antinociceptive Effect
Josee Guindon

TU27. Altered Sound Localization Ability in a Mouse Model of Fragile X Syndrome
Elizabeth McCullagh

TU28. Gut-Brain Axis in Hypertension: Role of the Afferents
Jasenka Zubcevic

POSTER SESSION II

WEDNESDAY, JANUARY 30, 2019 • SALON A

Posters will be available for viewing from 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. and removed by 8:30 p.m. on Wednesday.

W1. Headset VR Clinical Challenges Combined With Neuroscience Training to Enhance Clinician Action and Capability

Bradley Tanner

W2. Enhancing Neuroscience Knowledge of Secondary School Children via a PlayStation VR Game

Bradley Tanner

W3. Neurophobia - What Causes It?

Sybil Stacpoole

W4. H3.3 Barcoding of Nucleus Accumbens Transcriptional Activity Identifies Novel Molecular Pathways Associated With Cocaine Self-Administration in Mice

Mathieu Wimmer

W5. Homecage Observation for Mouse Experiments (HOME) Device for Longitudinal and High-Throughput Measures of Physical Activity

Nanami Miyazaki

W6. Effects of Nicotine and THC Co-Administration via Vapor Inhalation in the Rat

Michael Taffe

W7. Serotonin 5-HT2A Agonist Facilitates Extinction of Incubated Palatable Food Memories

David Martin

W8. Self-Regulation of the Dopaminergic Reward Circuit in Cocaine Users With Mental Imagery and Neurofeedback

Matthias Kirschner

W9. Fatal Overdose in Recently Detoxified HIV-Positive Persons With Opioid Use: The Role of Naltrexone in Prevention

George Woody

W10. Role of HDAC3 in D1R- Vs D2R- MSNs in Regulating Cocaine-Induced Plasticity and Behaviors

Rianne Campbell

W11. Modulation of the Ventral Tegmental Area and Reward Seeking by Inhibitory and Excitatory Ventral Pallidum Output Pathways

Jessica Tooley

W12. Removal of Perineuronal Nets in the Medial Prefrontal Cortex Alters Cocaine Reinstatement and Excitability of Parvalbumin Fast-Spiking Interneurons

Emily Jorgensen

W13. Lack of GPR88 Alters Motivational Processing in Mouse Touchscreen Tests

Monica Langiu

W14. Genetic Dissection of Catecholaminergic Innervation of the Cognitive Cerebellum

Erik Carlson

W15. Serotonin and Oxytocin Regulation of Social Approach/ Avoidance Response After Social Defeat Conditioning

Luanne Hale

W16. Frontostriatal Circuit, Receptor and Neural Coding Mechanisms Underlying the Cognition-Improving vs. Cognition-Impairing Actions of Psychostimulants

Robert Spencer

W17. EEG Correlates of Working Memory Gating: Link to Reinforcement Learning?

Rachel Rac-Lubashevsky

W18. Proactive Control, Reactive Control, and Impulsivity in the Imagen Data

Dan Scott

W19. Concussion Self-Management Concepts Among United States Air Force Academy Cadets

Michelle Weber

W20. Maternal Nicotine's Effects on Learning and Memory in Adolescent Mice

Shahrdad Lotfipour

W21. Real-Time Striatal Measurements of Oxidative Stress and Dopamine in Hemiparkinsonian Rats Expressing L-Dopa Induced Dyskinesias

Leslie Sombers

W22. (-)-Phenserine (Phen): Prevention of Pre-Programmed Cell Death (PPCD) in Mild Traumatic Brain Injury (mTBI) and Alzheimer's Disease (AD)

Nigel Greig

W23. Neuroimmune and Epigenetic Mechanisms Regulate Adult Loss of Cholinergic Neurons Following Adolescent Binge Ethanol Treatment

Fulton Crews

W24. Characterization of the VPS35 p.D620N Knock-In Mouse Model of Parkinson's Disease

Stefano Cataldi

W25. Diurnal Fluctuations of Perineuronal Nets in the Prefrontal Cortex

John Harkness

W26. ACEA Chronic Administration Failed to Prevent Tumor Growth in an Ectopic Ovarian Cancer Model

Josee Guindon

W27. Improving Outcomes for Treatment-Resistant Schizophrenia: The Efficacy of ECT in Clozapine-Refractory Patients

Sana Ali

W28. Anesthesia Alters Neuronal Interactions Across the Hierarchy of Rat Visual Cortex

Anthony Hudetz

POSTER SESSION III

THURSDAY, JANUARY 31, 2019 • SALON A

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Thursday. 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. and removed by 8:30 p.m. on Thursday.

TH1. Incubation of Discriminative-Stimulus-Controlled Cocaine Craving During Abstinence

Rajtarun Madangopal

TH2. Impact of Gut Dysbiosis on Cocaine-Seeking in Adolescent and Adult Male Rats

Gregory Suess

TH3. Sexual Divergence in Reward and Immune Responses Following Experimental Adolescent Traumatic Brain Injury

Lee Anne Cannella

TH4. Sigma-1 Receptor Control of Extracellular Vesicle Release and Cocaine-Induced Endocannabinoid Signaling in the Ventral Tegmental Area (VTA)

Dilyan Dryanovski

TH5. C-terminus Phosphorylation of Mu-Opioid Receptor Regulates Acute and Chronic Sensitivity to Opioids

Sweta Adhikary

TH6. Cell Type Specific Control of Basolateral Amygdala Plasticity via Entorhinal Cortex Driven Feedforward Inhibition

Ethan Guthman

TH7. Dorsal Raphe Dual Serotonin-Glutamate Neurons Drive Reward by Establishing Excitatory Synapses on VTA Mesoaccumbens Dopamine Neurons

Huiling Wang

TH8. Stress and Drugs of Abuse Alter GABAergic Transmission in the Ventral Tegmental Area via Chloride Cotransporter KCC2 Downregulation

Alexey Ostroumov

TH9. Investigating Accumbal Encoding of Effortful Behavior

Bridget Matikainen-Ankney

TH10. Adaptive Immune Signaling at the Meningeal Barrier: Neuroimmune Interactions Underlying Stress-Induced Mood Disruption

Miles Herkenham

TH11. Shared and Dissociable Features of Apathy and Reward System Dysfunction in Bipolar I Disorder and Schizophrenia

Matthias Kirschner

TH12. Oscillations in Basal Serotonin and Psychiatric Disorders

Yangguang Ou

TH13. Medial Amygdala Dopamine Receptor Activity Regulates Social Avoidance Response Following Social Defeat Stress in Prairie Voles (Microtus Ochrogaster)

Maria Tickerhoof

TH14. Value-to-Choice Transformation in the Orbitofrontal Cortex and Midbrain Dopamine Neurons in Monkeys Performing an Economic Decision-Making

Mengxi Yun

TH15. Effects of Adiposity on Postural Control and Cognition in Older Adults

Stacey Gorniak

TH16. Mesoscale Wave Turbulence in the Hippocampus

Alex Sheremet

TH17. Consider the Cascade- A Classical Physics Turbulence Description of LFP Energy Interaction in the Hippocampus

Andrew Maurer

TH18. OpenBehavior: Accelerating Behavioral Neuroscience With Open-Source Tools

Lex Kravitz

TH19. Poster Withdrawn

TH20. Targeted Delivery of Two Transgenes to Modulate Protein Expression in the Brain Using MRI–Guided Focused Ultrasound

Kelly Markham-Coultes

TH21. Peptide Mediated Transport of SiRNA to the CNS Across the Blood-Brain Barrier

Brian Spencer

TH22. Evidence of Neuronal Dedifferentiation Following Spinal Cord Injury in Adult Zebrafish

Angelo Milli

TH23. Development of a Novel Stem Cell-Based Culture System to Study Axonal Outgrowth and Neuronal Differentiation

Jeffery Plunkett

TH24. Sodium Channel Dysfunction in Dravet Syndrome is Mutation-Specific

Peter Ruben

TH25. Ascot Identifies Key Regulators of Photoreceptor-Specific Splicing

Jonathan Ling

TH26. Subthalamic Nucleus Activity Associated With Freezing of Gait

Neil Mahant

TH27. Cortical Transcriptome Analysis Reveals a Persistent Neuroinflammatory Phenotype in a Mouse Model of Gulf War Illness

Kimberly Kelly

TH28. Controlling Receptor Trafficking by AAV Gene Therapy to Prevent Neuropathic Pain

Andreas Sørensen

POSTER SESSION IV

FRIDAY, FEBRUARY 1, 2019 • SALON A

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 set up by 11:30 a.m. and removed by 10:00 p.m. on Friday.

F1. Cell Type Plasticity in the Nucleus Accumbens Core and Shell Following Remifentanil Self-Administration

Aric Madayag

F2. Inhibition of Nucleus Accumbens D1 Expressing Neurons Facilitates Extinction of Sign-Tracking

Rifka Derman

F3. Neuron Subtype-Specific Role of Methylated DNA Cytosine Dioxygenase TET1 in Cocaine Addiction

Haiyang Xu

F4. Hyperdopaminergic States Enhance Orbitofrontal-Striatal Pathway Function

Sebastiano Bariselli

F5. Wireless Near-Field Optogenetic Manipulation of the Paraventricular Thalamic Projection to Nucleus Accumbens in Heroin-Seeking Rats

Giuseppe Giannotti

F6. Differences in Striatal Dopamine Release and Its Modulation by Nicotinic Acetylcholine Receptors in Adolescent and Adult Rats

Elizabeth Pitts

F7. Regulation of Nucleus Accumbens Core Dopamine to Differentially Mediate Drug-Taking and Drug-Seeking

Ryan Farero

F8. FAAH Genetic Variation Enhances Mesolimbic Dopamine Function and Vulnerability to THC-Seeking Behavior in Female Adolescent Mice

Caitlin Burgdorf

F9. Medial Septum Activation Enhances Reversal Learning via Actions on Ventral Tegmental Area and Substantia Nigra Dopamine Neurons

David Bortz

F10. Excessive Alcohol Drinking Disrupts Stress Reactions Through Alterations in BNST Dynorphin in Mice

Lara Hwa

F11. Operant Social Interaction Inhibits Drug Self-Administration and Incubation of Drug Craving in Rat Addiction Models

Marco Venniro

F12. Characterization of Activity-Dependent Neuronal Ensembles in the Prefrontal Cortex Following Cocaine Place Conditioning in Fos-tTa Mice

Leslie Whitaker

F13. Corticotropin Releasing Factor (CRF) Increases Excitability of Dorsal Raphe Glutamatergic Neurons

Jorge Miranda-Barrientos

F14. Poster Withdrawn

F15. Optogenetically-Induced Norepinephrine Release in the Bed Nucleus of Stria Terminalis is Altered Following Chronic Restraint Stress in Mice

Karl Schmidt

F16. Stress Susceptibility Differentially Predicts Anxiety-Like Behavior in Male Versus Female Mice

Elizabeth Cogan

F17. Dynamic Regulation of Cue-Triggered Reward Seeking by the Basolateral Amygdala and Orbitofrontal Cortex

Kurt Fraser

F18. Stress Uncouples mGlu3 and mGlu5 Co-Signaling in the Hippocampus to Impair Contextual Fear

Branden Stansley

F19. Inhibition of Matrix Metalloproteinase-9 Activity to Correct Auditory Hypersensitivity in Fragile X Syndrome

Patricia Pirbhoy

F20. β-Amyloid Disrupts Synaptic CaMKIIα Signaling

Sarah Cook

F21. A Prefrontal-Bed Nucleus Circuit Coordinates the Suppression of Both HPA Output and Passive Coping Behaviors

Shane Johnson

F22. Oligodendrocytes Contribute to Brain Glutamate Homeostasis

Wendy Xin

F23. Glutamatergic Innervations From the Parabrachial Nucleus to the VTA Produce Aversion

Smriti Mongia

F24. Behavioral and Synaptic Characterization of a Mouse Model of Syndromic Autism

Adam Harrington

F25. Mutations in the Dopamine Transporter Associated With Movement-and Neuropsychiatric Disease Drives Exploratory Behavior in Mice Through Altered Dopamine Release and Uptake Dynamics

Freja Herborg

F26. Metabotropic Glutamate Receptor 1 Potentiation Enhances Prefrontal Cortical Inhibitory Transmission and Rescues Schizophrenia-Like Deficits Induced by NMDAR Hypofunction

James Maksymetz

F27. Basal and Diet-Induced Differences in Intrinsic Excitability of Medium Spiny Neurons in the NAc Core of Female Obesity-Prone and Obesity-Resistant Rats

Yanaira Alonso-Caraballo

F28. Localization of Spillover-Mediated Glutamate Transmission Onto Cerebellar Molecular Layer Interneurons

Reagan Pennock

F29. Recycling Endosomes Mediate Local, Golgi-Independent Secretory Trafficking in Dendrites and Spines

Aaron Bowen

F30. Evolutionarily Conserved Site on Neurexin3-Alpha Modulates Balance Between Excitation and Inhibition

Susana Restrepo

F31. Engineering Photoactivatable Neurotoxins for Light-Dependent Synapse Silencing

Brooke Sinnen

Panel Session Abstracts

TUESDAY, JANUARY 29, 2019

Opening Plenary

PLENARY • TUESDAY • 8:30 A.M. – 9:30 A.M. • SALON A & B

Parental Delivery: Somatic Signals Impacting Neurodevelopment

Presenter: Tracy Bale

Parental lifetime exposures to perturbations such as stress, infection, malnutrition, and advanced age have been linked with an increased risk for offspring disease, including a strong association with neurodevelopmental disorders. While maternal insults during pregnancy can directly impact somatic cells and fetal development, the mechanisms by which lifelong parental experiences can alter germ cell programming and affect offspring brain development are just beginning to be examined. This session will discuss preclinical research that has begun to define the windows of vulnerability for both transgenerational and intergenerational programming and the unique epigenetic mechanisms involved. We have developed mouse models of both paternal and maternal life stress contributions to offspring brain development in which adult mice are exposed to chronic stress, prior to breeding or during pregnancy, as sensitive windows important in development. In our mouse model of early prenatal stress (EPS), stress exposure during the first week of gestation imparts long-term developmental programming deficits in male, but not female, offspring resulting in hypersensitivity to stress, cognitive impairments, and alterations in metabolic programming. The placenta, a fetally-derived tissue reflecting fetal sex chromosome complement, acts as an arbitrator between the mother and fetus, providing necessary factors for early fetal neurodevelopment. We identified the X-linked, stress sensitive, nutrient sensor O-linked-N-acetylglucosamine (OGT) as a placental biomarker of prenatal stress. Genetic placental-specific reduction of OGT recapitulates the developmental and metabolic impairments associated with our mouse model. We found that OGT determines genome-wide sex differences in H3K27me3 and gene expression in placental trophoblasts. Our studies have currently focused on demonstrating the prenatal resilience for females that is programmed by the high levels of this transcriptionally repressive histone mark. In paternal transmission of life stress experience, our mouse model of paternal stress produces offspring with stress dysregulation. Paternal semen

examined for changes in miRNA content established distinct expression patterns that were changed in both semen extracellular vesicles (EVs) as well as sperm from stressed mice. To test the relevance and potential mRNA targets of these miRNAs, we previously injected the miRNAs into single cell zygotes and found that the resulting offspring recapitulated the stress phenotype from paternal stress sires. We have demonstrated that the epididymal epithelial cells secreting miRNA-containing EVs were responsible for the programming that occurs at fertilization. Our recent studies have examined the role of glucocorticoid receptors in these epididymal cells in responding to paternal stress and altering the secreted EV miRNA content. Using genetic targeting strategies, we can rescue the paternal transmission of the offspring phenotype by reducing glucocorticoid receptors specifically in these cells. Overall, these results demonstrate that parental life experience can induce germ cell epigenetic reprogramming and impact offspring neurodevelopment and may therefore offer novel insight into factors influencing disease risk. Identification of the specific miRNA in germ cells may point to unique biomarkers that could identify at-risk populations. Studies were funded by NIMH, NICHD and NIEHS.

Pioneer Session #1: Barry Levin

PIONEER SESSION • TUESDAY, 9:45 A.M. – 11:00 A.M.• CATHEDRAL PEAK

Individual Differences Make the Experimental World Go Round

Pioneer: Barry Levin
Chair: Lloyd Fricker
Investigators: Carrie Ferrario, Jessica Barson

Individual differences exist in many variables among humans, and in the animal models we use as surrogates for the study of human diseases; most studies ignore such individual differences. In the 1980's, I was frustrated by the large variances of outcome variables in rats made obese on a 32% fat, 25% sucrose "high energy" (HE) diet. On closer inspection, weight and fat gain on HE diet was bimodal and a large number of molecular, cellular, biochemical, metabolic and physiological variables segregated according to whether rats developed diet-induced obesity (DIO) or were diet-resistant (DR). Selective breeding of rats showed that the DIO/DR phenotypes are polygenically inherited, as in most humans. Also, like humans, and unlike most rodent obesity models, once DIO rats become obese, they defend their elevated body weight set-point in the face of long-term caloric restriction. Most importantly, DIO rats have many pre-existing differences from DR rats that predispose them to become obese on HE diet. These include abnormalities in central neurotransmitter and -peptide signaling, neuronal metabolic sensing, responses to stress, anxiety, sucrose

preference, wheel running, spontaneous physical activity and sympathetic nervous system activity. Many of these DIO abnormalities can be ascribed to early postnatal molecular, cellular, metabolic and physiological defects in leptin signaling. These defects cause abnormal development of hypothalamic pathways mediating energy homeostasis and can be exacerbated or corrected by gestational and early life interventions. In addition to my work, Carrie Ferrario will present her DIO/DR studies demonstrating that differential obesity susceptibility influences motivational responses to food cues and plasticity in the nucleus accumbens. In another model, Jessica Barson will show that PACAP signaling in the paraventricular thalamus mediates individual differences in the susceptibility to drink high levels of ethanol. The overall message is that experimental consideration of individual differences within animal models is likely to provide important insights for the treatment of human diseases.

Career Development Workshop #1

SPECIAL SESSION • TUESDAY, 2:00 P.M. – 3:30 P.M.• CASTLE PEAK AUDITORIUM

New Funding Approaches in Biomedical Research and Development

Chair: Kari Stoever
Participants: James Kelly, LaTese Briggs

The national fundraising landscape remains hyper-competitive with more than 1.5 million nonprofits generating $2.3B in revenue. Donor interests can be broad and cross multiple sectors. Assessing data on major gifts for life sciences paints an even bleaker outlook. While annual private funding is estimated at $1B, inclusive of life sciences, physical sciences and mathematics, the vast majority of that funding goes to just five institutions. Within this hyper-competitive funding landscape, medical research nonprofits are increasingly implementing hybrid business models with earned revenue opportunities. Universities benefit from student fees, donations and accumulated endowment. For-profit organizations are fueled by commercial sales and can access needed capital through investors. Nonprofits do not typically have any of these sources of funding. New hybrid business models, which strike a balance between social mission and commercial enterprise, is an emerging frontier. This session will highlight innovative approaches utilizing philanthropy, markets and governmental funding to accelerate translational research and bridge the valley of death.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • ALPINE SPRINGS

The Opioid Epidemic: Unraveling Opioid-Induced Respiratory Depression

Chair: Erica Levitt

Presenters: Erica Levitt, Gaspard Montandon, James Zadina, Andrea Kliewer

Every day 115 Americans die from opioid overdose, totaling over 40,000 deaths per year. Overdose is now the most likely cause of death for adults under 50 years old. The cause of death from opioid overdose is respiratory failure, yet the mechanisms of opioid-induced respiratory depression are poorly understood. Development of strategies to counter opioid-induced respiratory depression, or therapeutics that retain the analgesic effect of opioids and avoid negative effects, such as respiratory depression, is critical. Presenters from the opioid and control of breathing fields will discuss cellular and in vivo effects of opioids on the neurons that control breathing, the role of G protein pathways in opioid-induced respiratory depression and identification of novel compounds lacking respiratory depression. Erica Levitt (University of Florida) will describe opioid inhibition of neurons in the pons that provide drive to breathe, and the under-appreciated contribution of these neurons to opioid-induced respiratory depression. Gaspard Montandon (University of Toronto) will discuss opioid-mediated respiratory depression that occurs through G protein-mediated mechanisms in the brainstem respiratory network. He will also describe a drug screening program in zebrafish designed to develop safe opioid therapies. James Zadina (Tulane University) will describe a novel, highly effective analgesic with reduction of several major side effects. Respiratory depression is reduced despite intact recruitment of beta-arrestin2. Using mice that express only phosphorylation-deficient mu opioid receptors, and therefore do not recruit arrestin. Andrea Kliewer (Jena University) will present further evidence that opioid-mediated activation of G-protein pathways leads to respiratory depression, along with other side effects. This panel aims to unravel the cellular and neural mechanisms regulating opioid-induced respiratory depression, so safe opioid pain therapies can be identified.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • CASTLE PEAK AUDITORIUM

Beyond Inflammation: Neuroimmune Pathways in Alcohol Use Disorders

Chairs: Florence Varodayan, Angela Ozburn
Presenters: Sean Farris, Florence Varodayan, S. Alex Marshall, Angela Ozburn

Neuroimmune pathways regulate brain function to influence complex behavior, and their dysfunction is associated with psychiatric disease. This symposium will highlight neuroimmune pathways as important targets in the treatment of alcohol use disorder (AUD). Dr. Farris will show that chronic alcohol elicits convergent neuroimmune signatures in mouse, rat and human AUD brain tissue. These data indicate that glucocorticoid receptor (GR) dysregulation is associated with the induction of specific neuroimmune pathways, suggesting FDA-approved GR inhibitors (mifepristone) may be used to treat AUD. Dr. Varodayan will show that interleukin-1 (IL-1) signaling can induce pro-survival or pro-inflammatory responses in the medial prefrontal cortex, and alcohol dependence produces a pro-inflammatory bias to increase cortical inhibition. As the IL-1 receptor antagonist (kineret) is FDA approved, this work underscores its wider therapeutic potential. Dr. Marshall will discuss how astrocytes in the amygdala regulate drinking. Astrocytes secrete and respond to cytokines, and their neuroimmune state affects Gq signaling and thus glutamate tone. Dr. Marshall's data show that DREADD activation of astrocytic Gq signaling reduces drinking and ameliorates intoxication-induced inhibition of glutamate. Dr. Ozburn will discuss the role of phosphodiesterase type 4 (PDE4) in binge-like drinking. PDE4 inhibition increases cAMP and reduces pro-inflammatory cytokines. Dr. Ozburn will show that the FDA-approved PDE4 inhibitor (apremilast) reduces drinking to intoxication in mice, supporting its use as a new AUD treatment. The overall translational impact of these studies is high as they integrate transcriptome data across species, elucidate roles of cell-types and brain regions in AUD models, and employ physiology and behavioral drug-repurposing approaches. Thus, this work highlights the importance of broadening the spectrum of AUD medications to include drugs that target key neuroimmune pathways.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • CATHEDRAL PEAK

Novel Approaches to Studying CNS Nutrient-Sensing

Chairs: Carrie Ferrario, Darleen Sandoval
Presenters: Karen Ryan, Susanne La Fleur, Carrie Ferrario, Darleen Sandoval

One important aspect of feeding is nutrient-sensing, the process by which the body recognizes different fuel sources (e.g., sugars, proteins, and fats) and determines how to use and store them. This process is mediated by complex

gut-brain interactions that influence caloric intake in order to meet energy demand and provide building blocks to support cell growth, maintenance and repair. Like many feeding, related processes, nutrient-sensing is altered by hunger state, nutrition, and by obesity. In this session, we will present unpublished data describing how nutrient-sensing influences protein intake and gut-brain communication. We'll also present data describing the contribution of the nucleus accumbens to nutrient-sensing. Dr. Karen Ryan (UC Davis) will begin by describing a novel neuroendocrine mechanism underlying the homeostatic control of dietary protein intake. This is critical to understanding how the body maintains an adequate supply of amino acids, for which there is no easily-accessible storage as there is for carbohydrates and lipids in the form of glycogen and fat. Next, Dr. Susanne La Fleur (University of Amsterdam) will discuss how the nucleus accumbens responds to hypoglycemia and provide evidence that increases in striatal dopamine regulates systemic glucose metabolism. Dr. Carrie Ferrario (University of Michigan) will then discuss how oral ingestion or gastric infusion of glucose alters neurotransmitter levels within the nucleus accumbens and will provide evidence that glucose rapidly enters the nucleus accumbens where it is utilized in neurotransmitter synthesis. Finally, Dr. Darleen Sandoval (University of Michigan) will discuss how anatomical rearrangement of the gut via bariatric surgery, one of the most effective long-term treatments for obesity, influences nutrient-induced neural activation and the success of this surgical intervention for obesity.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • OVERLOOK

Plasticity and Homeostasis in Cortical Circuits During Sleep/Wake Cycles

Chair: Alfredo Kirkwood
Presenters: Kaiwen He, Michelle Bridi, Sara Aton, Keith Hengen

The processing and storage of new information requires the remodeling of synaptic connectivity, as well as homeostatic mechanisms to maintain the neural firing within an optimal range. Mounting evidence suggests that both mechanisms are required not only during behavior, but also during subsequent sleep-dependent consolidation. The four speakers assembled in this multidisciplinary panel will present novel findings and insights on sleep-related functional changes in cortical circuitry that are relevant to information storage. Dr. Kaiwen He (Chinese Academy of Science, Shanghai) investigates the balance of excitation and inhibition (E/I ratio), which is crucial for controlling the propagation of neural activity in time and space. Surprisingly, she shows that the E/I ratio is not constant, as usually assumed, but undergoes a large (many fold) sleep-dependent change over the light/dark cycle. This change is largely due to daily oscillations of excitation and inhibition, which are regulated in opposite directions. Dr. Michelle Bridi (Johns Hopkins

University) will discuss her finding that the daily oscillation of the E/I balance is disrupted and decoupled from sleep cycles in two distinct mouse models of autism. Interestingly, this disruption occurs in different ways in each model. Dr. Sara Aton (University of Michigan) will discuss the critical role of specific sleep-associated network oscillations in promoting functional plasticity and the consolidation of information storage in brain circuits. Dr. Keith Hengen (Washington University) performed large-scale recordings to analyze how cortical networks self-organize to "criticality", a computationally optimal regime for firing at the border of excessive inhibition and excessive excitation. Notably, networks converge on this set-point during sleep, and are perturbed during wake. This is precisely the opposite expression pattern of firing rate homeostasis.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • SALON B

Decoding Value and Motivation in the Ventral Pallidum

Chairs: Thomas Hnasko, Meaghan Creed
Presenters: Lauren Faget, Bo Li, Jocelyn Richard, Ilya Monosov

The ventral pallidum (VP) rests at the nexus of striatopallidal and mesolimbic neurocircuitry and is crucial for integrating and updating the valence and value of objects, goals, and associated stimuli (e.g., cues)—thereby shaping our desire to pursue or avoid them. The advent of ever more refined molecular tools has revealed a level of functional heterogeneity within VP much greater than once appreciated. However, new findings have exposed additional unknowns that require new hypotheses and new paradigms, to resolve precisely how VP circuits contribute to the control of adaptive and maladaptive behaviors. This panel will explore these themes by focusing on recent findings and discussing what the converging evidence tells us about the function of VP today, and where we need to go tomorrow. In opening remarks, Dr. Creed will give a very brief introduction of VP circuitry and highlight seminal human studies that implicate VP activity in the pathophysiology of substance use disorders. Dr. Faget will discuss recently published and follow-on work that uses optogenetics to describe opposing roles for two parallel pathways emanating from VP in motivated behavior in mice. Dr. Li will expand on this topic, describing unpublished work that incorporates in vivo recordings and sophisticated behavioral assays to suggest that these two VP pathways work together to coordinate reward seeking and punishment avoidance. Dr. Richard will describe ongoing studies, employing single-unit recordings and models of drug-seeking behavior in rats, to explain how VP circuits are differentially engaged by distinct types of predictive cues. While Dr. Monosov will explicate on the role of VP within wider striatopallidal circuit architecture on decision making in a primate model. The proposed panelists are working at the cutting edge of systems neuroscience to address the next generation of questions, and this panel will provide a diverse, wholistic, and up-to-date view of VP circuitry in behavior.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • SALON C

Ventral Hippocampal Circuits in Addiction-Related Behaviors

Chairs: William Griffin, Jacqueline Barker
Presenters: Rutsuko Ito, William Griffin, Jacqueline Barker, Jeffrey Weiner

The ventral hippocampus (vHC) is implicated in the regulation of emotional, goal-seeking and inhibitory/avoidance responses, which become dysregulated in addiction. Underscoring its involvement in addiction-related behaviors are numerous anatomical connections linking the vHC to regions like the nucleus accumbens (NAc) and basolateral amygdala (BLA). Our first speaker, Dr. Rutsuko Ito, will show data from pharmacological/optogenetic inactivation studies indicating that inhibiting the ventral CA3 subfield increases approach behaviors and inhibiting the ventral CA1 subfield increases avoidance behaviors, indicating that the vHC exerts bidirectional control over approach-avoidance behaviors. This suggests disrupting this control contributes to addiction-related behaviors. Next, Dr. William Griffin will present data from chemogenetic studies in mice indicating that activation of the vHC to NAc pathway reduces alcohol drinking in alcohol dependent mice, while inactivation tends to increase drinking in non-dependent mice. This suggests an active role of this pathway in curtailing alcohol drinking that is compromised by alcohol dependence, permitting greater drinking. Next, Dr. Jacqueline Barker, also using a chemogenetic strategy in mice, will show that inhibition of the vHC to NAc pathway restores goal-seeking behavior but spares cue-guided behavior and extinction learning. These findings implicate this pathway in promoting habitual response strategies common in addicted individuals. Finally, Dr. Jeffery Weiner will show that rodent models of addiction vulnerability and dependence preferentially dysregulate synaptic excitation in the vHC and that chemogenetic inhibition of an excitatory BLA-vHC projection reduces operant alcohol drinking behaviors. In summary, panelists will present convergent evidence from different model systems implicating vHC adaptations in addiction-related behaviors.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • SALON D

Understanding and Correcting Excitability Defects in Fragile X Syndrome

Chair: Hye Young Lee
Presenters: Leonard Kaczmarek, Vitaly Klyachko, Anis Contractor, Hye Young Lee

Neuronal hyperexcitability and seizures are common in many intellectual disability (ID) disorders, including Fragile X syndrome (FXS). This panel will present recent findings of translation-dependent and independent

mechanisms underlying excitability defects in FXS, and novel approaches to their normalization. Leonard Kaczmarek will discuss new findings on how mRNA translation can be directly stimulated by activation of neuronal ion channels, and how this process is regulated by the Fragile X Mental Retardation protein (FMRP). Vitaly Klyachko will focus on the role of ion channel defects in hippocampal circuit hyperexcitability in the Fragile X mouse model. He will describe an unexpected role of voltage-independent SK channels in reduced action potential threshold and increased neuronal firing in hippocampal microcircuits. He will show that these excitability defects arise from altered calcium sensitivity of the SK channels rather than changes in the channel expression levels. Finally, he will demonstrate the ability of SK channel openers to normalize cellular and circuit excitability defects in the Fragile X mice. Anis Contractor will discuss work in his laboratory that has demonstrated alterations in critical period timing that are dependent on altered GABA signaling in Fragile X Syndrome. He will discuss how multiple phenotypes in mouse and human derived neurons converge at the level of GABA, and describe studies aimed at reversing some of these synaptic and circuit disruptions. Hye Young Lee will talk about the contribution of the voltage-gated potassium channel, Kv4.2 to behavioral phenotypes of FXS. She will discuss her recent study that has demonstrated successful rescue of altered repetitive behaviors by gene editing of the mGluR5 gene in FXS using CRISPR-Nanoparticles. This panel thus will present new approaches to understanding the mechanisms of hyperexcitability in FXS and will discuss new avenues towards its treatment.

PANEL • TUESDAY, 4:30 P.M. – 6:30 P.M. • SALON E

Treating Neurodevelopmental Disorders in the Post-Genomic Era: From Animal Models to Clinical Trials Using Artificial Intelligence

Chair: Francois Bolduc, Sean McBride
Presenters: Francois Bolduc, Sean McBride, Sarah Lippe, David Hessl

The gap between improved genetic diagnosis and clinical pharmacological treatments for neurodevelopmental disorders (NDD) has only increased in the last decade with the progressive clinical implementation of exome and genome wide sequencing. Our panel will focus on a biomarker-based approach to treatment. We will also highlight knowledge in animal model genetics that has become highly relevant to human NDD in this genomic testing era. We will also show how Artificial Intelligence (AI) can help resolve some of the current limitations to clinical care improvement. Our panel is composed of leaders in the field of translation of basic science to clinical trials in NDD. Francois Bolduc will present evidence on how animal models of genetic based NDD can help identify treatment when combined to pathway analysis. He will show new evidence for divergence between driver mutation role and associated

pathways function in Drosophila. He will then translate those findings to results of next-generation sequencing in individuals with NDD while reviewing current challenges and artificial intelligence solutions in clinical diagnostic. Sean McBride will discuss the neuro-psychiatric aspects of common cause of NDD and share novel treatment strategies aimed at identifying overlapping pathways for large cluster of NDD genes. Sarah Lippe will present innovative approach to biomarker analysis using personalized signature mapping of learning and memory using human electrophysiological testing in NDD. She will show how AI can help resolve issues of limitation in data. Dr. Hessl will present results of clinical treatments in human based on basic science research in animal models. 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 NDD.

Tuesday Evening Panel Sessions

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • ALPINE SPRINGS

Advanced Whole-Brain Imaging Methods in Awake or Freely-Moving Animals

Chair: Zsolt Lenkei
Presenters: Hanbing Lu, Zsolt Lenkei

Imaging brain function in awake animals is a major goal in neuroscience, since a growing body of evidence shows that key aspects of neuronal function in the awake brain cannot be directly inferred from activity recorded in anesthesia. With recent development in novel methods, imaging at the whole-brain level has become feasible in freely moving and behaving animals, enabling to overcome limitations of general anesthesia and to avoid the negative side-effects of the stress associated with full-body animal restraint. Dr. Hanbing Lu (NIDA, Baltimore) will present recent developments in resting state fMRI technique in rodent models, and the application of this technique to rodent models of drug addiction and aging. Dr. Zsolt Lenkei (INSERM, Paris, France) will present results on cannabinoid-induced changes in brain structure and connectivity by using functional ultrasound (fUS), a novel whole-brain imaging technique for functional connectivity mapping, with elevated sensitivity, spatiotemporal resolution and operating simplicity, which was recently adapted to freely-moving awake mice. Each presenter will describe the strengths and limitations of the experimental model. Ample time will be allowed for questions and an open forum discussion.

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • CASTLE PEAK AUDITORIUM

Developing and Investigating Animal Models of Compulsive Drug Taking

Chairs: Cody Siciliano, Mark Ferris
Presenters: Olivier George, Lindsay Halladay, Cody Siciliano

Drug abuse results in over 600,000 deaths and costs over 500 billion dollars in the United States annually. Despite efforts to elucidate the precise mechanisms by which drug-induced cellular dysregulation can lead to addiction, there has been limited success in translating findings into treatments. Recent technological advances allow for unprecedented insight into neural circuitry controlling behavior; however, the impact of these technologies on our understanding of human addiction is inherently limited by the validity of the animal models that they are used to investigate. This panel will focus on animal models of drug taking in the face of punishment, or compulsive drug taking, a cardinal facet of addiction. All participating investigators are at the forefront of developing innovative rodent models of compulsion and examining synaptic and circuit dysregulation with cutting-edge techniques. First, Dr. George will present his work on developing rodent models of compulsive psychostimulant seeking, and the use of genetic and optical approaches to dissect the role of neuronal ensembles in the prefrontal cortex and striatum in these models. Dr. Halladay will discuss models of compulsive alcohol drinking in genetically diverse mice, and how electrophysiological and optogenetic interrogation reveals a role for cortico-limbic circuit dysregulation in driving these behaviors. Finally, Dr. Siciliano will present a novel model of compulsion vulnerability and discuss how the activity of single neurons in the prefrontal cortex during animals' first drinking experience can predict the development of compulsive alcohol consumption. Dr. Ferris will serve as co-chair and will provide introductions and lead discussion. Together, this session will highlight the importance of developing translational addiction models and will showcase the most recent advances in applying novel technologies to advance our understanding of the mechanisms controlling these behaviors.

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • CATHEDRAL PEAK

Neural Activity in Cognition and Disease

Chair: Erin Hascup
Presenters: Heather Boger, Kevin Hascup, Jesse Jackson

Parkinson's and Alzheimer's diseases share several etiologies including neurodegeneration, altered neurotransmission, and decreased cognition, and both diseases may be exacerbated by stress. Here, we will present data from models of Parkinson's disease (PD) and Alzheimer's disease (AD) to explore

disease-specific changes in neurotransmission, as well as potential associated mechanisms and novel therapeutics. We will also introduce the claustrum as a potential common structure that may have implications for mediating stress and cognition in both PD and AD through neural activity organization and information flow in the brain. Dr. Erin Hascup (SIU School of Medicine) will chair and provide a brief overview of the session. Dr. Heather Boger (MUSC) will present data from her laboratory demonstrating how various mechanisms interact to result in progressive motor impairment and PD-like pathology. Furthermore, she will discuss recent work assessing the use of vagus nerve stimulation as a multi-mechanistic treatment strategy for PD. Dr. Kevin Hascup (SIU School of Medicine) will present data detailing alterations in neurotransmission spanning the Alzheimer's disease continuum and how these changes can be manipulated to alter disease outcome. Dr. Jesse Jackson (University of Alberta) will share recent data supporting the claustrum as a critical node controlling inhibitory tone in the cortex and how deficits in claustrocortical communication, possibly due to neurodegeneration in the claustrum, may lead to neurophysiological hallmarks of AD and PD. Data presented in this panel will use a range of molecular, cellular, in vivo, behavioral, and computational approaches to address similarities and differences between the two diseases to come to a better understanding of the role of neural activity in disease progression and cognition.

WORKSHOP • TUESDAY, 7:00 P.M. – 8:30 P.M. • OVERLOOK

So, You Want to Be a Billionaire: Is Entrepreneurial Neuroscience in Your Future?

Chairs: David Devilbiss, John Mendelson

This will be a participatory workshop with experienced entrepreneurs to explore the path from academia to the board room and examine key differences between achieving success in research and start-ups. Many scientists dream of funding their research and treatment programs during times of lean funding by forming companies and attracting investors. Alternatively, many scientists develop innovative tools or make discoveries that can grow to be the core of billion-dollar companies. What does this road look like and how can you navigate it?

The panel members of this workshop include two regular WCBR participants with emerging companies. Panel members will initially review their paths to founding companies and provide advice and encouragement to those brave enough to attempt this transition. John Mendelson will describe DxRx, his entrepreneurial approach to treating alcohol use disorder. Despite availability of safe and effective pharmacotherapies, only a trivial number of patients receive evidence-based treatment. Mendelson will discuss key stages in launching a company, from recruiting the team to achieving first revenue. David

Devilbiss will describe Cerora, a company developing clinical tools for aiding in the diagnosis of concussion. Although the incidence and repercussions of concussion have been brought to the public's attention, diagnosis and assessment of recovery remains highly subjective. Devilbiss will discuss critical decisions developing prototypes and raising capital to begin the FDA submission process.
Because this is a participatory workshop, audience members will be encouraged to present their ideas for a start-up and panel members will discuss the path from discovery to successful company for these concepts.

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • SALON B

Voltage-Gated Ion Channels in the Pathophysiology and Treatment of Brain Disorders

Chair: Elizabeth Tunbridge
Presenters: Elizabeth Tunbridge, Jeremy Hall, Brady Maher

Voltage-gated ion channels regulate many aspects of the function of electrically-active cells, including neurons. Alterations in cation regulation have long been observed in various brain disorders. Information emerging from genomic studies now points to a causative role for voltage-gated ion channels in a wide range of brain disorders. For example, both rare and common variants are associated with the major psychiatric illnesses. Therefore, there is a need to understand the biology of these channels in human brain, and to explore their therapeutic potential. This panel will consider the role of these channels in the pathophysiology of brain disorders and will reflect on their therapeutic potential in this context. Liz Tunbridge (University of Oxford) will introduce the session, outlining the challenges and opportunities associated with targeting voltage-gated ion channels, and evidence for their role in disease, before presenting her findings indicating the presence of multiple novel L-type calcium channel isoforms in human brain. Jeremy Hall (University of Cardiff) will build on this introduction by outlining evidence that alterations in MAP/ERK signalling might mediate changes in behaviour, gene expression and electrophysiological measures associated with altered function of the CaV1.2 voltage-gated calcium channel. Finally, Brady Maher (Lieber Institute for Brain Development) will demonstrate that the relevance of voltage-gated ion channels for brain disorders extends beyond calcium, presenting his recent research focused on how the psychiatric risk gene TCF4 regulates the expression of voltage-gated sodium channel Nav1.8. Together, these presentations will provide an overview of recent findings implicating voltage-gated ion channels in brain disorders, as well as a critical appraisal of their therapeutic potential and the challenges that need to be overcome in order to advance their candidacy as novel drug targets.

What do the PFC and the Hippocampus Tell the Nucleus Accumbens? Implications for Addiction and Depression

Chair: Scott Thompson
Presenters: Lucas Sjulson, Tara LeGates, Matthew Hearing

The high comorbidity of addiction and stress-related neuropsychiatric disorders, and shared pathologies related to affect and cognition, suggest that stress and drugs of abuse target overlapping neurobiological substrates. The nucleus accumbens is a locus of convergent input from mesocorticolimbic regions – positioning it as a critical substrate in integrating cognition, associative learning, reward processing, and affective behavior. This panel of young investigators will discuss how circuit-specific synaptic adaptations within cortico-accumbens circuits uniquely contribute to symptoms of depression and addiction. Lucas Sjulson will discuss cocaine-induced modifications within hippocampal-NAc (HPC-NAc) circuits that drive the development of drug-context associations. In vivo evidence that this conditioning involves hippocampal place cell recruitment of specific D1 vs. D2-medium spiny neuron (MSN) circuits will be discussed. Tara LeGates will present work characterizing plasticity within HPC-NAc circuits underlying the encoding of contextual information associated with reward learning and goal-directed behavior and provide in vivo evidence regarding how modifications in the strength of these circuits may be differentially impacted by aversive experiences and causally contribute to the emergence of negative affect following stress exposure. Matthew Hearing will present data characterizing bimodal adaptations in synaptic transmission and intrinsic physiology in medial prefrontal cortical layer 5/6 pyramidal and striatal medium spiny neuron circuits based on anatomical connectivity and the expression of dopamine D1 versus D2 dopamine receptors. The impact of biological sex and functional implications of these changes in cognitive dysfunction and abnormal affective behavior will be discussed. In summary, we will provide new results regarding information conveyed to the NAc and how changes in this process contribute to dysfunction in addiction and depression.

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • SALON D

Biological Predictors of PTSD Development in the Aftermath of Trauma

Chair: Vasiliki Michopoulos
Presenters: Vasiliki Michopoulos, Felicia Gould, Rebecca Hinrichs

Post-traumatic stress disorder (PTSD) is a severe, heterogeneous psychiatric condition that can develop in 10-20% of trauma-exposed individuals. While a number of effective early interventions that can be deployed in Emergency Departments (EDs) that diminish the development of PTSD symptoms, limited access to these treatments and resources necessitates the ability to quickly identify individuals at the highest risk for developing PTSD. In our symposium, we will discuss recent findings from a large prospective study from the EDs of Grady Memorial Hospital in Atlanta, GA and Jackson Memorial Hospital in Miami, FL that highlight biological risk factors for PTSD development in the aftermath of trauma. Dr. Vasiliki Michopoulos (Assistant Professor, Emory University) will discuss the overall study design of this prospective study, and summarize recent data linking altered immune profiles in the immediate aftermath of trauma to prospective PTSD risk. Dr. Felicia Gould (Assistant Professor, University of Miami) will discuss genetic risk and epigenetic factors associated with risk for PTSD development. Rebecca Hinrichs (Research Project Manager, Emory University) will present data showing that skin conductance response to a standardized trauma interview in the ED in the immediate aftermath of trauma predicts subsequent development of chronic PTSD. Overall, the findings discussed will highlight biomarkers of prospective PTSD development.

PANEL • TUESDAY, 7:00 P.M. – 8:30 P.M. • SALON E

Subclinical MRI Biomarkers of Cerebral Small Vessel Disease in the Pathogenesis of Vascular Cognitive Impairment and Dementia

Chair: Clinton Wright
Presenters: Clinton Wright, Michelle Caunca, Richard Leigh

It is well established that vascular cognitive impairment and dementia (VCID) plays a role in Alzheimer's disease (AD). In this panel we explore how MRI biomarkers for cerebral small vessel disease (CSVD) may inform us about the pathogenesis of VCID focusing on both the normal aging population as well as patients with cerebrovascular disease. Clinton B. Wright, who is the associate director of NINDS and the director of the Office of Clinical Research, will provide an overview the Northern Manhattan Study (NOMAS) and the NIH Natural History of Stroke Study (NHS). NOMAS is a prospective

cohort study of a clinically stroke-free, racially and ethnically diverse, older adult population based in Northern Manhattan, NY. The NOMAS includes an MRI Sub-Study with 1290 participants who have available structural MRI and neuropsychological data. The NIH NHS study is an observational study of patients who have suffered and ischemic stroke who are followed with serial MRI. Patients in this study, who are followed for many months, provide an ideal population for studying the relationship between acute stroke and the evolution of CSVD on MRI. Michelle Caunca, who is an MD/PhD candidate at the University of Miami, will give the second talk entitled: Population-based prevalence of Cerebral Microbleeds, Subclinical Brain Infarcts, and WMH and its associations with cognition: NOMAS. In this session data on the prevalence and distribution of various CSVD markers, their associations with domain-specific cognitive performance and decline, and recent data on regional metrics of WM lesion load will be presented. Richard Leigh, who is an Assistant Clinical Investor in the intramural Stroke Branch of NINDS, will present the third talk entitled: Blood-Brain Barrier (BBB) Disruption in Acute and Chronic Cerebrovascular Disease: NIH NHS Study. This talk will focus on the relationship between acute stroke and subsequent cognitive decline using a novel MRI biomarker for BBB disruption.

WEDNESDAY, JANUARY 30, 2019

Wednesday Morning Panel Sessions

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • ALPINE SPRINGS

Ski Knees? Altered Cyclic Nucleotide Signaling May Be to Blame

Chair: Michy Kelly
Presenters: Michy Kelly, Annemieke Kavelaars, Carmen Dessauer, Hanting Zhang

The opioid epidemic has placed a spotlight on the need to better understand the molecular mechanisms of pain and to identify novel, non-addictive therapeutic interventions to prevent or block chronic pain. This panel will explore the potential role that altered 3',5'-cyclic nucleotide signaling may play in the transition to—and maintenance of—chronic pain states. Michy Kelly will describe how the recovery of normal mechanical sensitivity following injection of the inflammatory agent zymosan may be regulated by PDE11A, a dual-specificity PDE selectively expressed in the hippocampal formation, dorsal root ganglion, and somatostatin-positive neurons in the spinal cord. Annemieke Kavelaars will describe how elevated cAMP signaling in nociceptors leads to only transient pain in normal conditions but chronic pain under conditions of G-protein coupled Receptor Kinase 2 deficiency. She will further describe how this pathological transition to chronic pain is related to a biased cAMP-induced Epac1-to-Rap1 signaling that ultimately leads to an upregulation of a novel pain regulator PI16. First-time attendee, Carmen Dessauer will then explore how macromolecular complexes of adenylyl cyclase, AKAPs, and cAMP effectors may contribute to spontaneous firing of nociceptors, which has been associated with numerous chronic pain states, and how dampened opioid regulation of this complex may be a key molecular mechanism driving chronic pain. Finally, Hanting "Hunter" Zhang will demonstrate that repeated administration of PDE4 inhibitors (rolipram and roflumilast) reduces mechanical hypersensitivity in a mouse model of partial sciatic nerve ligation, possibly by preventing downregulation of Cx43 expression in the spinal dorsal horn. Together, these studies identify novel therapeutic targets within the cyclic nucleotide signaling cascades that may prevent the transition to—or maintenance of—chronic pain states.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • CASTLE PEAK AUDITORIUM

Effects of Exercise on Alcohol and Drug Addiction: Mechanisms and Clinical Implications

Chair: Howard Becker
Presenters: Matthew Solomon, Marissa Ehringer, Jean Abel, Mark Smith

Preclinical and clinical evidence suggests that exercise may be an effective nonpharmacological intervention for alcohol/drug addiction. Animal models have been valuable in advancing our understanding of the mechanisms underlying the therapeutic potential of this behavioral strategy. This panel will highlight recent findings on neurobiological mechanisms underlying the ability of exercise to impact addictive behaviors in rodent models. Howard Becker (Medical University of SC) will provide a brief introduction on the topic. Matthew Solomon (Medical University of SC) will present recent findings indicating that exercise (wheel running) blunts escalation of voluntary alcohol drinking associated with dependence in mice, an effect related to elevated BDNF expression/signaling in the prefrontal cortex. Marissa Ehringer (University of Colorado) will describe results from genomic analyses that indicate sex and mouse strain differences in striatal gene expression related to wheel-running and alcohol consumption. Jean Abel (University of Virginia) will present recent data indicating that exercise initiated during early, but not late abstinence, decreases cocaine relapse vulnerability in rats, an effect associated with changes in BDNF and glutamate receptor (mGluR5) signaling in the prefrontal cortex. Mark Smith (Davidson College) will present data showing that different modes (aerobic vs. resistance) and duration (acute vs. chronic) of exercise can reduce all phases of addictive behavior involving cocaine and heroin in rats (males and females), including acquisition, maintenance, and escalation of drug self-administration as well as relapse-like behavior following abstinence. Collectively, presentations in this panel will provide new insights about mechanisms by which exercise blunts various facets of alcohol/drug addiction, with significant clinical implications for the treatment of alcohol and drug addiction.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • CATHEDRAL PEAK

Novel Molecular Substrates and Circuits in the Epigenetic Regulation of Reward Learning

Chair: Jeremy Day
Presenters: Rianne Campbell, Mary Kay Lobo, Jeremy Day, Farah Lubin

Stable molecular adaptations in specific brain regions underlie memory formation, including that associated with reward processing. This allows drugs of abuse to 'hijack' brain reward circuitry, leading to the chronic cycle of drug

taking, abstinence and relapse. While it is clear that epigenetic regulation of gene expression plays a key role in this process, direct causal evidence of the precise mechanisms remains elusive. This panel will present novel findings on reward- and memory-related chromatin regulation in previously understudied brain areas, including the habenula complex (Hb), using highly innovative methods of circuit-specific gene regulation. Dr. Jeremy Day (University of Alabama) will provide general remarks. Dr. Rianne Campbell (University of California-Irvine) will present evidence that cocaine-primed reinstatement of conditioned place preference engages habenula circuitry. Further, epigenetic regulation of nuclear receptor subfamily 4 (Nr4a2), specifically in cholinergic neurons of the medial habenula, is required for this process. Dr. Mary Kay Lobo (University of Maryland) will further evince the role of the habenular complex in cocaine self-administration behavior. RNA-scope and circuit-specific CRISPRa/i, are used to validate and mediate circuit-specific gene expression in VP-LHb neurons. Dr. Jeremy Day (University of Alabama) will present novel findings on the precise mechanisms by which dopamine treatment and cocaine administration induce DNA demethylation, via striatal Gadd45b function. Finally, Dr. Farah Lubin (University of Alabama) applies CRISPRa/i to show that learning-induced increases in histone ubiquitination are critical for recruitment of the euchromatin mark H3K4me3 to learning-permissive genes in the hippocampus. Together, these studies highlight novel advances in the gene- and circuit-specific manipulation of the epigenome to reveal the precise mechanisms of transcriptional regulation in the context of reward learning.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • OVERLOOK

Vulnerabilities to Disorders of Motivation and Reward

Chairs: Mark Ferris, Elizabeth Pitts
Presenters: Mark Ferris, Joshua Beckmann, Amy Johnson, Daniel Covey

There is plurality in environmental factors that influence vulnerability to substance use disorders. Our panel will present four distinct environmental or phenotypic factors that determine drug use and relapse vulnerability. This panel will explore their commonalities/differences with respect to behavioral models of substance use disorder in rodents and their corresponding changes in brain mesolimbic circuits that underlie learning, motivation, and reinforcement. Factors of vulnerability will include time-of-day/circadian cycles, environmental enrichment as a model of socio-economic status, sex differences, and comorbid disorders that alter neurochemical modulation of motivation. Dr. Ferris will first speak about circadian control of incentive motivational properties of reward and drug paired cues, and how nicotine amplifies cue-induced motivation only during certain times of day that correspond to greater control of mesolimbic dopamine release by acetylcholine and nicotinic receptors. Dr. Beckmann will then speak about how enriched

vs. impoverished environments and the amount of alternative reinforcers to drugs of abuse can influence economic demand and choice for cocaine and serve as an economic substitute for drugs of abuse. Dr. Johnson will speak about female vulnerability to substance use disorder. She will show behavioral and neurochemical work detailing estrous cycle dependent variation in reward seeking in response to cocaine-paired cues as well as estrous dependent variation in economic demand for cocaine. Dr. Covey will close the session by discussing how endocannabinoid (eCB) signaling controls dopamine neuron function and motivated behavior. He identifies cell type-specific mechanisms by which eCBs influence goal seeking. Dr. Pitts will co-chair the panel, assist in the introduction(s), and lead discussion. Together, this panel will highlight the importance of understanding multiple factors that confer vulnerability to drug use initiation and relapse.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • SALON B

Trafficking Events That Underlie Synaptic Plasticity and Memory

Chair: Jason Shepherd
Presenters: Kristen Harris, Jason Shepherd, Matthew Kennedy, Don Arnold

The encoding and storage of information in the brain requires unique cell biology, which comprises a number of trafficking events at synapses. This panel will highlight new insights into these events, incorporating novel paradigms and tools. Dr. Kristen Harris will present new work on the role of subcellular structures in mediating long-term potentiation (LTP) of synaptic strength. Using 3D electron microscopy, the Harris lab found altered localization of various subcellular structures such as polyribosomes, smooth endoplasmic reticulum, and mitochondria after LTP. The trafficking of these structures elucidates how the synapse readies itself for subsequent 'learning'. Dr. Jason Shepherd (Chair) will describe a new mechanism for intercellular trafficking of proteins and RNA. The immediate early gene Arc is critical for long-term synaptic plasticity and memory. The Shepherd lab found that Arc protein self-assembles into viral-like capsids that can transfer Arc mRNA cell-to-cell, acting in a non-cell autonomous manner to regulate neural circuit plasticity. These findings posit new mechanisms that may regulate information storage in the brain. Dr. Matthew Kennedy is using new tools that allow spatiotemporal control and visualization of protein trafficking in neuronal dendrites. He will describe new work on how key postsynaptic proteins are delivered to synapses in response to neuronal activity. Dr. Don Arnold has developed a new light-activated system based on the intrinsically photocleavable protein PhoCl that can be used to target proteins to synapses in order to modify synaptic function. He will present new work using this system to study homeostatic mechanisms by which individual synapses respond to perturbations in synaptic strength.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • SALON C

Thalamus: Cell Type, Function and Plasticity

Chairs: Xiaoke Chen, Huizhong Tao
Presenters: Anton Schulmann, Antoine Adamantidis, Carey Y. L. Huh, Stanislav Zakharenko

The thalamus is situated in a unique position to integrate information from the periphery and cortex and have important roles in sensory processing and cognitive control. Classical studies have divided the thalamus into over 30 nuclei, however, the cellular composition, connectivity and function of these nuclei remain largely unknown. Recent technological advances such as optogenetics, in vivo imaging and high-throughput single cell sequencing have transformed neuroscience studies, making it possible to determine the cell types, functions and plasticity of the thalamic nuclei. The speakers in this panel are at the forefront of thalamic study. Dr. Anton Schulmann (Janelia) will describe their recent work on profiling the transcriptomes of projection neurons from nearly all of the characterized thalamic nuclei to provide an unbiased view of cellular diversity. The work has uncovered a single genetic axis of diversity that is cross modal and closely aligned to the medial lateral axis of thalamus. Dr. Huizhong Tao (USC) and Dr. Antoine Adamantidis (University of Bern) will focus on the function of two subthalamic nuclei, the zona incerta and centromedial thalamus. Dr. Tao will report the roles of zona incerta in regulating defensive behaviors in experience- and context-dependent manners, and Dr. Adamantidis will discuss the role of firing patterns of centromedial thalamic neurons in sleep-wake control. Dr. Stanislav Zakharenko (St. Jude Children's Research Hospital) and Dr. Carey Huh (UC Irvine) will discuss thalamic mechanisms for regulating the critical period of cortical plasticity and thalamocortical plasticity induced by monocular deprivation. Dr. Zakharenko will focus on a role of adenosine signaling in gating thalamocortical plasticity, and Dr. Huh will report their findings on a surprisingly selective vulnerability of binocular thalamic axons to monocular deprivation using in vivo GCaMP6 axon imaging. Dr. Xiaoke Chen (Stanford) will lead the discussion.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • SALON D

Neuroplasticity Factors Contributing to Opioid Use, Escalation, and Relapse Vulnerability

Chair: Aric Madayag
Presenters: Nicholas Graziane, Emilia Lefevre, Christopher Olsen, Aric Madayag

Opioid-based drugs are mainstays for pain management despite their significant side effects and addictive liability. Increasing evidence suggest that neural circuit adaptations responsible for unique facets of opioid addiction withdrawal that

accompany dependence are not necessarily synonymous with those responsible for establishing drug seeking behavior and cue-/context associations that drive relapse. Moreover, it is unclear how experience-dependent modifications in the intrinsic state of these circuits, such as following stress or traumatic brain injury, may contribute to the risk and severity of opioid abuse. This panel of young investigators will discuss modifications in cortico-striatal circuits at the cellular, molecular and structural level, and they uniquely relate to negative affective states, development of conditioned associations and drug-seeking, and relapse vulnerability. Nicholas Graziane will present data assessing whether the length of abstinence from repeated opioids differentially alters the intrinsic physiology and inhibitory synaptic transmission at nucleus accumbens D1- vs D2-MSNs. Emilia Lefevre will present data showing the influence of different patterns of morphine administration result in divergent behavioral and synaptic adaptations – highlighting the contribution of inhibitory and excitatory synaptic plasticity within D1- and D2-MSN to this behavior. Chris Olsen will present neuroimaging data from a rodent model of co-morbid mild traumatic brain (TBI) injury and opioid abuse. Dr. Olsen will present structural and fMRI data to show the impact of repeated blast mild traumatic brain injury on basal corticostriatal function and its relationship to drug taking and seeking. Aric Madayag will discuss findings from studies investigating the impact of remifentanil self-administration on frontal cortex-accumbens synaptic plasticity within D1- and D2-MSN NAc circuits and the relevance of this plasticity to relapse.

PANEL • WEDNESDAY, 7:30 A.M. – 9:30 A.M. • SALON E

Neuroimaging Biomarkers of Treatment Response

Chair: Anil Malhotra

Presenters: Stephanie Winkelbeiner, Miklos Argyelan, Melanie Blair, Philipp Homan

Treatment algorithms for psychiatric illnesses are devoid of prognostic measures, and clinicians rely on trial and error. At the same time, neural mechanisms underlying response to treatment remain unclear, resulting in a lack of potential targets for novel treatment development. In this panel, we will present data from studies that utilize structural and functional neuroimaging to dissect the heterogeneity of treatment response. Stephanie Winkelbeiner (University of Bern) will discuss the methodological challenges that the estimation of individual treatment response can entail when based solely on data from randomized controlled trials (RCTs). Possible alternatives, including Bayesian hierarchical modelling approaches, and preliminary results from a neuroimaging study of Transcranial Magnetic Stimulation (TMS) will be presented. Miklos Argyelan (Hofstra) will present on the mechanism of action of Electroconvulsive Therapy (ECT). His study on 151 depressed patients undergoing ECT treatment with longitudinal MRI showed a strong

association between the spatial distribution of the ECT induced electrical field and clinical response. Melanie Blair (CUNY) will discuss the effects of cannabis use on previously validated biomarkers of antipsychotic response in schizophrenia (N=41). For patients without cannabis use disorder (CUD), striatal connectivity predicted clinical improvement; for those with CUD, the relationship was not significant. Finally, Philipp Homan (Hofstra) will present new data on an important side effect of treatment, antipsychotic drug-induced weight gain, from a study of 82 early-phase patients. He found a synergistic effect of striatal structure and function on weight gain, suggesting that an imaging marker at baseline may identify patients at risk for substantial weight gain during treatment. Taken together, it is hoped that this panel will provide a comprehensive overview of new work in the area of neuroimaging biomarkers of treatment response.

Wednesday Afternoon Panel Sessions

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • ALPINE SPRINGS

Circuit-Specific Synaptic and Structural Plasticity in Addiction

Chair: Jacqueline McGinty

Presenters: Jacqueline McGinty, Michael Scofield, Kathryn Reissner, Matthew Hearing

Addictive drugs cause complex neuroadaptations in the prefrontal cortex and nucleus accumbens that trigger relapse to drug seeking. This panel will discuss synaptic and structural adaptations in both structures that are consequences of cocaine or heroin self-administration. Jakie McGinty will discuss evidence that there is an increase in spine head size and plasticity-related proteins (pCREB, GluA1) in layer V pyramidal neurons of the prelimbic cortex projecting to the nucleus accumbens core (PL-NA core) that emerges during the first week of abstinence from cocaine or heroin self-administration. Michael Scofield will discuss how exposure to heroin impacts the structural properties of cortical astrocytes and their interaction with neuronal synapses. The morphological profiles of protoplasmic astrocytes were analyzed in relationship to excitatory synapses in the prelimbic cortex. Heroin self-administration increased astrocytic process branching and enhanced association of astrocytic processes with synapses both of which were reversed by treatment with the antioxidant, N-acetylcysteine (NAC). Kathryn Reissner will describe how cocaine self-administration affects structural properties of nucleus accumbens astrocytes, following varying self-administration paradigms and periods of extinction or withdrawal. The functional consequences of cocaine-dependent reductions in structural properties of astrocytes and astrocyte-synapse colocalization on NMDA receptor function and synaptic processing in the accumbens will be discussed. Matthew Hearing will discuss the impact of biological sex on

opioid-induced plasticity in prelimbic pyramidal cells and prelimbic-to-core D1/D2-MSN circuits following remifentanil self-administration and the relevance of this plasticity to relapse and cognition.

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • CASTLE PEAK AUDITORIUM

Novel Mechanisms for the Regulation of CRF Signaling in Stress and Alcohol Drinking

Chairs: Melissa Herman, Candice Contet
Presenters: Carolina Haass-Koffler, A. Leslie Morrow, Marcus Weera, Candice Contet

Corticotropin releasing factor (CRF) has a well-established role in stress and addiction. CRF and CRF1 receptors promote stress- and dependence-associated escalation of alcohol drinking, but the underlying signaling mechanisms and circuitry remain unclear, which limits therapeutic utility. This panel will provide new perspectives on CRF by highlighting novel molecular mechanisms and compounds regulating CRF expression and signaling in the ventral tegmental area, as well as new neural pathways connecting the lateral hypothalamus and the parasubthalamic nucleus to the central amygdala (CeA). First, Dr. Carolina Haass-Koffler (Brown University) will discuss the role of CRF2 receptors and CRF binding protein in CRF-induced potentiation of N-Methyl-D-aspartic acid receptor transmission in ventral tegmental area dopamine neurons and describe new compounds targeting this mechanism. Dr. Leslie Morrow (University of North Carolina) will present evidence that the neurosteroid, 3a,5a-THP (allopregnanolone), reduces CRF in macrophage cells, the ventral tegmental area of alcohol-preferring P rats, and Neuro-2a cells by a unique mechanism involving TLR4 receptor activation. Dr. Marcus Weera (Louisiana State University) will show that traumatic stress activates CeA projections to the lateral hypothalamus and discuss the role of CRF1+ neurons projecting from the CeA to the lateral hypothalamus in stress-induced escalation of alcohol drinking. Finally, Dr. Candice Contet (Scripps Research Institute) will present evidence that CRF neurons located in the parasubthalamic nucleus project to the CeA, promote alcohol drinking, are activated during alcohol withdrawal, and contribute to withdrawal-associated behaviors. Dr. Melissa Herman (University of North Carolina) will lead discussion of the presentations. Together, these panelists will introduce new data highlighting recent advances in our understanding of the interplay between CRF signaling and stress-related psychopathologies.

Preclinical and Clinical Gene Therapies for Neurodegenerative Diseases: Carving Opportunities and the 'off-Piste' Challenges of an Emerging Platform

Chair: Warren Hirst

Presenters: Warren Hirst, Isabelle Aubert, Anurag Tandon, Kathrin Meyer

Adeno-associated viral (AAV) vectors are emerging as the most promising platform for gene therapy in neurodegenerative disorders. A single, potentially non-invasive, treatment holds the promise of enduring clinical benefit. However, key challenges remain to be resolved including cell-type specific expression and optimal delivery, topics which will be covered in this panel. Mutations in GBA1 cause Gaucher disease and are the most significant risk factor for Parkinson's disease. Warren Hirst (Biogen) will discuss the opportunities for gene therapy for GBA1, evaluating the effects of cell-type specific expression, in neurons vs. astrocytes, of AAV-GBA1 on enzyme expression and function. The inefficient passage of antibodies and viruses across the blood-brain barrier (BBB) is a major challenge for both immunotherapy and gene therapy. Isabelle Aubert (Sunnybrook Research Institute) will present her work to establish gene therapy approaches to encode and release antibodies in the brain. She will present recent progress in combining AAV delivery with MRI-guided focused ultrasound to overcome the BBB in mouse models of Alzheimer's disease. Anurag Tandon (U. Toronto) will further demonstrate the benefits of focused ultrasound-mediated delivery of AAV vectors to multiple brain regions in a targeted and non-invasive manner. He will present data assessing the benefits of a-synuclein knockdown in a spreading synucleinopathy model, showing rescue of behavior and pathology, even at sites distal to the a-synuclein vector delivery. Kathrin Meyer (Nationwide Children's Hospital) will speak about intrathecal AAV9 based gene therapy approaches for neurodegenerative pediatric diseases and their translation from the bench to the clinic. She will present data from a phase I/II clinical trial using AAV9 for treatment of Spinal Muscular Atrophy. She will also discuss the clinical translation of this approach for CLN6 Batten Disease, a severe neurodegenerative lysosomal storage disorder.

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • OVERLOOK

But Can I Still Ski? Effects of Traumatic Brain Injury on Emotion and Motivated Behavior

Chair: Jessica Barson
Presenters: Alana Conti, Ramesh Raghupathi, Servio Ramirez, Patricia Molina

Traumatic brain injury (TBI), even when mild, can induce long-lasting changes in emotion and motivated behavior. These changes may be due not just to neuronal damage at the site of impact, but to alterations in remote brain regions. This panel will describe changes in behavior that occur following TBI in rodents, and the molecular changes that underlie them. Jessica Barson will provide introductory comments. Alana Conti will present evidence of altered extinction of conditioned fear behaviors following mild TBI in adult mice and the novel role of Class IIa histone deacetylases (HDACs) in mediating synaptic plasticity associated with these changes. She will describe the importance of subcellular nuclear localization of HDAC4 in this process and the behavioral effects of Class IIa HDAC inhibition on fear extinction learning. Ramesh Raghupathi will present evidence of depressive- and anxiety-like behaviors in adult female rats following mild TBI in adolescence. He will discuss how these behaviors are dependent on estrous phase and can be reversed either by activation of mesocorticolimbic dopamine or accumbal corticotropin releasing factor or kappa opioid receptor systems. Servio Ramirez will describe findings that the reinforcing properties of psychostimulants in adult mice are exacerbated by adolescent TBI. He will present results showing that there are unique inflammatory signatures in the mesolimbic and corticostriatal pathways during the chronic phase of TBI. Patricia Molina will present findings that show neurochemical and behavioral impairments associated with escalation of alcohol consumption in adult rats following TBI. She will discuss her ongoing studies aimed at elucidating the mechanisms leading to this escalation in alcohol drinking post-TBI. These presentations will highlight the diverse means by which TBI can affect behavior, long after the disappearance of acute effects, and they will suggest ways in which clinicians can approach treatment for TBI.

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • SALON B

Lifting Dopamine Into a New Era: Illuminating the Slopes With New Fluorescent Tools

Chairs: Amy Newman, Ulrik Gether
Presenter: Lin Tian, Claire Deo, Ulrik Gether, Kenneth Madsen

The neurotransmitter dopamine exerts its actions across diverse neurocircuitry to regulate voluntary movement, feeding, reward, memory and learning. Thus, it's not surprising that dopaminergic dysfunction is a critical factor in disorders

such as Parkinson's disease, schizophrenia, restless leg syndrome, ADHD and addiction. Despite decades of research, the lack of tools to investigate how dopamine release alters the function of its target circuits or how drugs that bind to dopamine receptors or the dopamine transporter affect behaviors, in a spatiotemporal way, has been stymied. However, recent experimental progress has moved the field into a new era. Indeed, the use of advanced fluorescent tools has opened up entirely new avenues for addressing fundamental questions related to dopamine biology and pathophysiology. In this panel, Lin Tian will begin by discussing ultrafast neuronal imaging of dopamine dynamics with designed genetically encoded sensors enabling measurements of dopamine levels in the brain with unprecedented temporal and spatial resolution. Claire Deo will follow with the design and development of new synthetic fluorescent neural activity indicators that can be applied to single molecule microscopy of the dopamine system. Ulrik Gether will describe the implementation of such indicators as well as the use of super-resolution microscopy to study the nanoscale architecture of dopaminergic nerve terminals and how this might change during different functional conditions. Finally, Kenneth Madsen will discuss how the use of genetically encoded second messenger sensors can unravel principles for how dopamine exerts its functions via yet unappreciated subpopulations of dopamine receptors. Summarized, the new era of high-resolution imaging of dopamine dynamics is ready to "lift" our understanding of how dopamine signaling regulates neurocircuit function and to illuminate novel strategies for treatment of pathologies characterized by dopaminergic dysfunction.

SHORT COURSE • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • SALON C

The Epilepsies: Current Trends in Diagnosis, Treatment, and Research

Chair: Thomas Swanson
Presenters: Ian Miller, Amy Brooks-Kayal, Thomas Swanson

Epilepsy impacts 1 in 26 people with no geographic, sex, or race boundaries. The mainstays of treatment include small molecules, electrical stimulation devices, and surgery. A substantial group of patients will be refractory to these therapies and constitute a significant portion of the 50,000 people each year that die of epilepsy. Basic research in epilepsy engages a disparate group of researchers across many different disciplines, including electrophysiology, pharmacology, immunochemistry, molecular and cellular biology, imaging, engineering, computer science, behavior, and genetics. The overall strategic plan of this course is to stimulate participant interest in pursuing research on this group of disorders. Our panel will examine the clinical evaluation / treatment of epilepsy and explore exciting "state-of-the-science" topics in epilepsy research. Tom Swanson will discuss the approach to diagnosis of spells

and seizures, the role of EEG, and how to design individually tailored treatment approaches. Ian Miller will discuss the role of electrical stimulation devices, special pediatric and neonatal considerations in evaluation and treatment, and epilepsy surgery. Amy Brooks-Kayal will talk about current trends in basic-translational epilepsy research and advances in development of precision and disease-modifying therapies. Tom Swanson will close with a focused discussion on cannabinoids in epilepsy. Emphasis will be placed on identifying fertile areas of research in this clinically and scientifically fascinating field.

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • SALON D

Learning Structure in the World: The Computational and Neural Basis of Bayesian Models of Reinforcement Learning

Chairs: Bruno Averbeck, Michael Frank
Presenters: Frederike Petzschner, Angela Langdon, Michael Frank, Bruno Averbeck

Learning to predict whether choices will lead to reward or punishment is critical to survival and the brain contains multiple, interacting neural systems that underlie these processes. In this symposium we will describe recent progress towards understanding the computational and neural mechanisms underlying reinforcement learning (RL), focusing on sophisticated forms of learning based on Bayesian inference. For example, in probabilistic reversal learning paradigms, after experiencing several reversals, the subjects come to expect that reversals will occur. This corresponds to learning a model in which the world is in one of two states, depending upon which option is being rewarded. Choosing options using this state inference model is more efficient than using slow model-free value updates. This symposium will focus on this emerging area across species and highlight the neural and computational mechanisms related to hidden state inference, including corticostriatal interactions, plasticity, and attractor dynamics. Frederike Petzschner will discuss the influence of serotonin on hidden state learning in healthy participants and changes in state learning in patients with Obsessive-Compulsive Disorder as a result of long-term cognitive behavioural therapy. Angela Langdon will discuss the computational role of temporal expectations in RL, and how neural and behavioral timing processes support inference about hidden task states during reward prediction and learning. Michael Frank will present computational models of how agents infer one of several potential task structures during learning and relate that hidden state inference to neural dynamics (either DA in mice or EEG activity in humans). Bruno Averbeck will discuss results that show that monkeys infer state switches during reversal learning tasks, and large populations of dorsal-lateral prefrontal neurons represent these state switches during learning.

PANEL • WEDNESDAY, 4:30 P.M. – 6:30 P.M. • SALON E

The Function and Role of AMPA Receptors in Human Disease

Chair: Stephen Traynelis

Presenters: Ingo Greger, Michael Maher, Linda Nowak, Stephen Traynelis

Fast excitatory synaptic transmission is overwhelmingly mediated by the AMPA receptors family, encoded by the GRIA family of genes. The AMPA receptors can co-assemble with a broad range of accessory subunits, which alter virtually all aspects of their function. The members of the AMPA receptor proteome show differential expression in terms of region and time, providing an opportunity to therapeutically intervene at specific synapses. This panel will present recent advances in our understanding of AMPA receptor function, pharmacology, and role in disease. Ingo Greger will present novel structural and functional data highlighting the dynamic nature of the AMPAR extracellular region (ECR), and refined insight into their interaction with auxiliary proteins. He will also describe new data on the role of the ECR in AMPAR clustering at synapses. Of particular interest among accessory subunits, TARP-g8 is highly expressed in the hippocampus and is absent in hind- and mid-brain regions. Mike Maher will present on the discovery and characterization of compounds with exquisite selectivity for the AMPAR/TARP-g8 complex. These compounds possess a novel mechanism-of-action consistent with a partial attenuation of the interaction between the TARP and the pore-forming subunits of the channel. They show anticonvulsant and anxiolytic profiles in rodents, and are devoid of sedative and motor-impairing side effects. Linda Nowak will present single channel data showing differential tuning of AMPAR-channel gating by the anticonvulsant perampanel and other noncompetitive antagonists. Stephen Traynelis will summarize the growing number of human mutations found in gating regions of the AMPA receptor family, with a focus on their functional actions and relevance for disease symptoms.

Brain Talk Town Meeting

PLENARY • WEDNESDAY, 7:00 P.M. – 8:30 P.M. • SALON B

The Neuroscientist who Lost Her Mind

Presenters: Barbara Lipska, Elaine McArdle

Barbara Lipska is a neuroscientist. For over 40 years, she studied mental illness; first in her native Poland and then in the U.S. at the National Institute of Mental Health. Her specialty is schizophrenia, a devastating disease in which people struggle to recognize what is real and what is not. In January 2015, she was diagnosed with metastatic brain cancer, and given four to seven months to live. During therapy, she lost her mind.

THURSDAY, JANUARY 31, 2019

Thursday Morning Panel Sessions

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • ALPINE SPRINGS

Diverse Roles of the Hypothalamus and Hypothalamic Circuits in Motivation and Psychopathology

Chairs: Marisela Morales, David Barker
Presenters: David Barker, Adam Gordon, Alexander Johnson, Richard O'Connor

The hypothalamus is a diverse structure that participates in a wide variety of behaviors including feeding, neuroendocrine function, stress, and reward processing by communicating with the central nervous system through an intricate network of neurotransmitters and neuropeptides. One group of hypothalamic neurons that has long been associated with motivated behaviors is found along a continuum encompassing the lateral preoptic area and lateral hypothalamus. This panel will present emerging research that highlights the roles of the lateral preoptic area and lateral hypothalamus in guiding specific motivated behaviors. Dr. Marisela Morales (National Institute on Drug Abuse/NIH) will provide general remarks. Dr. David Barker (National Institute on Drug Abuse/NIH) will describe anatomical and ultrastructural work defining the connectivity of the lateral preoptic area and ventral tegmental area as well as a potential role for this pathway in aversive processing. Adam Gordon (the University of Texas at Austin) will present his work on the functional connectivity between the lateral preoptic area and the ventral tegmental area and its role in motivated behavior. Dr. Alex Johnson (Michigan State University) will present work on neuropeptide modulation of lateral hypothalamic neurons and its effects on ingestive and reward behaviors. Finally, Dr. Richard O'Connor (Icahn School of Medicine at Mount Sinai) will present his work showing that lateral hypothalamic inputs to lateral habenular neurons control food preference in a leptin-dependent manner.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • CASTLE PEAK AUDITORIUM

Embracing the Diversity of Self-Administration Protocols in Drug Addiction Research

Chair: Matthew Wanat
Presenters: Sara Jones, Matthew Wanat, Rachel Smith, Yavin Shaham

Addiction is a complex disease associated with a wide array of behavioral symptoms. Unfortunately, no single preclinical behavioral procedure can effectively model the range of behaviors that accompany addiction. However, the diversity of behavioral models allows us to identify the neural circuits

mediating specific aspects of addiction-related behaviors. We will present recent findings examining the neural systems contributing to drug taking and seeking using different drug self-administration and relapse procedures. Sara Jones (Wake Forest) will discuss the influence of the pattern of cocaine intake on dopamine dynamics and motivational behavior measured with a "threshold" procedure based on behavioral economics principles, with a specific emphasis on restricted, intermittent exposure versus extended access training procedures. She will also discuss sex and estrous phase differences in the sensitivity to cocaine self-administration patterns. Matt Wanat (UTSA) will discuss how dopamine release to cocaine infusions is affected by the reinforcement schedule as well as how these findings contrast with the dopamine response to food rewards. Rachel Smith (Texas A&M) will discuss a novel method of outcome devaluation developed to distinguish between goal-directed and habitual response strategies for intravenous cocaine self-administration and will describe research investigating a link between habits and punishment resistance using this outcome devaluation method and a seeking-taking chained schedule of cocaine self-administration. Yavin Shaham (NIDA) will describe new models of relapse after voluntary abstinence achieved via either adverse consequences (punishment) or choice of an alternative reward (palatable food or social partner) and discuss similarities and differences in circuit mechanisms. This panel will highlight the importance of using a diverse array of behavioral procedures to understand the underlying neurobiology contributing to drug taking and seeking.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • CATHEDRAL PEAK

New Insights Into the Workings of Synapses

Chair: Andres Maricq
Presenters: David Bredt, Katherine Roche, Roger Nicoll, Andres Maricq

In this panel we will provide new mechanistic insights into the function of important classes of synaptic proteins. Bredt will describe how genome-wide cDNA screening has identified three new accessory proteins that complement NACHO to reconstitute α6β2β3 channels to control nigrostriatal dopamine release. These studies unravel the molecular complexity of α6β2β3 biogenesis and enable physiological studies of this crucial neuropharmacological target. Roche will discuss recent findings from her lab on the regulation of the postsynaptic adhesion molecules neuroligins. She will present evidence for isoform-specific posttranslational regulation (including phosphorylation and activity-dependent cleavage) of neuroligins that affects synaptic transmission and intracellular signaling. A better understanding of these molecular mechanisms will yield insight into the role of neuroligins in disorders such as autism and glioma. Nicoll will present data on the role of the delta1 glutamate receptor (GluD1) at hippocampal excitatory synapses. Although GluD1 fails

to evoke synaptic currents, it is required for both excitatory synapse formation and synapse maintenance in the hippocampus. The action of GluD1 requires the presence of the soluble glycoprotein cerebellin2 (Cbln2). Furthermore, the GluD1 actions require the presence of presynaptic neurexin 1β (+S4). Thus, GluD1 is a component of a transynaptic tripartite molecular complex in which the ligand Cbln2 binds with presynaptic neurexin 1 β (+S4) and postsynaptic GluD1. Maricq will describe the mechanism of action of the recently identified presynaptic protein NRAP-1, which associates with postsynaptic NMDARs forming a signaling complex. In the absence of NRAP-1, NMDARs are on the cell surface, but are silent because glutamate does not gate open the receptors. Thus, NRAP-1 is rate limiting for the number of functional postsynaptic NMDARs, a finding that suggests a novel mechanism for the regulation of synaptic strength.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • OVERLOOK

Psychiatric Risk Factors in the Development of Non-Combat Related PTSD

Chair: Felicia Gould
Presenters: Felicia Gould, Mackenzie Jones, Vasiliki Michopoulos

Post-traumatic Stress Disorder (PTSD) is a significantly disabling mental disorder that partially results from direct or indirect exposure to a traumatic event. The disorder is characterized by intrusive memories of the event, avoidance, negative mood and disordered arousal, reactivity and thoughts. It has been estimated that 50% to 60% of people experience a potentially traumatizing event. Due to increasing evidence that large-scale exposure to traumatic events (e.g., natural disasters and acts of violence/ terrorism) is increasing, the need to characterize the development of PTSD and identify those psychological and biological markers which best predict PTSD development is pressing, particularly within civilian populations. It is hoped that the identification of these important risk factors will enable the earliest and most successful interventions. This session will review PTSD and principle psychological risk factors and psychobiological markers. We will present key findings from a recently completed and large-scale prospective study of PTSD. We will present data on 713 diverse participants recruited in 2 different metro areas who were assessed up to 4 times, over the one-year period following a trauma exposure. Dr. Felicia Gould will present an overview of the disorder and the study in general. Ms. Mackenzie Jones will present on drug abuse and its impact on PTSD development. The differential impact of specific subtypes of street drugs on the brain and their distinct contribution to PTSD risk will also be discussed. Finally, Dr. Vasiliki Michopoulos will present findings on sex-differences in the development of PTSD. The role of sex-related neuroendocrine factors will also be highlighted.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • SALON B

When the Terrain Goes From Exhilarating to Aversive: Expression and Function of the Kappa Opioid Receptor

Chair: Elyssa Margolis

Presenters: Lee-Yuan Liu-Chen, Charles Chavkin, Elyssa Margolis, Anushree Karkhanis

Physical and psychiatric challenges drive the hypothalamic-pituitary-adrenal axis, activating a physiological stress response and readying the organism to behave appropriately. While stress can drive adaptive behavior, stressors can also be aversive, and under certain conditions, they drive physiological changes and maladaptive behaviors including relapse to addiction, depression, anxiety, and PTSD. Animal models indicate that the kappa opioid receptor (KOR), and its endogenous neuropeptide ligand dynorphin, underlie the aversive component of stressful experiences. In this panel, we will describe the latest insights into the organization of the KOR in the CNS, new findings in its endogenous function, and changes in function that occur following aversive stress. Lee-Yuan Liu-Chen will introduce the kappa opioid receptor anatomical distribution, describing its CNS localization as revealed by a novel mouse line in which the KOR is conjugated in-frame to tdTomato 5' to the stop codon. Next, Charles Chavkin will present recent insights about functional selectivity of KOR ligands and the anatomical sites of dynorphin action in brain responsible for specific aspects of the pro addictive and pro depressive stress response. Elyssa Margolis will describe a switch in KOR signaling from inhibitory to excitatory in midbrain dopamine neurons caused by acute stressors as well as corticotrophin releasing factor. Finally, Anushree Karkhanis will describe long lasting changes in adult KOR control of dopamine reuptake in the striatum following early life stressors. Together these talks will communicate the latest understanding of the key brain circuits controlled by and altered function in the KOR-dynorphin system that contribute to aversion and maladaptive behavior.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • SALON C

Functional and Molecular Heterogeneity of CNS Stem and Progenitor Populations

Chair: Francis Szele

Presenters: Francis Szele, Steven Levison, Teresa Wood, Wendy Macklin

Progenitor and stem cell diversification is a powerful mechanism for generating distinct cohorts of differentiated cells throughout development and in response to disease. The extent to which progenitors develop and maintain distinct molecular characteristics as well as lineage potentials is still poorly understood. Phenotypic characterization and functional neurodevelopmental studies have shed some light on the diversity of stem and progenitor cells. Bulk and

single cell RNAseq have proven invaluable in uncovering heterogeneity of stem and progenitor cells at different stages of development. Francis Szele (Oxford) will discuss work showing epigenetic regulation of the postnatal subventricular zone stem cells and also present data showing gene expression similarities and differences in subventricular zone and hippocampal subgranular zone neurosphere cultures. Steve Levison (Rutgers) will describe antigenic, transcriptomic and functional heterogeneity of postnatal subventricular zone stem and progenitor cells. Terri Wood (Rutgers) will discuss recent single cell RNA-seq work detailing transcriptomics differences in oligodendrocyte cell subtypes between CNS regions and in response to alterations in signaling pathways. Wendy Macklin (University of Colorado) will discuss molecular changes in oligodendrocyte progenitor cells and oligodendrocytes when the Akt/mTOR pathway is altered during development, focusing on regional heterogeneity of spinal cord and brain oligodendrocyte populations.

PANEL • THURSDAY, 7:30 A.M. – 9:30 A.M. • SALON D

Structure and Function of Glutamate Receptors

Chairs: Johannes Hell, R. Suzanne Zukin
Presenters: Bernd Fakler, Elva Diaz, Terunaga Nakagawa, R. Suzanne Zukin

The vast majority of synapses in the brain are glutamatergic. AMPARs are responsible for most of basal synaptic transmission whereas NMDARs mediate calcium influx and thereby synaptic plasticity. Dysregulation of glutamate receptor function is at the basis of many mental and neurological disorders. This panel is co-chaired by Suzanne Zukin, who will give one of the talks, and Johannes Hell, who will present the introduction and not give a full talk. Our panel will evaluate different aspects of the trafficking and composition of glutamate receptors and their regulation and function. Bernd Fakler will talk about AMPAR biogenesis in the ER and its in fact crucial significance for activity-dependent synaptic plasticity and learning. Elva Diaz will discuss the role of the auxiliary factor SynDIG4/Prrt1 in supporting a pool of extrasynaptic GluA1-containing AMPA receptors, which is important for synaptic plasticity. Terunaga Nakagawa will present cryo-EM and electrophysiology data of AMPA receptors in complex with various auxiliary membrane proteins and lipids addressing mechanisms by which auxiliary proteins modulate AMPA receptor properties. Finally, Suzanne Zukin will present unpublished data that mice expressing the NMDAR subunit GluN2B lacking serine 1166 exhibit greatly diminished TBS-LTP. She will present evidence that phosphorylation of Ser1166 is required for transient incorporation of GluA2-lacking, Ca2+-permeable AMPARs (CP-AMPARs), a mechanism critical to TBS-LTP. Strikingly, the KI mice also exhibit a marked deficit in cognition.

Ski-Atal Processing in Decision Making and Maladaptive Choice

Chairs: Natalie Zlebnik, Jennifer Wenzel
Presenters: Natalie Zlebnik, Barry Setlow, Erik Oleson, Catharine Winstanley

Decisions are a regular part of our lives. While some decisions are relatively benign ("Which panel should I attend?" "Should I skip the poster session for more time on the slopes?"), others involve risk ("Can I have another whiskey before I give my talk?"). Consequently, insults to underlying neurobiology may lead to pathological decision making, like that observed in addiction. A wide body of evidence supports a role for striatal processing in decision making. However, the roles of distinct striatal inputs and neurotransmitter systems remain unclear. This panel will present exciting new research examining dorsal and ventral striatal circuits in both normal and aberrant decision making. Jen Wenzel (U. Maryland School of Medicine) will provide introductory comments, and she and Natalie Zlebnik (U. Maryland School of Medicine) will lead discussion of the presentations. Natalie Zlebnik will talk about the role of frontal cortical projections to ventral striatum and striatal endocannabinoid control of impulsive choice in rats performing a delay-discounting task. Barry Setlow (U. of Florida) will discuss the contributions of amygdala-prefrontal-striatal circuitry to risky decision making in a rat model, with a particular focus on temporally distinct roles of the basolateral amygdala and its efferents in different stages of the decision process. Erik Oleson (U. of Colorado-Denver) will discuss work combining behavioral economics with electrochemistry and optogenetics to characterize how accumbal dopamine release represents reinforcer cost and causally modifies the price rats will pay to receive reward and avoid harm. Catharine Winstanley (U. of British Columbia) will present novel data indicating sex differences in the dopaminergic regulation of risky decision making versus motor impulsivity in rats, using a well-validated rat gambling task, and discuss the disparate ways in which both of these cognitive phenomena may contribute to addiction vulnerability.

Pioneer Session #2: Oswald Steward

PIONEER SESSION • THURSDAY, 9:45 A.M. – 11:00 A.M. • CATHEDRAL PEAK

Getting the Message From Genes to Synapses

Pioneer: Oswald Steward
Chair:R. Suzanne Zukin
Investigators: Shannon Farris, Patricia Pirbhoy

CNS neurons receive tens or even hundreds of thousands of synaptic contacts, each of which terminates on a postsynaptic membrane specialization containing a distinct set of proteins that make the synapse work. An important mechanism of plasticity is to modify the molecular composition of synapses based on the activity of that particular synapse. It was unknown how neurons were able to construct, maintain and modify individual postsynaptic sites located hundreds of micrometers away from the nucleus membrane until Dr. Steward discovered outposts of protein synthetic machinery (polyribosomes and associated membranes) selectively localized beneath dendritic spines. The paper that reported this discovery (Steward & Levy 1982) proposed the idea that local synthesis of proteins at synapses was critical for establishing the molecular composition of synapses in development and allowing rapid modification of molecular composition as a mechanism of synaptic plasticity. Although controversial at the time, this idea is now broadly accepted and many labs have contributed to the evolution of the story. It is noteworthy that one of the first pre-publication presentations of the key discovery was at WCBR in a session organized by Bill Greenough. This was the first time Dr. Steward attended WCBR. Following on the initial discovery, Dr. Steward's studies defined mechanisms of selective transport of mRNA into dendrites, discovered the remarkable ability of one mRNA (Arc) to localize selectively at active synapses, and elucidated many details about localization and local translation of Arc and other mRNAs in dendrites. In this pioneer session, Dr. Steward will describe his path of discovery, with consideration of how discoveries are made, and will highlight emerging concepts and unresolved paradoxes and puzzles. Follow-up presentations are by two of Dr. Steward's recent students who made fundamental contributions to the story of local protein synthesis at synapses and are now pursuing related stories on neuron-specific dendritic transcriptomes (Farris) and molecular mechanisms involved in auditory hypersensitivity in Fragile-X Syndrome (Pirbhoy).

Career Development Workshop #2

SPECIAL SESSION • THURSDAY, 2:00 P.M. – 3:30 P.M. • CASTLE PEAK AUDITORIUM

Career Development Workshop: Skills for the New Investigator

Chair: Lakshmi Devi
Participants: Carrie Ferrario, Travis Brown, Lique Coolen, George Wilcox

Young neuroscientists face a number of challenges when establishing their own research laboratory and developing an independent research program. This workshop brings together a panel of experienced neuroscience researchers to discuss the various hurdles newly-independent scientists face in pursuing a career in academics. Participants will discuss the issues including, how to recruit scientific staff, how to find mentors/be a mentor, how to handle the demands for publication, find opportunities for collaboration, navigate the road to tenure and promotion and get better at work life integration. The panelists will also advise new investigators on how to obtain funding for their research, including advice on navigating the NIH peer review process and advice on exploring other funding sources to support their science.
Lakshmi Devi, Professor and Dean for Academic Development and Enrichment, Icahn School of Medicine at Mount Sinai, will introduce the panelists and lead the discussion. The other panelists and their affiliations are: Carrie Ferrario, Assistant Professor in Pharmacology, at the University of Michigan, School of Medicine; Travis Brown, Associate Professor at the University of Wyoming, School of Pharmacy; Lique Coolen, Associate Dean in College of Arts and Sciences and Professor in Biological Sciences, at Kent State University; and George Wilcox, Professor in Neuroscience, at the University of Minnesota.

Thursday Afternoon Panel Sessions

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • ALPINE SPRINGS

From Molecules to Mind: Genetic Defects in Cell-Cell Signaling That Cause Neurological Disorders

Chair: Cedric Asensio
Presenters: Cedric Asensio, Lakshmi Devi, Lloyd Fricker, Iris Lindberg

The ability to regulate the secretion of peptides and proteins plays a central role for many aspects of biology, but is particularly essential to brain neuropeptide function in behavioral processes. The regulated release of opioid peptides, for example, influences pain perception as well as the reward pathway known to be

subverted by drug addiction. Hypothalamic neuropeptide secretion controls a wide range of physiological behaviors, from feeding to sleep to reproduction. The peptide-containing secretory vesicles involved in regulated secretion are called large dense core vesicles (LDCVs), and their exocytosis can be triggered by an extracellular, physiological stimulus. The basic machinery responsible for their regulated exocytosis consists of specific membrane proteins present both at the plasma membrane and on LDCVs. The molecular composition of LDCVs thus partly dictates their release properties, but, surprisingly, the mechanisms controlling the formation, trafficking and exocytosis of LDCVs still remain poorly understood. In this session, Cedric Asensio will introduce the field and discuss the role of the peripheral membrane protein HID-1 in the formation of LDCVs; patients bearing mutations in this protein show neurological defects. Lakshmi Devi will discuss a non-enzymatic role for the Prolyl Endopeptidase-Like (PREPL) protein in regulating peptide secretion and its known impact on neurodegeneration. Lloyd Fricker will present data on mouse models showing neuropeptide involvement in both depression and addiction. Iris Lindberg will wrap up the session by discussing the potent anti-aggregation effects of an LDCV chaperone protein, proSAAS, and its potential involvement in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • CASTLE PEAK AUDITORIUM

Parabrachial Nucleus: A Nexus of Affective Pain

Chair: Asaf Keller
Presenters: Asaf Keller, Sarah Ross, Yarimar Carrasquillo, Marisela Morales

Asaf Keller (Univ. Maryland) will introduce the parabrachial nucleus (PBN) as a nexus of the perception of affective pain, and of descending pain modulation. He will demonstrate that chronic pain is associated with hyperexcitability of PBN neurons, and that this relates to reduced inhibition from central nucleus of the amygdala (CeA). He will demonstrate how this hyperexcitability results in pain facilitation through 5HT release from descending pain pathways. Sarah Ross (Univ. Pittsburgh) will show that distinct subregions of the lateral PBN (lPBN) project to different targets, and that activation of these pathways generates unique aversive responses. The external lPBN projects to the external amygdala, and photo-stimulation of this pathway evokes avoidance behavior. The dorsal lPBN projects to hypothalamus and periaqueductal gray, and produces explosive locomotor behavior. Only lPBN–>PAG photo-stimulation reduces tail flick responses to noxious heat. Yarimar Carrasquillo (NCCIH, NIH) will show that PKCδ-expressing neurons in CeA (CeA-PKCδ), but not somatostatin-expressing CeA neurons, are the main recipients of nociceptive inputs from PBN. She will demonstrate that persistent pain is associated with plasticity in intrinsic properties CeA neurons: CeA-PKCδ cells show increased excitability, and chemogenetic inhibition of these neurons reduces

tactile hypersensitivity. In contrast, CeA-somatostatin neurons show decreased excitability during chronic pain, and inhibition them induces hypersensitivity in the absence of injury. These results suggest that the CeA functions as a pain 'rheostat', amplifying or suppressing pain in a cell-type-specific manner. Marisela Morales (NIDA, NIH) will show that the lPBN is directly innervated by the dorsal raphe, and that optogenetic activation of this input promotes both place preference and optical cranial self-administration. She will suggest that this previously unknown reward pathway may be involved in pain perception.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • CATHEDRAL PEAK

Dysregulation of Abused-Substance Intake by Kappa-Opioid Signaling

Chair: Paul Phillips

Presenters: Sara Jones, Lara Hwa, Ryan Farero, George Koob

A core symptom of substance use disorders is the diminished ability to regulate drug consumption. This process is progressive during chronic substance use and has both acute and chronic negative consequences. During this progression, levels of stress-related neurochemicals increase, including peptides of the dynorphin family. Emerging evidence suggests that signaling by dynorphins at the kappa-opioid receptor disrupts the regulation of drug consumption. This panel will discuss the neurobiological mechanisms that regulate drug intake and their change following chronic drug use in rodent models, focusing on the dynorphin/kappa-opioid system. Paul Phillips (University of Washington) will introduce the session. The first speaker, Sara Jones (Wake Forest), will describe changes in the kappa-opioid system following chronic alcohol use and how they influence dopamine transmission in the nucleus accumbens. Next, Lara Hwa (University of North Carolina) will discuss how changes in kappa signaling influence binge alcohol consumption. Ryan Farero (University of Washington) will discuss interactions between kappa-opioid signaling and dopamine transmission in the regulation of cocaine consumption. Finally, George Koob (NIAAA) will describe the role of the dynorphin/kappa-opioid system in the escalation of drug consumption across classes of drugs.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • OVERLOOK

Epigenetic Substrates of Experience-Dependent Plasticity and Their Dysregulation in Psychiatric Disease

Chair: Philipp Mews
Presenters: Mary Kay Lobo, Philipp Mews, Erin Calipari, Christoph Anacker

Neuronal circuit activity mediates the expression of behavior and the ability to update information in real-time. Recent studies implicate dynamic epigenetic regulation in this process. This panel will present data converging on the notion that epigenetic processes arbitrate the stabilization of new information and learned behaviors. In neurons, epigenetic signatures 'gate' neuronal activity to regulate the temporally sensitive transcription of genes involved in synaptic plasticity. In this manner, neurons are incorporated into functional ensembles via epigenetic controls that strengthen their synaptic connections. Mary Kay Lobo (U. of Maryland) employs cell-type and circuit selective approaches to probe neuro-epigenetic mechanisms that mediate maladaptive motivational diseases. She will present novel insights into how epigenetic processes mediate selective molecular adaptations in the two divergent ventral striatal projection neurons. Philipp Mews (Mount Sinai) will discuss how chromatin remodeling in the distinct neuronal subtypes of the striatum is linked to drug-induced and long-lasting changes in gene regulation and circuit connectivity. Erin Calipari (Vanderbilt U.) will share new data on phospho-acetylation of chromatin as a key player in drug-induced changes in gene expression and circuit function that make animals vulnerable to relapse. Christoph Anacker (Columbia U.) will speak about his work using in vivo calcium imaging in the hippocampus of freely moving mice, which revealed how adult neurogenesis regulates information processing and circuit activity. Together, this session will showcase how 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. Deep mechanistic understanding of how neural circuit activity and neuro-epigenetic regulation interact to shape behavior may pave the way for novel therapeutic interventions in neuropsychiatric disorders.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • SALON B

Ch-Ch-Changes: Redefining the Role of the Basolateral Amygdala and Orbitofrontal Cortex in Tracking Value

Chair: Kurt Fraser
Presenters: Kurt Fraser, Melissa Malvaez, Caitlin Orsini, Vincent Costa

Making flexible and adaptive choices is critical to survive in the constantly changing world and failures in this essential process is an underlying symptom of many psychiatric illnesses. Despite this, many studies of associative learning

and decision making have used conditions that are fixed and stable which obscure dynamic reward-seeking and decision making. Decades of work has suggested that activity within the basolateral amygdala (BLA) and orbitofrontal cortex (OFC) are critical not only for learning cue-reward and action-outcome associations, but also for behavioral adjustments in response to environmental changes. This panel will emphasize a new role for the BLA and OFC in the continual monitoring and integration of internal and external information to produce continually adaptive reward-seeking and decision making. First, Kurt Fraser will discuss a novel preparation of flexible Pavlovian reward-seeking, called occasion setting, and how activity within the BLA and OFC supports adaptive cue-triggered reward-seeking. Second, Dr. Melissa Malvaez will discuss the dissociable OFC-BLA circuitry through which reward memories are encoded and retrieved to guide adaptive reward pursuit decisions. Third, Dr. Caitlin Orsini will describe how the contribution of BLA activity to decision making involving risk of punishment dynamically changes over the course of the decision-making process. Finally, Dr. Vincent Costa will describe how BLA and OFC contribute to decisions about when to forego immediate rewards and explore unknown options to learn if they yield more profitable outcomes in the future. The panel will emphasize the use of sophisticated behavioral paradigms in a variety of model organisms that allow for dynamic reward-seeking behaviors that when combined appropriately with modern neuroscience techniques can provide novel insight into the circuits supporting ongoing behavioral processes.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • SALON C

New Circuit and Synaptic Mechanisms of Dopamine Function

Chair: Chris Ford
Presenters: Paul Kramer, Brooks Robinson, Talia Lerner, Chris Ford

Dopamine neurons of the SNc and VTA project to multiple target regions where they underlie a variety of goal directed and motor behaviors. In this panel speakers will discuss recent work examining the regulation and actions of dopamine neurons. Speakers will present cellular, synaptic and systems data examining the mechanisms underlying the release of dopamine at synaptic sites, the regulation of dopamine axon input activity and how dopamine regulates striatal circuits and associated behaviors. Paul Kramer will (NIH) present data on electrophysiological recordings from dopamine neuron axons examining GABAergic input to these axons. Brooks Robinson (Vollum Institute) will discuss studies in which the visualization of both dopamine release and native D2 receptors are used to investigate the properties of dendrodendritic transmission. Talia Lerner (Northwestern) will talk about how dopamine is a crucial neurotransmitter for both motivated behavior and motor control. She

will discuss how the architecture of the midbrain dopamine system connects these functions, allowing transitions from goal-directed behavior to automatic motor skills and habits. Christopher Ford (University of Colorado) will present data on how dopamine inputs regulate the activity of striatal cholinergic interneurons to regulate the balance of cholinergic transmission across the dorsomedial and dorsolateral striatum. Together these presentations will cover new methods and findings in the field of dopamine research.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • SALON D

Pursuing Reward Cues: Sign-Tracking in Models of Learning, Addiction and Risky-Decision Making

Chair: Jonathan Morrow

Presenters: Jonathan Morrow, Sam Bacharach, Nadia Chaudhri, Mariya Cherkasova

Sign-tracking is a learned, Pavlovian attraction toward reward-associated cues. Sign-tracking is difficult to restrain and shares several features in common with psychiatric disorders like addiction and gambling that involve excessive reward-seeking behavior. In contrast, goal-tracking is Pavlovian approach behavior that is directed toward the location of reward delivery, instead of toward the cue itself. Goal-tracking seems to reflect more cognitive and contextual influence over cue-triggered responses and is thought to be protective against dysfunctional reward-seeking. This panel will explore what sign- and goal-tracking can tell us about psychological and neurobiological processes that contribute to drug addiction, gambling, and reward-seeking behaviors in general. Jonathan Morrow from the University of Michigan will show how manipulations of the predictive and incentive properties of cues and rewards can differentially affect sign- and goal-tracking behaviors in rats. Sam Bacharach from the University of Maryland School of Medicine will present data from sign-tracking rats probing the extent to which cannabinoid-1 (CB1) receptor signaling mediates two critical properties of incentive stimuli; their ability to attract and their ability to reinforce behavior. Nadia Chaudhri from Concordia University will present data from rats showing how the use of amphetamines and alcohol can influence both dopaminergic activity and the propensity to sign- or goal-track. Mariya Cherkasova from the University of British Columbia will discuss the putative relationship between sign-tracking and the ability of reward-concurrent cues to promote risky decision making, in both humans and rodents. Although human sign trackers show greater preference for more uncertain outcomes, whether cues can amplify this trait, appears to depend on whether cues are present at the time of decision or delivered when subjects discover the outcome of the gamble.

PANEL • THURSDAY, 4:30 P.M. – 6:30 P.M. • SALON E

Treatment for Traumatic Brain Injury: One-Size Doesn't Fit All

Chair: Cole Vonder Haar
Presenters: Edward Hall, Olga Kokiko-Cochran, Akiva Cohen, Kris Martens

More than 2.8 million traumatic brain injuries (TBIs) occur each year in the United States. This staggering statistic is further compounded by the vast number of comorbid problems that occur in the wake of a TBI: conditions as varied as Alzheimer's disease, epilepsy, and psychiatric disorders. The current panel seeks to address this heterogeneity by pulling a diverse set of viewpoints from young and established investigators and across multiple potential therapeutic mechanisms. Edward Hall (University of Kentucky) will address the acute side of TBI and show data on antioxidant strategies to mitigate mitochondrial dysfunction after focal brain injury. Olga Kokiko-Cochran (Ohio State University) will present work elucidating links between poor sleep after TBI, neuroinflammation, and activation of the hypothalamus-pituitary-adrenal axis in mice. Akiva Cohen (University of Pennsylvania) will discuss the implications for circuit-level disruptions in behavioral function and potential therapeutic avenues for resulting behavioral dysfunction. Kris Martens (West Virginia University) will share data on the efficacy of transcranial direct current stimulation of the forebrain to reduce chronically-elevated impulsivity in a rat model of focal TBI. We will conclude with a panel discussion highlighting both the challenges facing the field, but also offering opinions on therapeutic strategies going forward, including combination therapies and the treatment of secondary disorders in TBI populations.

Thursday Evening Panel Sessions

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • ALPINE SPRINGS

The Importance of Choice Procedures in Addiction Neuroscience

Chair: Marco Venniro
Presenters: Marco Venniro, Matthew Banks, Margaret Haney

The ability to choose between multiple alternatives is crucial to our survival, health, and happiness. Dysfunction in decision-making is characteristic of the symptoms underlying various neuropsychiatric diseases, including drug addiction. Substance-use disorders are increasingly being conceptualized as disorders of behavioral misallocation between drug and nondrug reinforcers. Based on this, the goal of addiction treatment should be promoting a reallocation of behavior toward nondrug-related activities. We will present

recent findings exploring the behavioral, pharmacological and clinical features of choice procedures from rodents to humans in drug addiction. Marco Venniro (NIDA) will describe new models of relapse after voluntary abstinence achieved via choice of an alternative reward (palatable food or social partner) and discuss underlying mechanisms. Matthew Banks (Virginia Commonwealth University) will discuss results evaluating the effectiveness of three candidate medications: the 5-HT2C agonist lorcaserin, a heroin vaccine, and G-protein biased mu-opioid receptor agonists, on heroin vs. food choice in monkeys, compared to previous results with current FDA-approved treatments naltrexone and buprenorphine. Margaret Haney (Columbia University Medical Center) will present data from the human laboratory showing the effects of a range of medications on the choice between self-administering a drug of abuse (cocaine, cannabis) or receiving money. Collectively, this panel will illustrate the importance of incorporating choice procedures into neuroscience-based addiction research and support the wider incorporation of alternative nondrug-based addiction treatments.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • CASTLE PEAK AUDITORIUM

Synaptic Pathologies in Schizophrenia, Autism and Alzheimer Disease

Chair: Zachary Wills
Presenters: Zachary Wills, Bruce Herring, Robert Sweet

Schizophrenia, Autism and Alzheimer's Disease are among the most prevalent neuropsychiatric disorders in the US and worldwide. Despite some obvious differences between them (age of onset, presence of identified insoluble protein aggregates and neurodegeneration), these syndromes nevertheless share a number of aspects of their expressed phenotypes. Clinically, they are characterized by cognitive deficits and positive symptoms (delusions and hallucinations). Further, they share impairments of neocortical dendritic spine structure and synaptic proteostasis. This panel will present new data informing the underlying mechanisms of dendritic spine impairments in these syndromes. Dr. Wills will present data on the role of inhibition of new synapse assembly in dendritic spine loss in model systems of AD, and delineate a new mechanism by which soluble Aβ induces a Nogo receptor-mediated deficit in synapse assembly via targeted inhibition of T-type calcium channels. Dr. Herring will present data on disease-related mutations in synaptic GEF proteins that suggest Autism and schizophrenia-associated alterations of synapse function occur at distinct periods of brain development. Dr. Sweet will present data revealing hyperphosphophorylation at multiple sites in microtubule-associated protein 2 (MAP2) in subjects with schizophrenia. New data demonstrating how phosphorylation at one such site (S426) contributes to impaired synaptic protein synthesis in schizophrenia will also be presented.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • CATHEDRAL PEAK

New Trends in Advancing Clinical Imaging of Neurological Disorders

Chair: Olaf Paulson
Presenters: Xiaoping P. Hu, Darren Kadis, Olaf Paulson

Neuroimaging has undergone a major evolution during the last few decades and development in imaging of several neurological disorders has led to a plethora of advanced techniques. The evolution continues with both new hardware and analytical methods. The present symposium focuses on these aspects. Xiaoping Hu will present the recent advances his group and his collaborators have made in developing MRI tools for imaging Parkinson's disease. More specifically, he will describe methods for neuromelanin imaging and iron imaging and their applications for providing potential early biomarkers for Parkinson's disease. Darren S. Kadis will review the current state of presurgical language mapping using magnetoencephalography (MEG) and describe novel connectivity and network-based methods for localization of critical langue sites in children undergoing surgery for medically intractable epilepsy. He will present preliminary data showing that eloquent margins can be appreciated through an entirely data-driven, multilayer network-based mapping approach. Olaf B. Paulson will talk about the clinical use of ultra-high field MRI at 7 Tesla (7T) in presurgical evaluation of patients who are candidates for epilepsy surgery. 7T MR gives a resolution not achievable at conventional field strength. What is the clinical add on value? This will be discussed based on preliminary data in 15 patients with focus on the structural aspects and the potential value of connectivity analysis.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • OVERLOOK

Understanding and Improving Concussion Self-Report: An Interdisciplinary and Multi-Method Perspective on Military Academy Cadets

Chair: Christopher D'Lauro
Presenters: Christopher D'Lauro, Michelle Weber, Karin De Angelis, Julianne Schmidt

Concussions have gained significant interest in both the neuroscience, medical, and lay communities over the past decade. Despite the seriousness of concussions, roughly 50% go unreported. Service members are at a particular risk for sustaining concussions, but little work has investigated the concussion reporting environment for military members. Multiple members of this panel have received an NCAA-Department of Defense grant aimed at examining and improving concussion disclosure among athletes and the military. The panel will discuss this general topic, as well as the collaborative in-depth qualitative

study they conducted on concussion reporting in military academy cadets. Chris D'Lauro (US Air Force Academy) will introduce multi-year quantitative assessment on concussion reporting at the Air Force Academy. Michelle Weber (University of Georgia) will describe qualitative interview study methods and results she used to explicate prior quantitative results on perceived costs of concussion disclosure, identified reasons to disclose a concussion, and more. Karin De Angelis (US Air Force Academy) will add broader sociological context to these findings within a military population. Julianne Schmidt (University of Georgia) will discuss barriers to concussion reporting in collegiate sports settings, associations between immediate reporting and better clinical outcomes after concussion, and concussion efforts aimed at changing athlete concussion reporting behaviors. The panel discussants – a multi-disciplinary group including two kinesiologist/certified athletic trainers, a sociologist, and a neuroscientist – are new to WCBR and will inform the neuroscience community on the latest developments in concussion reporting and interventions.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • SALON B

Calcium Channel Regulation and Synaptic Plasticity: Pre and Post

Chair: William Catterall
Presenters: Ivan Kadurin, Johannes Hell, Mark Dell'Acqua

This panel will connect calcium (Ca) channel regulation in presynaptic and postsynaptic compartments of synapses to short- and long-term synaptic plasticity, changes in gene expression, and spatial learning and memory. Voltage-gated Ca channels trigger neurotransmitter release and they are crucial for Ca signaling in the postsynaptic compartment. Cav2.1 channels that conduct P/Q-type Ca current and Cav2.2 channels that conduct N-type Ca current initiate neurotransmitter release at fast synapses. Their regulation by Ca and second messenger pathways generates presynaptic facilitation and rapid depression of synaptic transmission. Postsynaptic Ca entry through Cav1.2 channels generates L-type Ca currents that induce long-term potentiation and initiate excitation-transcription coupling and regulation of gene transcription in the nucleus. Catterall will introduce the Panel and will present experiments showing that regulation of presynaptic Cav2.1 channels induces short-term synaptic facilitation followed by rapid synaptic depression. This regulation is crucial for sustaining excitation/inhibition balance in hippocampal circuits and for spatial learning and memory. Kadurin will present recent work showing that alpha-2-delta subunits of presynaptic Ca channels are key regulators of channel insertion and function in the presynaptic active zone in nociceptive pathways. Hell will present recent work showing that Cav1.2 channels form a postsynaptic signaling complex that includes beta-2 adrenergic receptors and is crucial for

local Ca signaling that induces long-term potentiation. Dell'Acqua will present experiments that elucidate the coupling of Ca entry through cell-surface Cav1.2 channels to regulation of gene expression in the nucleus, via calcineurin specifically bound to the Cav1.2 and activation of NFAT signaling to induce gene expression in the nucleus. The panelists will discuss the significance of these findings for learning, memory, and neuropsychiatric disease.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • SALON C

Chaos at the Controls: Recent Avenues in Examining Cognitive Dysfunction in Addiction

Chair: Justin Gass
Presenters: Marek Schwendt, M. Foster Olive, Justin Gass

Drug addiction is one of the most prevalent psychiatric conditions in the U.S. and the social and financial burden is immense. We need to gain a better understanding of the pathophysiological changes that result from repeated drug use. It is critical to understand how these brain changes lead to deficits in cognitive function. Cognitive deficits resulting from chronic drug use includes memory deficits, decision-making, planning, cognitive control, and goal-directed activity. These deficits likely result from changes in frontal regions, such as the prefrontal cortex (PFC), that are known to mediate executive function. The goal of this panel is to bring together a diverse group of researchers who focus on different drugs of abuse and their effects on cognitive behavior. The findings show a strong translational emphasis from rodent to human studies. Dr. Marek Schwendt will present research on markers of aberrant neural activity in the PFC underlying persistent working memory deficits and drug-craving in rats with a history of chronic cocaine self-administration. He will also discuss a potential cognitive toll of reducing cocaine-seeking with metabotropic glutamate receptor (mGlu) 5 antagonists. Dr. Olive will present results demonstrating neuroinflammation and cognitive impairments following long term self-administration of the synthetic cathinone MDPV in rats. Dr. Olive will also discuss recent findings regarding the ability heroin self-administration to reduce prosocial behaviors, as well as the ability of chemogenetic activation of insular cortex to reverse these social behavior deficits. Dr. Justin Gass will present his latest findings on the impact of chronic alcohol exposure on measures of cognitive flexibility, risky decision-making, and fear learning. He will also discuss how targeting glutamatergic transmission in subregions of the PFC can prevent and attenuate cognitive deficits from chronic alcohol and stress exposure in both adolescent and adult rodents.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • SALON D

Reactive Astrocytes as a Target in Neuropathologies - Context-Dependent Responses and Treatment Opportunities

Chair: Milos Pekny
Presenters: Milos Pekny, Elly Hol, Kristian Franze

Recent scientific discoveries have unraveled the functions of astrocytes in the central nervous system (CNS) and provided growing evidence that these cells are essential for the establishment and control of neuronal synapses, the regulation of synaptic transmission and waste clearance, and for regenerative processes in the healthy and diseased CNS. Thus, astrocytes have emerged as major players in the maintenance of brain health with critical roles in CNS diseases. This symposium will focus on the current concepts of common and context-specific responses of astrocytes in specific neurological disorders. Milos Pekny will introduce the field and will focus on reactive gliosis in models of neurological diseases, including the characterization of astrocyte subpopulations and their responses to CNS injury. Elly Hol will present the latest results from both human and animal studies unravelling the role of reactive astrocytes in neurodegeneration and cognitive decline. Kristian Franze will present recent data on the importance of mechanical signals in regulating astrocyte activity and resulting pathophysiological conditions.

PANEL • THURSDAY, 7:00 P.M. – 8:30 P.M. • SALON E

Improving the Therapeutic Index of NMDAR/nNOS Signaling Cascade Inhibitors (HINT: Delve B-Low the Surface)

Chair: Carolyn Fairbanks
Presenters: Andrea Hohmann, Carston Wagner, Carolyn Fairbanks

The neuroplasticity underlying chronic pain, opioid tolerance, and opioid addiction has long been associated with excessive glutamate signaling and is often dependent on the N-methyl-D-aspartate receptor (NMDAr) and nitric oxide synthase (NOS) cascade. While the NMDA receptor antagonists have been comprehensively pursued as a non-opioid analgesic and co-adjuvant class of compounds, clinical applications have been hampered by side effects. However, strategies focused on targeting NMDA receptor subtype selective subunits or downstream contributors to the NMDA receptor/NOS signaling cascade may result in improved therapeutic outcomes. The three speakers will feature distinct opportunities to optimize targeting of the NMDA receptor/NOS signaling cascade. Dr. Andrea Hohmann will describe a series of new compounds that target NMDA receptor-scaffolding protein interactions. Dr.

Carston R. Wagner will introduce a line of new antihyperalgesic compounds that inhibit the action of HINT1, an enzyme associated with mu opioid receptor-NMDA receptor interactions. Dr. Carolyn Fairbanks will feature the broad therapeutic index of a series of agmatine based therapeutics that target the NR2B receptor subunit of the NMDA receptor to alleviate neuropathic pain. These three distinct and complementary strategies contribute to the urgent national call for identification of new non-opioid based targets for the treatment of chronic pain.

Friday Morning Panel Sessions

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • ALPINE SPRINGS

Modulation of Signaling and Plasticity Induced by Cannabinoids

Chair: Shane Hentges
Presenters: Alex Straiker, Sade Spencer, Henrietta Szutorisz, Olivier Manzoni

Cannabis is the most widely used illicit substance in the world and its use continues to increase due to both its rewarding properties and its medicinal potential. Yet, there is still much to be understood regarding signaling by endogenous and exogenous cannabinoids and acute and lasting changes at the synaptic and developmental levels with use. After a brief introduction by Shane Hentges (Colorado State University), panelists will describe recent work on cannabinoid actions in various settings and systems. Alex Straiker (Indiana University) will discuss how terpenes modulate endocannabinoid-mediated synaptic plasticity. Specific therapeutic qualities and interactions with THC have been attributed to specific terpenes. The lab's current results suggest some terpenes directly affect endocannabinoid-mediated synaptic plasticity. Sade Spencer (Kalivas lab, Medical University of South Carolina) will describe a novel model of THC and cannabidiol intravenous self-administration that she used to examine how contingent cannabis use and cue-induced cannabinoid seeking alters glutamatergic neurotransmission and synaptic plasticity in the nucleus accumbens core. Henrietta Szutorisz (Icahn School of Medicine at Mount Sinai) will discuss the long-term epigenetic contribution of prenatal and adolescent cannabis exposure to the development of neuropsychiatric phenotypes, with specific emphasis on multigenerational consequences. This research has demonstrated changes in striatal gene regulation with marked sex-specific effects. Olivier Manzoni (Aix-Marseille University, INSERM) will present studies revealing sex differences in cannabis effects throughout lifetime. Together, the work presented will address novel aspects of cannabis actions from synaptic to epigenetic with developmental consequences and sex differences discussed.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • CASTLE PEAK AUDITORIUM

Restoring Cellular and Circuit Function to Prevent Epilepsy and Its Co-Morbidities

Chair: John Huguenard
Presenters: Chris Dulla, Amy Brooks-Kayal, Mark Beenhakker, Anne Anderson

Remarkable progress has been made in understanding the cellular and circuit mechanisms that may contribute to the process of epilepsy development (epileptogenesis). One of the great challenges facing the epilepsy research field is how to harness this knowledge to modify the epileptogenic process and prevent or lessen the severity of seizures and cognitive impairments that characterize this disorder. In this panel, we will present recent progress toward this goal. Dr. John Huguenard will chair the session, providing introductory comments and leading the discussion of the presentations. Dr. Chris Dulla (Tufts University) will present work on how traumatic brain injury can predispose cortical circuits to generate abnormal epileptiform activity by compromising inhibitory function, and describe exciting recent results demonstrating that modulation of metabolic activity can have cell-type specific effects on neuronal activity and can prevent cortical network dysfunction following brain injury. Dr. Amy Brooks-Kayal (University of Colorado) will present work on how alterations in JAK/STAT signaling contribute to cognitive comorbidities in acquired epilepsies, and how modulation of JAK/STAT activity at the time of brain injury can improve long-term cognitive function. Dr. Mark Beenhakker (University of Virginia) will describe how environmental factors regulate thalamocortical circuits underlying generalized epilepsies, and how tuning such factors may provide new opportunities for seizure contro. Finally, Dr. Anne Anderson will describe epileptogenic changes in iGluR receptors (NMDA and AMPA) that persist in chronic epilepsy involving the temporal lobe.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • CATHEDRAL PEAK

BNST or B-Friendly: The Bed Nuclei of Stria Terminalis as an Integrative Control Center for Adaptive and Maladaptive Behaviors

Chairs: William Giardino, Lara Hwa
Presenters: Lara Hwa, Lindsay Halladay, William Giardino, Travis Goode

Our Panel focuses on the bed nuclei of stria terminalis (BNST), an extended amygdala structure that drives emotional and behavioral states associated with many psychiatric conditions, particularly anxiety and substance use disorders. The genetic heterogeneity and broad input-output connectivity of the BNST historically limited understanding of its multifaceted functions.

We assembled a panel representing expertise in cutting-edge physiological, genetic, and neurochemical approaches for dissecting the roles of precise BNST subpopulations and neurocircuits in rodent behavioral models. We will present exciting new unpublished data on specific BNST neuronal ensembles in stress adaptation, binge alcohol intake, fear, and social affiliation. Dr. Lara Hwa will describe how long-term intermittent alcohol drinking alters stress reactivity associated with changes in BNST neurons containing the kappa opioid receptor ligand dynorphin (DYN). Whole cell recordings and viral knockdown in BNST DYN neurons revealed physiological and behavioral representations of allostatic shifts in stress coping after alcohol. Neuropeptide signaling imbalance may underlie this complex relationship between alcohol and stress. Dr. Lindsay Halladay will discuss the BNST in the context of sex differences in alcohol-induced changes to social behavior. Dr. Halladay will present in vivo electrophysiological data showing that a subset of socially responsive BNST neurons are sex-specifically modulated by alcohol administration. Dr. William Giardino will present data illustrating how genetically-defined BNST neurons driving stress and reward display unique functional interactions with hypocretin/orexin lateral hypothalamus neurons. Dr. Travis Goode will examine BNST regulation of fear and defensive behaviors in the presence of ambiguous threat signals. Data suggest that the BNST and its circuits are particularly attuned to temporally uncertain threats, which may be a factor in its contributions to anxiety.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • OVERLOOK

History Matters: How Drug Type and Use Pattern Influences Addiction Vulnerability and Treatment

Chair: Mary Torregrossa
Presenters: Jacqueline Barker, Mary Torregrossa, Jamie Peters, Timothy O'Neal

Drug addiction is a serious burden on our society, with rates of opioid use disorder rising at an alarming rate and continued abuse of other substances. Current treatment strategies include behavioral and pharmacological approaches, but relapse rates remain high. Given that people abuse a variety of drugs in diverse combinations and patterns, treatments may need to be tailored to each individual based on their own history. Indeed, in a series of studies using animal models, this panel will present data providing evidence that the circuits and signaling systems controlling drug seeking behaviors are altered by addiction severity, pattern of drug exposure, and type of drug used. Jacqueline Barker will present evidence that the establishment of alcohol dependence alters the development of habitual behaviors by disrupting glutamatergic signaling and subsequently the ability of metabotropic glutamate receptor modulators to alter addiction-related behaviors. Next, Mary Torregrossa will present data showing that the pattern of cocaine self-administration can alter

the effectiveness of extinction learning-based therapies for addiction treatment. Further, she will show that the shift to extinction-resistant cocaine seeking likely involves altered plasticity in amygdala circuits. Jamie Peters will then discuss data showing that the circuits driving cocaine versus heroin relapse after extinction are not completely overlapping in the infralimbic prefrontal cortex. Finally, Tim O'Neal will present data showing that direct and indirect pathway neurons in the nucleus accumbens can differentially regulate cue-induced relapse to heroin seeking based on addiction severity. Taken together, these data demonstrate that the efficacy of both pharmacological and behavioral treatments for addiction may depend on the severity of the disorder and type of drug used, potentially requiring the targeting of specific molecules and circuits.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • SALON B

A New Age of Monoamine Detection Following Synaptic Stimulation

Chair: John Williams

Presenters: Tommaso Patriarchi, Aya Matsui, Armando Salinas, Haining Zhong

Detection of neurotransmitter release has been studied for decades using a number of techniques including; dialysis, voltammetry and electrophysiology. Each method has strengths and weaknesses. The goal however is to gain high spatial and temporal resolution in combination with a functional postsynaptic outcome following the release of transmitter. The recent development of genetically targeted fluorescent sensors that are expressed on the plasma membrane or in specific cellular compartments is a giant leap forward. These optical-based molecules offer spatial and temporal resolution that has not been possible previously. Tommaso Patriachi will present work using a dopamine sensor and more recent developments in the detection of monoamine transmitters. Aya Matsui will speak about a 5-HT sensor that is expressed in the ventral pallidum. Armando Salinas will present work with an acetylcholine sensor expressed in the striatum. Haining Zhong will present work describing the downstream activation of monoamine receptors that activate Protein Kinase A.

The Use of In Vivo Imaging Techniques to Link Neural Function and Behavior

Chairs: Samuel Centanni, Alexander Smith
Presenters: Erin Calipari, Samuel Centanni, Alexander Smith, Jenna McHenry

Real-time examination of neural circuit dynamics in behaving animals has long been a challenge in neuroscience. Overcoming this hurdle and linking the contributions of specific neural circuits to behavior will promote the development of novel, more effective diagnostic and therapeutic tools for neurological disorders. Recent advances in tools to study neuronal Ca2+ transients in awake, behaving animals, now allow researchers to begin bridging this gap in knowledge at an unprecedented rate. This panel will present exciting new data using innovative imaging approaches to monitor neural activity in precise circuitry and determine encoding that underlies reward processing, motivation, and addiction. First, Erin Calipari (Vanderbilt) will speak about the temporally specific neuronal signals originating from ventral striatal D1 and D2 medium spiny neurons and define their role in valence-based decision-making using fiber photometry. Next, Sam Centanni (Vanderbilt), will discuss data using fiber photometry to measure BNST neural activity in negative affective behaviors associated with stress and alcohol withdrawal, and regulation of BNST activity by glutamatergic projections from the insular cortex. Alex Smith (Mount Sinai) will present work using single-photon miniscopes to examine the role of the anterior dorsolateral striatum in instrumental conditioning, and differential roles of D1- and D2-MSNs to goal-directed and habitual behaviors. Lastly, Jenna McHenry (Duke University) will present data utilizing 2-photon deep-brain imaging in a hypothalamic-midbrain circuit to uncover how social networks are intertwined with positive valence systems to direct motivational states. Together, this session will highlight the various ways that advances in in vivo calcium imaging techniques have expanded our ability to assess the complex neural circuitry regulating intricate behaviors and how this information can be applied to enhance our understanding and treatment of disease states.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • SALON D

It's All Down Hill From Here, or is it? How Life Experiences can Alter the Hormonal Trajectory for Risk and Resilience

Chair: Gretchen Neigh

Presenters: Gretchen Neigh, Deena Walker, Liisa Galea, C. Neill Epperson

Hormones can exert profound influences on neural function and behavior. An individual's response to hormone exposure is multifaceted and is influenced by magnitude and duration of exposure, receptor expression and distribution, and epigenetic modification of target genes transcribed by hormone receptor engagement. Although both males and females are influenced by hormone exposure, the dramatic fluctuations in sex steroid exposure within females have greater potential to create a dynamic range of hormone-induced behavioral outcomes. This panel will examine the mechanisms by which earlier life exposures can alter hormone responses and explore clinical implications for risk and resilience created by early life experiences on behavioral consequences of hormonal changes during the aging process. Dr. Gretchen Neigh of Virginia Commonwealth University will lead off the session with a presentation examining the influence of adolescent experience on cognitive behavior and transcription factor engagement with a focus on estrogen receptors. Dr. Deena Walker of the Icahn School of Medicine at Mt. Sinai will demonstrate that adolescent social isolation alters sex-specific behavior through reprograming the transcriptome of the medial amygdala. Dr. Liisa Galea of the University of British Columbia will provide insight to the mechanisms by which reproductive experience interacts with hormones to influence neuroplasticity and behavior in middle age. Dr. C. Neill Epperson of the University of Colorado will extend the preclinical work discussed early in the session to the realm of clinical and translational research with demonstration of the influence of earlier life experiences on the affective and cognitive responses to the hormonal transitions of aging. Collectively, these talks will demonstrate the levels at which experience influences neural plasticity and how these earlier life modifications shape the neural and behavioral response to the hormonal changes that accompany aging.

PANEL • FRIDAY, 7:30 A.M. – 9:30 A.M. • SALON E

Mechanisms of Chronic Pain in Primary Afferents and the Spinal Cord

Chair: Juan Carlos Marvizon
Presenters: Annemieke Kavelaars, Juan Carlos Marvizon, James Zadina, George Wilcox

Juan Carlos Marvizon (Chair, UCLA/VA) will introduce the panel with a short overview on the current state of research on the mechanisms of chronic pain. Annemieke Kavelaars (University of Texas) will discuss the key role of immune system to nervous system communication in preventing the transition from acute to chronic pain. Her findings demonstrate that T lymphocytes and interleukin 10 signaling to nociceptors are required for the resolution of acute pain. In the absence of T cells or interleukin-10, the pain response is prolonged. Juan Carlos Marvizon (UCLA/VA) will explain the latent sensitization model of chronic pain and show that during in it stress switches from inducing analgesia to inducing hyperalgesia. Using of DREADD to activate and inhibit neurons in the central amygdala expressing corticotropin-releasing factor, he will show that these neurons mediate the hyperalgesic effect of stress during chronic pain. James Zadina (VA/Tulane University) will discuss the mechanisms that mediate the effects of ZH853 in multiple models of acute and chronic pain. ZH853 is an endomorphin analog with antinociceptive effects equal to or greater than morphine but with reduction or absence of adverse properties. It does not activate glia or exacerbate chronic pain like morphine does. It also reduces latent sensitization in inflammatory pain. George Wilcox (University of Minnesota) will show that inhibitors of the HINT1 protein, which directly couples mu-opioid to NMDA receptors, inhibits the development of spinal morphine tolerance and the development of neuropathic pain after nerve injury. Using receptor knockout strategies, he will show the involvement of mu-opioid-NMDA receptor coupling in the development of hyperalgesia.

Friday Afternoon Panel Sessions

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • ALPINE SPRINGS

Behavioral and Computational Properties of the Anterior Cingulate Cortex

Chairs: Alicia Izquierdo, Alireza Soltani
Presenters: Alicia Izquierdo, Aaron Gruber, Ilya Monosov, Sarah Heilbronner

The anterior cingulate cortex (ACC) has been assigned a diversity of roles ranging from learning and responding to rewards and punishments, signaling value and uncertainty, and supporting decisions involving effort costs, to

name a few. In this panel we discuss the mechanisms that support these varied processes and possibilities for unifying theoretical frameworks. Our collective recent research suggests that ACC may be important in multiplexing various dimensions of the environment: the availability of options, the probability of reward, tracking of recent choice history, and the valence of outcomes, as examples. This information is vital for adaptive behavior, and ACC is anatomically well-positioned to integrate reward, cognitive, and action plans in both rodents and primates. We will present evidence in rats and monkeys gathered using a combination of behavior, neural recording and imaging, circuit-level manipulations, anatomical tract-tracing, and theoretical-computational approaches. First, Alicia Izquierdo will present data on two anterior-posterior ACC targets (Cg1) in rat: the anterior involved in estimating uncertainty and the posterior in the selection between two different-valued options, as revealed via calcium imaging and DREADDs. Next, Aaron Gruber will show evidence for prospection in rat ACC, and will discuss the theoretical and computational basis for how ACC units encode abstract representations optimized for rapid learning that help drive shifts in behavioral responses. Ilya Monosov will then show data that link uncertainty-selective neurons in monkey ACC with the motivation to reduce uncertainty by seeking advance information about upcoming salient events. And lastly, Sarah Heilbronner will present tract-tracing studies in both rat and monkey ACC, suggesting that there may be homology in the anterior-posterior domain, resulting in potentially interesting functional translations.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • CASTLE PEAK AUDITORIUM

Astrocyte Regulation of Reward Circuit Function and Behavior

Chair: Carlos Paladini
Presenters: Aric Madayag, Xinzhu Yu, Wendy Xin, Carlos Paladini

Astrocytes are ubiquitous and abundant neural cells in the brain. Astrocyte dysfunction is a significant factor in behaviors related to the reward circuit. This panel will discuss how astrocytes impact reward circuit function, leading to potential deficits in motoric and drug-evoked behavior. Aric Madayag will discuss the generation and characterization of an astrocyte-selective gas knockout. Though astrocyte Ca2+ signaling garners the bulk of the attention of investigators, astrocytes also respond to extracellular signals that activate GsGPCR signaling. Dr. Madayag will present data showing baseline behavioral phenotyping as well as psychostimulant-evoked behavior in these mice. Xinzhu Yu will present a novel genetic approach developed at the Khakh laboratory to silence astrocyte calcium signaling in a brain-area-specific manner in adult mouse brain. Attenuating astrocyte calcium signaling in the adult mouse striatum in vivo causes an excessive self-grooming phenotype by

altering medium spiny neuron activity. The mechanisms involve astrocyte-mediated neuromodulation facilitated by ambient GABA and was corrected by blocking astrocyte GABA transporter 3. Wendy Xin will present recent work characterizing the functional and molecular properties of ventral midbrain astrocytes, differing from telencephalic astrocytes both in gene expression profile and physiological properties. Ventral midbrain astrocytes have very low inward-rectifying potassium channel-mediated current, are extensively coupled to surrounding oligodendrocytes, and can be dynamically modulated by dopamine D2 receptor signaling. Carlos Paladini will present how VTA astrocytes tune glutamatergic signaling selectively on local inhibitory GABA neurons via the GLT-1 glutamate transporter, ultimately leading to inhibitory tone on dopamine neurons. The increased inhibition of dopamine neurons elicits real-time and learned avoidance behavior sufficient to impede expression of learned preference for reward.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • CATHEDRAL PEAK

Fetal Origins of Adult Disease (FOAD)-Relevance in Psychiatry

Chair: Amanda Law

Presenters: Daniel Weinberger, Amanda Law, C. Neill Epperson, Thomas Hyde

Adverse intrauterine experience is a predictor of lifetime disease susceptibility and evidence supports the contribution of genetics and environment on prenatal brain development to later neuropsychiatric risk. Evidence supporting the FOAD hypothesis is documented for several adult conditions including, type 2 diabetes and cancer and emerging data supports the hypothesis for brain disorders. This panel will present innovative strategies focused on study of the intrauterine environment, fetal brain development and risk for later mental illness; combining GWAS with biological studies of- postmortem human brain, placentae and mouse models of novel in-utero manipulation strategies. Dr. Weinberger will show that genes mapping to schizophrenia GWAS loci interact with obstetrical complications to multiplicatively increase risk and that these genes are differentially expressed in placentae from complicated-vs. normal pregnancies. Dr. Law will present novel evidence that maternal gestational choline supplementation impacts maturation of cortical E/I balance in offspring mediated via the NKCC1/KCC2 switch and improves adult behaviors relevant to schizophrenia. Dr. Epperson will describe findings from a trans-species model (mouse-human) demonstrating impact of maternal early life stress on maternal-fetal-pup/infant HPA-A development and response to acute stress. Finally, Dr. Hyde will present data from the Lieber Institute's human brain repository- dedicated to neuropsychiatric and neurodevelopmental research and consisting of over 1800 cases from the second trimester of fetal development through aging. Examples of the insights gleaned from molecular

study of genes relevant to human brain development and psychiatric illness will be presented. A focus on early brain development and the impact of genetic and prenatal environmental influences is necessary to shed light on mechanisms of later psychiatric risk and aid in the identification of prevention/intervention strategies.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • OVERLOOK

Ketamine, Psilocybin and Psychedelics in Psychiatry: Data, Mechanisms and Trends

Chair: David Pickar
Presenters: Gerard Sanacora, Carla Canuso, David Erritzoe, Alan Schatzberg

David Pickar will chair this panel regarding the use of ketamine, psilocybin and psychedelics in psychiatry. The panel will address clinical, preclinical and policy aspects of this, one of the most intriguing developments in psychiatry in recent years. Gerard Sanacora will present extensive clinical experimental data in the use of ketamine to treat depression and put it in context with the expanding use of psychedelics in psychiatry. Carla Canuso will present data from Janssen Pharmaceutical's unique and extensive Phase III investigations into the use of intranasal esketamine for treatment of depression and suicide ideation. David Erritzoe will present experimental data regarding the experimental use of psilocybin and other psychedelic drugs in psychiatric patients currently underway in the UK and Europe. Alan Schatzburg will present recent data related to opiate antagonist effects during ketamine administration, raising the issue of which opiate receptors may be involved in ketamine response. David Pickar who will chair the session will comment on the earlier use of these compounds in studies of schizophrenia and bring current regulatory perspectives into focus. The Panel will include an opportunity for discussion among participants in a panel format and welcome audience participation in this innovative area of clinical and preclinical research.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • SALON B

Advances in Understanding Dopamine Dynamics and Contribution to Decision-Making

Chair: Arif Hamid
Presenters: Geoffrey Schoenbaum, Claire Stelly, Ali Mohebi, Arif Hamid

Dopamine is a key regulator of learning and motivation, but mechanistic and computational details of how dopamine promotes flexible behaviors continue to be refined. The prevailing dopamine theory emphasizes its role in learning about reward availability. This view relies on brain-wide, scalar prediction error signals (RPEs) that are broadcast to projection targets for incremental

updating of stored (cached) appetitive values. This panel will present a set of compelling studies that critically examine the nature of learning supported by dopamine and how regionally and temporally coordinated signals contribute to decision-making.
First, Geoff Schoenbaum (National Institute on Drug Abuse) will present data that indicate dopamine neurons can support learning that is beyond (and orthogonal) to what can be explained using classic cached-value or model-free mechanisms. Next, Claire Stelly (University of Texas at San Antonio) will speak on the role of dopamine in negative reinforcement, demonstrating that ventromedial striatal dopamine reflects the negative valence of shock-predictive cue, which is strikingly distinct from ventrolateral striatal responses. Ali Mohebi (University of California, San Francisco) will discuss his work using complimentary methods to compare midbrain dopamine cell firing and release in the striatum, emphasizing that motivation-related dopamine dynamics in ventral striatum do not arise from VTA dopamine cell firing. Finally, Arif Hamid (Brown University) will report a novel set of spatio-temporal trajectories of DA axon activity across the dorsal striatum that are organized into directional waves synchronized by reward. Together this session will showcase the application of novel technical and conceptual methods to address how dopamine promotes goal-directed behaviors.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • SALON C

Excite Me or Excite Me Not: Homeostatic Plasticity in Health and Disease

Chair: Hey-Kyoung Lee
Presenters: Patrick Kanold, Hey-Kyoung Lee, Elizabeth Quinlan, Hee Jung Chung

Homeostasis of neuronal activity is crucial for information processing and storage in the brain. Prolonged changes in activity, as would occur during development, alterations in sensory environment, or in disease state triggers homeostatic adaptation mechanisms. Multiple plasticity mechanisms acting on excitation and inhibition at different levels need to be coordinated to achieve proper functional compensation. In this panel, we will discuss a few of such mechanisms of homeostatic plasticity ranging from regulation of synaptic receptors, immediate early gene, extracellular matrix, and axon initial segment. Dr. Patrick Kanold (Univ. Maryland) will discuss how sensory activity shapes the development of glutamatergic synapses on interneurons and the role of NMDA receptors in the development of AMPAergic connections. Dr. Hey-Kyoung Lee (Johns Hopkins Univ.) will discuss how an abrupt increase in visual experience following a period of visual deprivation leads to specific reduction in the strength of intracortical synapses in visual cortex, which is mediated by mGluR5 and Homer1a signaling. Dr. Elizabeth Quinlan (Univ. Maryland) will present data demonstrating homeostatic regulation of matrix

metalloproteinase-9 (MMP-9) by dark exposure, which enables subthreshold visual stimulation to produce robust perisynaptic proteolysis and reactivation of structural and functional plasticity in visual cortex. This will be discussed in the context of how dark exposure reactivates adult cortical plasticity. Dr. Hee Jung Chung (Univ. Illinois) will talk about how homeostatic control of intrinsic excitability occurs by dynamic changes in axonal initial segment and voltage-gated ion channels within these axonal hillocks. In addition, she will talk about possible link between intrinsic excitability homeostasis and seizure propensity.

PANEL • FRIDAY, 4:30 P.M. – 6:30 P.M. • SALON D

The Role of Catecholamines in Mild Traumatic Brain Injury

Chair: David Devilbiss

Presenters: David Devilbiss, C. Edward Dixon, Floyd Thompson, Ramesh Raghupathi

Mild traumatic brain injury (mTBI) affects approximately 1.7-3.8 million Americans each year. MTBI is a complex pathophysiological process resulting in a number of cognitive problems including deficits in arousal, attention, working memory, decision-making, and other executive functions. In addition, mTBI is associated with affective changes and altered sensory processing leading to allodynia. These symptoms generally resolve within the first three months but can last for six months or more. Repeated injuries may have cumulative effects, increasing the susceptibility for further mTBI and progressing to long-term functional deficits. Catecholamine systems including norepinephrine and dopamine are critical regulators of these executive, affective, and sensory processes and are now becoming the focus of the pathogenesis of the cognitive and neuropsychiatric symptoms following and mTBI. David Devilbiss will present a review of current evidence implicating the catecholamine systems in the sequalae of mTBI. Edward Dixon will present current therapeutic strategies for mTBI that target these catecholamine systems and discuss the challenges of translating catecholamine-based therapies to clinical practice. Floyd Thompson will present recent data demonstrating changes in monoamine system function related to anxiety, and sensory/motor disability in a rodent model of closed head mTBI. Ramesh Raghupathi will present emerging evidence revealing a central role for the dopamine and hypocretin systems underlying the acute cognitive deficits in a rodent closed head mTBI model.

Translational Studies on the Impacts of Developmental Nicotine Exposure on Adolescent and Adult Learning, Memory and Addiction

Chair: Shahrdad Lotfipour
Presenters: Kay Linker, Shahrdad Lotfipour, Thomas Gould, Alexey Ostroumov

Adolescence is a critical time in development vulnerable to the harmful effects of nicotine and tobacco products. Nicotine is gaining popularity among teenagers via the use of electronic cigarettes. While tobacco smoking has reduced during adolescence, an exponential increase in e-cigarette use has been observed in high school students. The current panel evaluates the consequences of adolescent nicotine exposure through the use of translational animal models. First, Kay Linker from the Frances Leslie laboratory, will highlight her studies evaluating the impact of adolescent nicotine exposure on subsequence cocaine use. She will provide mechanistic evidence for the role of microglia in adolescent, but not adult, nicotine-induced enhancement of subsequent cocaine use. Dr. Shahrdad Lotfipour, will present translational evidence from human and animal studies on the impacts of maternal and adolescent nicotine/tobacco exposure on subsequent substance use, with insights in using the models for assessing the developmental effects of nicotine exposure on adolescent learning, memory and substance use. Dr. Thomas Gould will expand on these studies to highlight the use of animal models to assess the impacts of developmental nicotine exposure on cognitive processes after acute, chronic and withdrawal states. And, finally, Alexey Ostroumov from the John Dani laboratory will provide further mechanistic understanding for the pathways and circuitry influencing the nicotine gateway effects, including a focus on the ventral tegmental area GABAergic circuitry. Overall, the studies aim to provide translational evidence for the harmful effects of developmental exposure to nicotine on brain and behavior of adolescents and adults. The studies add to a growing body of literature highlighting an important need for policy and regulatory agencies to assist in developing and implementing prevention and intervention strategies for the reduction of adolescent nicotine/tobacco exposure.

SATURDAY, FEBRUARY 2, 2019

Saturday Morning Panel Sessions

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • ALPINE SPRINGS

Guidance of Reward Seeking Through Dynamic Neural Circuits

Chairs: James Otis, Vijay Mohan K Namboodiri
Presenters: Lauren Dobbs, Vijay Mohan K Namboodiri, James Otis, Meaghan Creed

Reward-seeking behaviors are governed by internal factors such as hunger, thirst, and attention, as well as external factors such as sensory stimuli and presence of reward/punishment. Despite this, how neural circuits control reward seeking in the face of these ever-evolving variables is unclear. In this panel, we discuss experiments that reveal how cortical and subcortical circuits can dynamically guide reward seeking. Lauren Dobbs will start by discussing in vivo calcium imaging data from freely-moving mice, revealing distinct cortical circuit elements that dynamically adjust their activity to reflect current task requirements in a changing environment. Next, Vijay Namboodiri will discuss in vivo calcium imaging and optogenetics data, wherein he shows how distinct cortical ensembles, such as those that project directly to the ventral tegmental area, encode and update their dynamics to guide cue-induced reward seeking. Similarly, James Otis will discuss data wherein he combines calcium imaging and optogenetics in vivo, to show how cortical and subcortical inputs to thalamo-striatal neurons allows multiplexed information processing for reward seeking. Finally, Meaghan Creed will discuss in vivo electrophysiology and optogenetics data, revealing a subcortical striato-pallidal circuit that may allow hedonic information to direct seeking and consumption of natural rewards or opiate drugs. Together, these studies begin to reveal how neural circuits can orchestrate reward-seeking behaviors based on multifaceted, dynamic variables.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • CASTLE PEAK AUDITORIUM

Collusion Between Dopamine and Its Collaborators in Motivated Behavior

Chair: Kate Wassum
Presenters: Margaret Rice, Kate Wassum, Benjamin Saunders, Jennifer Wenzel

Dopamine transmission is vital for motivated behavior and disruptions in such signaling are thought to contribute to a variety of mental illnesses and diseases of behavioral control, as well as to neurological conditions such as Parkinson's disease. Much focus has been given to the activity of midbrain dopamine neurons and the resultant release of dopamine into the striatum

during motivated behavior. Emerging evidence suggests that modulatory mechanisms within striatal terminals can regulate the 'decoding' of dopamine cell activity into chemical messages and, thus, regulate adaptive and maladaptive motivation. Margaret Rice will discuss how insulin and leptin, two vital homeostatic regulators of hunger and satiety, influence motivation by regulating dopamine release in the nucleus accumbens. Kate Wassum will discuss how accumbens acetylcholine regulates dopamine release to gate the ability of reward-predictive cues to motivate behavior. With modern circuit dissection tools, new research is emerging on the diversity of dopamine function. Benjamin Saunders will describe studies revealing elemental behaviors produced by distinct dopamine neuron projections during Pavlovian cue conditioning and will outline how phasic dopamine neuron signaling into striatal subregions can create and shape cue-triggered motivational states to orchestrate reward seeking. While accumbens dopamine has long been implicated in appetitive approach behaviors, new work suggests it may also contribute to avoidance. Jennifer Wenzel will discuss this work demonstrating dopaminergic regulation of avoidance via promoting active defense strategies. Together these talks will demonstrate new functions of dopamine and reveal how these might be achieved via interactions with its striatal collaborators.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • CATHEDRAL PEAK

Skiing With Friends and Avoiding Collisions With Others: Organization of Intracellular Signaling

Chair: Kim Neve

Presenters: Eric Janezic, Michel Bouvier, Roshanak Irannejad, Angela Wild

Receptors and ion channels modulate intracellular signaling pathways that are composed of numerous interactions among diverse proteins and other signaling molecules. Precise temporal and spatial control of these probabilistic interactions is achieved by stable or transient formation of protein complexes, subcellular compartmentalization to promote certain interactions and prevent others, and the movement of signaling molecules among cellular compartments. In this panel we present a variety of approaches to assess mechanisms and consequences of signaling at the cell membrane and in endosomes, the Golgi apparatus, and the nucleus. Eric Janezic will describe organization of signaling at the membrane by G protein-coupled receptor PDZ ligands. Michel Bouvier will present results of his studies of the formation and dissociation of signaling complexes at the plasma membrane and in endosomes and their implications for downstream cellular activities. Roshanak Irannejad will show that selective drug access to receptors located in distinct intracellular compartments can produce signaling bias. Finally, Angela Wild will discuss how calcium channel

signals generated at distal synapses are rapidly relayed to somatic signaling complexes to activate nuclear transcription factors. Kim Neve will provide introductory comments.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • OVERLOOK

The Inhibitory 'Edge' - GABAergic Circuit Control in Fear, Anxiety and Reward

Chair: Molly Huntsman
Presenters: Katharine Smith, Ethan Guthman, Melissa Herman, Molly Huntsman

GABAergic neurotransmission in the amygdala regulates microcircuitry associated with fear, anxiety and reward mechanisms. The goal of this panel will be to highlight the mechanisms that control and adapt to changing environments such as sensory input and stress; in addition to alterations in circuit development in rodent models of ethanol exposure and autism. The primary theme will be to illustrate how inhibitory circuits control these processes. Katherine Smith will illustrate how inhibitory circuits adapt to plasticity. This will be achieved by using the super-resolution imaging technique, 3D Structured Illumination Microscopy (SIM), to simultaneously image GABAARs and their primary scaffolding protein, gephyrin, together with presynaptic markers (either VGAT for labeling the entire inhibitory bouton, or Rim for labeling vesicle release sites). Ethan Guthman will present evidence of cell-type specific control of plasticity in basolateral amygdala feedforward circuits. This talk will reveal that dendritic targeting somatostatin interneurons are gating long term potentiation in the basolateral amygdala. Melissa Herman will show changes in inhibitory control of CRF1 in amygdala neurons with acute and chronic ethanol exposure. Molly Huntsman will illustrate how depleted inhibition in the basolateral amygdala in the Fragile X Syndrome (FXS) mouse model of autism alters the critical period of synaptic plasticity. This talk will reveal that altered inhibitory circuit development in FXS shifts the critical period for long term potentiation in the basolateral amygdala.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • SALON C

Seizures, Cannabidiol and the Developing Brain

Chairs: Claude Wasterlain, David Naylor
Presenters: Angus Wilfong, Anne Anderson, Claude Wasterlain, David Naylor

The interaction between seizures, the drugs used to treat them, and brain development remains an area of rapid progress and high controversy. Many new syndromes have been described, and the recent FDA approval of cannabidiol opens a new chapter, but our understanding of therapeutic mechanisms and developmental effects is limited. This session will also discuss work on the

effect of uncontrolled seizures on brain development, the dangers of the standard GABAergic drugs used to treat seizures for the immature brain, and how these drugs may have paradoxical effects through extrasynaptic receptors. Angus Wilfong, who has years of clinical experience in the use of cannabidiol-based therapies for seizures, will review the biological actions of cannabidiol and the clinical evidence for its use. Anne Anderson will discuss the role of uncontrolled seizures in the phenotypic expression of genetic syndromes. She studied the impact of early life seizures on excitability, EEG power, and cognition in a rat model of Angelman Syndrome. Claude Wasterlain will review the role of GABA-induced depolarization in the immature brain. The fact that GABAAR agonists may increase seizure activity and neuronal injury has been extensively discussed but never proven. Now a new rat pup model now provides evidence that phenobarbital (recommended by the ILAE) and midazolam can increase neuronal injury. David Naylor will discuss how data-optimized computational models suggest that seizure-induced 'spillover' of GABA to extrasynaptic receptors aggravates depolarizing GABA effects, and supports synchronization, seizure activity and excitotoxicity. Drugs such as barbiturates that act on extrasynaptic receptors may exacerbate this. This session is designed to be interactive, with brief presentations and an extensive discussion period. Registered audience participants will be allowed three minutes and a single slide during the discussion.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • SALON D

Auditory Pathway: From Circuits to Behavior

Chairs: Alfonso Junior Apicella, Li Zhang
Presenters: Shaowen Bao, Maria Geffen, Daniel Llano, Matthew McGinley

The panel will focus on discussing the latest progress in elucidating specific functional contribution of the corticocortical and corticofugal auditory pathways. It very well established how auditory information is processed along the canonical ascending and descending pathway. However, in the recent years, the detailed dissection of specific auditory pathway has opened an opportunity to examine how information can be processed and transformed beyond the canonical auditory neuroaxis. First, Dr. Bao (Univ. Arizona) will present evidence for the role of cortical PV+ interneuron in auditory processing and perception. Second, Dr. Geffen (Univ. Pennsylvania) will discuss how gain adaptation plays a key role in auditory target detection behavior by providing a mechanistic framework outlining the circuit components involved in gain control. Third, Dr. Llano (Univ. of Illinois) will talk about non-linear transmission of signals from the inferior colliculus to the auditory cortex in a colliculo-thalamocortical slice. Fourth, Dr. McGinley from Baylor will discuss how the changes in the external environment alter the motivational value of sound stimuli. Led by two organizers (Dr. Apicella from UTSA and Dr. Zhang

from USC), the panel will further discuss recent studies on functional roles of corticostriatal inhibitory projections and their role in associative learning behavior and the neural circuits responsible for transforming sensory signals to aversive emotion and behavioral avoidance. Together, these presentations will provide a diversified view on current research approaches to understanding the functional contributions of neuronal circuits in auditory processing.

PANEL • SATURDAY, 7:30 A.M. – 9:30 A.M. • SALON E

Glutamate Transporter -1 (GLT-1) Regulation in Health and Disease

Chair: Lori Knackstedt

Presenters: Lori Knackstedt, Kathryn Reissner, Michelle Olsen, Paul Rosenberg

Glutamate transport maintains glutamate levels within a homeostatic range to retain the integrity of glutamate signaling and prevent excitotoxicity. GLT-1 is the major glutamate transporter in the brain and is expressed in both astrocytes and axon terminals. The talks comprising this panel will focus on the molecular and physiological regulation of GLT-1 in both the healthy brain and in disease states such as drug addiction. Dr. Lori Knackstedt will present novel data on cocaine-induced GLT-1 trafficking in the nucleus accumbens, with a focus on the ubiquitin-proteasome pathway. Dr. Kathryn Reissner will present evidence that length of cocaine exposure and withdrawal both influence the transcriptional suppression of the GLT-1 gene, Slc1a2. She will also present data indicating that Slc1a2 is methylated following prolonged abstinence from cocaine, and that methylation inhibitors block the incubation of cocaine craving. Dr. Michelle Olsen will present data on GLT-1 interactions with Kir4.1, a glial-specific inwardly rectifying potassium channel that maintains the hyperpolarized resting membrane potential critical for efficient glutamate uptake. Genetic mutations in KCNJ10, the gene which encodes Kir4.1, are causative for a neurodevelopmental disorder which presents with seizures, ataxia and developmental disability. Dr. Olsen's data indicates that DNA methylation is a bidirectional modulator of astrocytic gene transcription and represents a candidate molecular mechanism to restore astroglial Kir4.1 expression following CNS insult. Dr. Paul Rosenberg will present data that investigates the putative function of neuronal GLT-1. He will present data from a variety of approaches applied to conditional GLT-1 knock-out mice, including gene expression, metabolic assessments and electrophysiology, that reveal disrupted synaptic physiology in the absence of neuronal GLT-1. Taken together, these talks will highlight the importance of GLT-1 in maintaining glutamate signaling.

PANEL • SATURDAY, 4:30 P.M. – 6:30 P.M. • ALPINE SPRINGS

The Intestinal Microbiota: Our Best Frenemy in Neurological Disorder and Disease

Chair: Kyle Frantz
Presenters: Kyle Frantz, Claire de La Serre, Laura Cox, Benoit Chassaing

We often refer informally to a "gut feeling" as a motivator or brake on behavior. We now understand that this term likely reflects literal connections between the gut and brain, with a central role played by the complex community of micro-organisms living in our intestine and referred to as the microbiota. Immunological, neural, and hormonal signals from the gut appear to affect many aspects of brain and behavior. Speakers on this panel will present recent findings demonstrating the role played by the microbiota in addiction, obesity, neurodegenerative disease, and neuropsychiatric disorder. First, Kyle Frantz will give a brief background on the gut-brain axis, followed by exploration of the effects of intestinal microbiota on cocaine-related behavior in rats, including possible interactions with gut inflammation. Next, Claire de la Serre will consider mechanisms that disrupt regulation of food intake and trigger overeating in rodents, with focus on diet-driven abnormalities in gut-brain signaling that are mediated by the microbiota. Laura Cox will mix basic and clinical research approaches to explore the hypothesis that emergence of neurologic diseases is linked to age-specific changes in the gut microbiome, with examples from autism (early-life), multiple sclerosis (mid-life), and Alzheimer's disease (late-life). Finally, Benoit Chassaing will present some recent findings regarding mechanisms by which some modern stressors of the intestinal microbiota are altering stress-related behavior, and how probiotics can be used to alleviate such altered gut-brain interactions. Overall, this panel will provide insights into the bidirectional interactions between the intestinal microbiota and neural system function in the regulation of behavior and onset of disease.

PANEL • SATURDAY, 4:30 P.M. – 6:30 P.M. • CATHEDRAL PEAK

Circuit and Synaptic Mechanisms of Compulsive Drug Seeking

Chairs: Christina Gremel, Rafael Renteria
Presenters: Carl Lupica, Frederic Hopf, Rafael Renteria, Lauren Dobbs

Drug use and abuse often descends into compulsive control over behavior. System and synaptic level investigations can provide mechanistic information on how drug use and dependence results in compulsive and habitual control. This panel brings together men and women participants, across career

stages from post-doctoral trainee to Senior Investigator, and from diverse backgrounds, to discuss unpublished findings on how system, circuit, and synaptic changes across the brain may contribute to compulsive drug-seeking behaviors. Carl Lupica will begin the session by presenting work on the contribution of lateral habenula and the cholinergic system to compulsive drug-seeking. He will present data examining the contribution of mACh receptors in the laberal habenula to cocaine-seeking as well as broader recruitment of cholinergic neural circuits during impulsive drug-seeking. Next, Frederic Hopf will explore work examining which aspects of compulsive drive are mediated by the noradrenergic system. He will present lickometry and systems data that examines insula and noradrenergic contributions to compulsive alcohol drinking. Rafael Renteria will describe his work investigating mechanisms underlying alcohol-dependence induced projection and cell-type specific changes observed in corticostriatal circuits that contribute to compulsive and habitual control. Lastly, Lauren Dobbs will present data on possible mechanisms underlying vulnerability to drug abuse in individuals with low striatal D2 receptors. Their findings suggest low striatal D2 receptors trigger a hypersensitivity of D1 receptors thereby altering response and vulnerability to drugs of abuse. Together, the largely unpublished data from these speakers will help to build a picture of brain changes that support compulsive behaviors in addiction.

PANEL • SATURDAY, 4:30 P.M. – 6:30 P.M. • OVERLOOK

Less is More: The Intermittent Access Model as an Alternative to Long/Continuous Access Models for Promoting Addiction-Like Behavior in Laboratory Animals?

Chair: Morgan James
Presenters: Florence Allain, Susan Ferguson, Alex Kawa, Morgan James

This panel captures the recent surge in the use of the intermittent access paradigm (first described by Roberts et al in 2012) as an alternative to the widely used long-access model for inducing an addiction-like phenotype in lab animals. Panelists will compare the behavioral phenotypes induced by intermittent vs. long/continuous access, as well as describe recent studies using the intermittent access model to unravel new brain circuits that underlie pathological drug seeking. Florence Allain (UdeM) will present evidence that when cocaine self-administration is intermittent, the amount of cocaine intake, escalation of intake or session length does not predict the development of increased incentive motivation for cocaine – a finding that directly contrasts with the long access model. Susan Ferguson (UW) will further discuss the relationship between escalation of intake on the intermittent access paradigm and addiction vulnerability, and will present evidence that different

patterns of cocaine self-administration produce distinct changes in baseline calcium signaling in the striatum. Both Alex Kawa (OHSU) and Morgan James (Rutgers) will describe studies using behavioral economics and other phenotyping procedures to show that the intermittent access model induces a stronger and more persistent addiction-like phenotype compared to the long access model. Dr. Kawa will also present data showing that the addiction-like behaviors that follow intermittent access experience are driven by sensitized dopamine release in the ventral striatum in response to cocaine. Dr. James will also present evidence showing that intermittent access experience is associated with an increase in the number and activity of a lateral subpopulation of orexin-expressing neurons, and discuss the orexin system as a potential novel target for addiction. It is hoped that these presentations generate thoughtful debate and discussion regarding the optimal approach to modeling addiction in laboratory animals.

PANEL • SATURDAY, 4:30 P.M. – 6:30 P.M. • SALON C

What's Love Got to Do With It? Oxytocin Treatment for Stress and Addiction

Chairs: Tiffany Love, Jill Becker
Presenters: Brian Trainor, Jill Becker, Tiffany Love, Harriet de Wit

First recognized for its role in reproduction and social behavior, oxytocin has emerged as an important regulator of the stress response as well as a significant neuromodulator capable of interfering with a variety of drug addiction processes. Oxytocin administration has been demonstrated to modify drug-taking behaviors by influencing the neural pathways which regulate stress, reward, and social behavior; however, the degree to which oxytocin affects behavior is exceptionally variable. Indeed, oxytocin's actions appear to be highly sensitive to context, species-dependent, and sex-specific. The aim of this panel is to discuss recent findings regarding the role of oxytocin in the modulation of stress and drug reward, consider how contextual factors and sex differences shape these effects, and discuss how these findings may have implications for considering oxytocin as a putative treatment for stress-related conditions and substance use disorders. First, Dr. Trainor will discuss neural circuits in which oxytocin promotes social approach (nucleus accumbens) or social anxiety (bed nucleus of the stria terminalis). These complementary neural circuits may help explain how oxytocin is capable of facilitating social approach or social anxiety. Dr. Becker will present new research examining the influence of oxytocin on stimulated dopamine release in the nucleus accumbens. She will also discuss the effects of oxytocin and social housing on self-administration of psychostimulants in male and female animals. Then, Dr. Love will discuss novel neuroimaging findings examining the sex-specific effects of oxytocin within stress and reward systems. Finally, Dr. de Wit will review the small

number of controlled human studies that have examined effects of oxytocin on drug craving in humans. These studies include effects of oxytocin in cigarette smokers, and in alcohol, marijuana, cocaine and heroin users. The results suggest that the effects of oxytocin are modest and inconsistent.

PANEL • SATURDAY, 4:30 P.M. – 6:30 P.M. • SALON D

Mechanisms by Which the Prefrontal Cortex Mediates Maladaptive Behaviors

Chairs: Lique Coolen, Devin Mueller
Presenters: James Otis, Devin Mueller, Jason Radley, Lique Coolen

The medial prefrontal cortex (mPFC) is an area of the brain critical for learning and memory and as such is involved in a wide variety of emotional behaviors and psychiatric disorders. In this symposium, we will highlight recent findings on the mechanisms by which neural alterations in different regions within the mPFC contribute to memory formation, and subsequent maladaptive responses to stress, natural and drug rewards. James Otis will discuss evidence suggesting that cue-evoked activity in mPFC projection neurons can maintain reward-associated memories, such that inhibition of cue-evoked activity can induce-long lasting memory disruption. Furthermore, by combining two-photon calcium imaging with optogenetics in vivo, he shows that such manipulations can perturb encoding of reward-predictive stimuli in downstream circuitry. Devin Mueller will present on the role of estrogenic signaling in the infralimbic mPFC in extinction of cocaine seeking, and interactions with brain-derived neurotrophic factor (BDNF). He will present evidence that the absence of gonadal estrogens induces persistent and extinction-resistant cocaine seeking, and that estrogens rescue this deficit by enhancing infralimbic neuronal excitability in a BDNF-dependent manner. Jason Radley will discuss recent evidence showing that the mPFC-bed nucleus pathway coordinates neuroendocrine and behavioral adaptations to stress, and will next highlight how chronic stress-induced structural plasticity in this circuit may lead to maladaptive responses to stressors. Lique Coolen will present findings of neuroplasticity in the anterior cingulate area of the mPFC driving maladaptive seeking of both sexual and drug rewards. She will show that social reward experiences during drug taking subsequently increase vulnerability for relapse of drug seeking. Moreover, she will demonstrate using chemogenetic manipulations that mPFC neuronal activity is critical for such increased vulnerability for addiction.

Understanding Others: Neural Circuits for Social Behavior and Autism-Associated Dysfunction

Chair: Ofer Yizhar
Presenters: Ofer Yizhar, Eunee Lee, Francesco Papaleo, Jaideep Bains

Social interactions are crucial for the survival and well-being of animals. Mammalian species display a wide array of social behaviors, from mating and grooming to aggression and parental care. Although many of these are innate behavioral sequences, learning plays an important role in many social functions. Social cognition allows individuals to transmit and receive information about the state of others, and impaired social cognition has been associated with a wide range of psychiatric disorders, from autism and schizophrenia to anxiety disorders and depression. This panel will provide a wide-ranging view of the neural circuits involved in regulating adaptive social communication and of the circuit-level mechanisms regulating these complex cognitive processes. Ofer Yizhar from the Weizmann Institute of Science will present work aimed at understanding the coding of social information in the medial prefrontal cortex (mPFC) and of autism-associated changes in these population activity patterns. Eunee Lee from the Institute of Basic Science in Korea will discuss the contribution of interneurons in the mPFC to social approach behavior and the changes in interneuron function associated with mutations in the autism-associated Shank2 gene. Francesco Papaleo from the Instituto Italiano di Tecnologia will present findings regarding the importance of prefrontal cortex interneurons in a novel emotion-recognition task. Finally, Jaideep Bains of Calgary University will present exciting findings regarding the transmission of stress between mice and synaptic plasticity occurring in hypothalamic circuits through this important form of social communication.

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Poster Abstracts

TUESDAY, JANUARY 29, 2019 • 3:30 P.M. – 4:30 P.M. • SALON A

TU1. Real-Time High-Precision Pharmacokinetic Measurements of Cocaine in the Brain

*Kyle Plonse, Netzahualcóyotl Arroyo-Curras, Julian Gerson, Kevin Plaxco, Tod Kippin**

It has long been recognized that cocaine evokes complex neurochemical responses that mediate their influence of neural circuits underlying behavioral control, such as the dopamine pathways that we now know drive reward anticipation. However, the time resolution with which existing methods can measure cocaine is orders of magnitude poorer than the resolution with which they can measure dopamine, and thus our understanding of the relationship between cocaine delivery/metabolism and the dopamine response is limited. In response to this problem, our group has recently developed a new technology, electrochemical aptamer-based sensors (E-AB sensors), which are the size of a human hair and can detect physiologically relevant concentrations of specific drugs in-situ, in awake, freely behaving animals. Here, we tested this new technology on rats that have been administered 5 mg/kg of cocaine intravenously, then measured concentrations of cocaine within the lateral ventricle concurrent with monitoring locomotor activity. We successfully measured the concentration of cocaine every 3 s for 20 minutes and generated a pharmacokinetic profile for cocaine within the lateral ventricle. As cocaine concentrations increased (from 0 to 25 μM), they directly corresponded with behavioral stereotypy, which is typically associated with increased dopamine, in rats. In conclusion, we have developed a novel, potentially revolutionary, technology that can measure the pharmacokinetics and pharmacodynamics of psychoactive drugs within the brain.

TU2. Effect of Drug History on Motivation and Craving in a Rat Model of Polydrug Abuse

Elizabeth Crummy, Elizabeth Donckels, Britahny Baskin, Susan Ferguson*

Polydrug abuse is commonly observed in drug abusers with reports of up to 80% of heroin addicts also using cocaine and having a 15-fold greater risk of developing a cocaine addiction. Nonetheless, little is known of the mechanisms underlying addiction severity and craving due to polydrug use. To investigate the impact of drug history on motivation and craving of heroin and cocaine consumption, rats were assigned to one of three groups: Rats

that self-administered a single drug daily, rats that alternated between drug and sucrose pellet administration, and rats that alternated cocaine and heroin administration. To establish drug history, each group underwent ten self-administration sessions per reinforcer. Sessions alternated between cocaine (Experiment 1) or heroin (Experiment 2) access + presentation of a white cue light above the drug lever (Lever A), and administration of cocaine, heroin, or pellets + presentation of a green cue light above the other lever (Lever B). Following the end of self-administration, motivation to maintain drug consumption was assessed with a behavioral economics threshold procedure, whereby the unit-price of the reinforcer was increased across sessions by reducing the drug concentration per infusion. In addition, craving was assessed by taking rats through extinction training before cue-induced reinstatement for the Lever A reinforcer, and through cue test sessions 1, 13 and 29 days after the last Lever B reinforcer administration session. While single- and poly-drug histories did not differentially impact these measures, drug-specific differences were observed in price and cue sensitivity. Specifically, we found that demand elasticity was lower for cocaine, whereas heroin-associated cues resulted in greater drug-seeking, despite access to alternative reinforcers in the abstinence period. These results suggest that there is greater motivation for cocaine, but higher rates of cue-induced craving for heroin.

TU3. Psychomotor Sensitization Following an Intermittent Access Schedule of Cocaine Self-Administration

Crystal Carr, Joyce Xia, Jack Hildenbrand, Carrie Ferrario, Terry Robinson*

The ability of self-administration procedures to produce symptoms of addiction is critical to understanding the neural and behavioral plasticity associated with the transition from controlled to compulsive intake. Traditionally, the amount of drug consumed was considered critical to the development of addiction-like behavior. More recently, the temporal pattern of use has been shown to be an important factor. To this end, the Intermittent Access (IntA) model of cocaine self-administration alternates brief periods of drug availability with longer periods of unavailability. Similar to the oft-used Long Access (LgA) procedure, IntA is capable of producing increases in cocaine demand, robust drug- and cue-induced reinstatement, and other hallmarks of addiction, despite far less total cocaine consumption. A recent report has shown tolerance to the psychomotor activating effects of cocaine when tested soon after discontinuation of LgA, although direct comparisons to IntA were not made. Therefore, here we asked whether IntA to cocaine produces more robust psychomotor sensitization than LgA in males. Behavioral sensitization has been associated with neuroadaptations in brain regions involved in reward processing and decision making, which are especially important for the transition to addiction. We report, relative to rats given LgA to cocaine (6 hours/day), rats given IntA

were sensitized to the psychomotor activating effects of cocaine following one day of withdrawal, evidenced by increased locomotor activity. After extended withdrawal, both IntA and LgA rats were engaged in focused stereotypy, indicating especially robust behavioral sensitization. These findings add to the growing literature that the IntA procedure is capable of producing more robust addiction-like behavior and is especially valuable for studying associated neuroadaptations. Finally, in ongoing studies potential sex differences in IntA-induced sensitization are being evaluated.

TU4. Divergent Expression of Methylated DNA Cytosine Dioxygenases in the Nucleus Accumbens of Mice Exhibiting Variable Ethanol Behavioral Sensitization

Graham Kaplan, Javed Chitaman, Amber Brown, Haiyang Xu, Rachel Hedinger, Mary Zent, Jian Feng*

Ethanol behavioral sensitization (EBS) is thought to underlie the transition from controlled to uncontrolled drinking in susceptible individuals. Importantly, mice exhibit differential sensitivity to developing EBS, where some are more sensitive to the locomotor-stimulating effects of chronic ethanol than the others. The aim of the present study was to investigate changes in relative expression of methylated DNA cytosine dioxygenase TET (TET1, TET2, TET3) transcripts in the nucleus accumbens (NAc) of mice during EBS. C57/Bl6 mice were given ethanol or saline i.p. for 21 days and assessed for EBS on days 1, 7, 14 and 21. Mice were classified as high vs. low response groups based on their locomotor activity on day 21. qPCR was utilized to examine changes in relative gene expression of the TET transcripts between the groups. We found significant differential expression of multiple TET mRNAs in the NAc of EBS-high vs. low response groups. Specifically, TET1 and TET3 mRNA are decreased in the NAc of EBS-low response mice relative to control and high response groups, while EBS-high response mice exhibited increased expression of TET transcripts relative to control and low-response groups. These findings represent a platform by which to investigate individual difference in alcohol addiction and imply a role for epigenetic mechanisms in the NAc in this divergent phenotype.

TU5. Controllability of Stressors Differentially Alters the Severity of Cocaine-Induced Encoding Deficits of Associative Cues Within the Nucleus Accumbens

Kayla Siletti, Keith McConomy, Alexandra Montgomery, Michael Saddoris*

Repeated experience with drugs of abuse alters neural function in behaviorally-relevant ways that persist long into drug abstinence. Dysregulation of mesolimbic circuit function is consistently altered in cocaine-experienced rats,

as evidenced by impairments in both associative learning and related neural signaling. For example, electrophysiological activity in the nucleus accumbens (NAc) core and shell both exhibit abnormal encoding of associative cues during Pavlovian conditioning for non-drug rewards. These animals subsequently demonstrate poor performance on tasks that require cue processing.
A significant body of work has demonstrated that stress can potently modulate drug-seeking behaviors, and these stress-associated effects involve many of the same neural circuits used for natural reward (e.g. food) learning. For example, stress can reinstate drug-seeking after periods of extinction. However, these stress studies have typically employed uncontrollable stressors (i.e., the stressful event cannot be avoided). Stressors over which animals can achieve behavioral control (such as an active escape response) may differentially alter reward learning circuitry and mitigate drug-induced deficits. To test this, after 14d of cocaine self-administration, rats received a single session of a shock stressor, wherein physically identical unsignaled tail shocks could either be terminated by wheel turn (Escapable Shock; ES) or were unavoidable (Inescapable Shock; IS); unstressed rats (homecage; HC) served as controls. We demonstrate that the controllability of the stress bidirectionally altered cue encoding in a subsequent Pavlovian conditioning task. Specifically, while ES rats exhibited rescued cue encoding, IS rats exhibited significantly blunted cue responsivity. These findings suggest that stress exposure during abstinence significantly affects subsequent learning, and in particular, that controllability may impart resilience against drug-related cognitive deficits.

TU6. Examining Neuroadaptations Following Oxycodone Self-Administration and Prolonged Forced Abstinence

Michael Stefanik, Marina Wolf*

The recurring desire to take drugs, even after years of abstinence, is among the most insidious features of addiction. It is often triggered by cues previously associated with drug use. Cue-induced craving progressively intensifies ('incubates') over weeks of forced abstinence or withdrawal. This 'incubation of craving' has been reliably observed during withdrawal from different classes of drugs of abuse in rodents and humans. Recently, prescription opioid abuse and dependence has increased to epidemic levels. A prominent contributor to this trend is oxycodone (Oxy), a semisynthetic opioid, and the most widely prescribed opioid painkiller. Currently, however, little is known about the incubation of Oxy craving.
Incubation for other drugs depends on time-dependent strengthening of AMPA receptor (AMPAR) transmission onto medium spiny neurons in the nucleus accumbens (NAc) through the accumulation of high-conductance, GluA2-lacking, Ca2+-permeable AMPARs (CP-AMPARs). Our studies assess the

incubation of Oxy craving and underlying neuroadaptations in the NAc. It is hypothesized that expression of the incubation of Oxy craving also depends on strengthening of NAc synapses via CP-AMPAR inclusion.
Male Sprague Dawley rats underwent 10 days of extended-access Oxy self-administration (6hr/day, 0.15mg/kg/infusion). Rats returned to the operant chamber for a 30-min test on withdrawal day 1 (WD1), and either WD15 or WD30, measuring the time course of cue-induced seeking. Results show that incubation of oxycodone seeking occurs at maximal levels around WD15. Next, animals were killed at each time point, and tissue from the NAc biotinylated to test whether Oxy incubation is accompanied by elevated cell surface levels of homomeric GluA1 receptors, the type of CP-AMPAR that is increased after incubation of cocaine craving. Analyses are currently underway. By understanding incubation's cellular basis, we gain insight into mechanisms underlying the persistent vulnerability to relapse.

TU7. Investigation of the Role of Neuroimmune Signaling in Oxycodone Seeking

Kyle Brown, Catherine Levy, Ryan Bachtell*

The abuse of prescription opioids, such as oxycodone (Oxy), is a major public health threat, yet current treatments have poor efficacy in reducing drug craving and promoting abstinence. Neuroimmune signaling has become a potential pharmacological target of interest for the prevention of abstinence in light of studies suggesting that opioids alter homeostatic neuroimmune function. In addition, there is indication that abnormal neuroimmune signaling may contribute to opioid- reinforcement and seeking behavior; however, the underlying mechanisms are not well understood. In order to begin to address the role of neuroimmune signaling in opioid seeking, we used a rodent Oxy self-administration (SA) and incubation of craving model. In our first study, Sprague-Dawley rats self-administered Oxy (0.075 mg/kg/infusion) in operant chambers during 12 daily 6-hour (hr) sessions. Following the last day of SA, rats underwent forced abstinence in their home-cage for 14 days. During the abstinence period, rats were treated with either the neuroimmune modulatory drug Ibudilast (7.5 mg/kg/day) or vehicle (30% polyethylene glycol). On day 14 of abstinence, rats were re-introduced to their Oxy SA chamber for a 2hr drug seeking session during which operant responses resulted in the delivery of a drug-paired cue (i.e., a light) but no drug. A significant reduction in drug-seeking was found in the Ibudilast treated group. The reduction in drug seeking was accompanied by a significant decrease in glial fibrillary acid protein expression in the nucleus accumbens (NAc) and ventral tegmental area (VTA). In a second study, a separate cohort of rats self-administered Oxy (0.075 mg/kg/inf.) or saline during 12 daily 6hr sessions. On days 1 and 14 of abstinence from Oxy SA, brain tissue was extracted and processed for microarray analysis

of mRNA expression of neuroimmune-related genes in the VTA and NAc. These data provide preliminary evidence for a role of neuroimmune function in opioid seeking.

TU8. Modulating Cue-Reactivity With Theta-Burst Stimulation to the Frontal Pole: A Novel Target With Transdiagnostic Relevance

Colleen Hanlon, Logan Dowdle, Daniel Lench, Tonisha Kearney-Ramos, Sarah Sneider, Warren Bickel, Joshua Smith, Sarah Book*

Background: Cue-reactivity is one of the most powerful predictors of relapse among multiple addiction phenotypes. In these populations, cues lead to consistent neural activity in multiple nodes of the salience network including the anterior cingulate cortex (ACC), insula and ventral medial prefrontal cortex (vMPFC). We have now performed a series of sham-controlled, multiday clinical trials which have evaluated the efficacy of continuous theta burst stimulation as a tool to dampen cue reactivity in multiple populations. Method: 76 treatment seeking individuals (cocaine, alcohol, nicotine users, compulsive eaters) participated in 1 of 4 clinical trials wherein they received a functional MRI assessment of cue-reactivity (tailored to their drug of choice) before and after a 5 or 10 day course of real or sham continuous theta burst stimulation (120% RMT, 3600 pulses;132 fMRI scans total). Brain reactivity to cues was quantified in apriori defined nodes of the salience and executive control networks. Multiple regression was used to assess the impact of time, treatment, and addiction-phenotype on cTBS related changes in cue-reactivity. Results: There was a significant interaction between treatment and time in the dorsolateral prefrontal cortex ($F(1,142)=7.38;p=0.007$), vMPFC ($F(1,142)=6.43;p=0.012$), Insula ($F(1,142)=6.97;p=0.009$), and ACC ($F(1,142)=5.42;p=0.023$). There was no significant effect of addiction-phenotype on modulation of these regions other than the ACC ($F=5.24;p=0.023$) wherein the effect was largest in the alcohol users. There was also no significant interaction with the Occipital cortex response to cues (control region). Discussion: These data demonstrate, for the first time, that a multiday course of real versus sham cTBS to the left frontal pole has a significant effect on cue-reactivity in multiple classes of patients. The feasibility and efficacy of this approach opens a de novo therapeutic possibility for changing cue reactivity with TBS.

TU9. Nicotine Gateway Effects Enhance Adolescent Alcohol Intake and Age-Independent Alcohol Preference in Male Mice

*Anjelica Cardenas, Yuexi Yin, Sally Liu, Shahrdad Lotfipour**

Introduction: Adolescence represents a vulnerable period of development where nicotine and alcohol are often co-used. Adolescent versus adult nicotine exposure is consistently reported to enhance later substance use in humans and animals, i.e. nicotine's gateway effects.
The objective of our current proposal tests whether adolescent versus adult nicotine exposure enhances alcohol intake and preference in male C57BL/6J mice. We use the behavioral methods of Drinking-in-the-Dark (DID) and the two-bottle choice preference task to measure alcohol intake and preference. We pretreat animals with low-dose nicotine (2x 0.5 mg/kg/s.c./day) or vehicle for 7-days followed by assessing alcohol intake and preference post a 7-day washout. Results: Adolescents exhibit enhanced overall fluid intake versus adults. Adolescents and adults exhibit increased alcohol versus water intake over time. Further, nicotine-pretreated adolescents illustrate quicker acquisition of alcohol intake versus adults or water drinking groups. While both adolescent and adult mice illustrate preference for alcohol, nicotine pretreated mice had a greater preference for alcohol intake in ethanol naïve, but not ethanol-experienced, animals, regardless of age. The findings are not confounded by changes in blood alcohol levels. Conclusions: Data provide support for nicotine's gateway effects on adolescent alcohol intake and age-independent preference in mice. The results have important public health implications, given the growing use of e-cigarettes in the adolescent human population.

TU10. Optogenetic Inactivation of Orbitofrontal Cortex Abolishes Devaluation-Sensitive Aspects of Behavior During Economic Choice

Matthew Gardner, Jessica Conroy, Davied Sanchez, Geoffrey Schoenbaum*

How humans and animals choose between complex and diverse options remains a critical question of cognitive neuroscience. There has been considerable evidence that several frontal brain regions, in particular the orbitofrontal cortex (OFC), are necessary for choice behavior when the value of an offer must be integrated across multiple dimensions of outcome features. We have previously demonstrated that rats performing an economic choice task, in which rats decide between biologically relevant goods which vary across features of food-type and size, are completely unaffected by inactivation of the lateral portion of the OFC during the choice period of the task. This showed that lateral OFC is not necessary for well-learned economic choice behavior. Yet this inactivation was done when the food reinforcers had relatively stable values

over time. Here we devalued one of the food pellets using sensory-specific satiety - we pre-fed one of the pellets prior to starting a session - and tested whether shifts in preference away from a sated pellet were dependent on OFC function. We found that the normally observed shifts in preference following specific satiety were abolished by OFC inactivation. This is consistent with the hypothesis that OFC is necessary for model-based behavior. Furthermore, this dependence on OFC only becomes apparent when model-based mechanisms are necessary for the current choice.

TU11. Representation of Environmental Structure by the Orbitofrontal Cortex and Hippocampus Within an Odor Sequence Task

Jingfeng Zhou, Matthew Gardner, Thomas Stalnaker, Seth Ramus, Andrew Wikenheiser, Marlian Montesinos-Cartagena, Yael Niv, Geoffrey Schoenbaum*

The orbitofrontal cortex (OFC) has long been implicated in signaling information about expected outcomes to facilitate adaptive or flexible behavior. Current proposals focus on signaling of scalar values versus the representation of a cognitive map of the task. While often placed in opposition, these models may represent two extreme ends of a continuum determined by the complexity of the environment and the subjects' experience in it. As learning proceeds, an initial, detailed cognitive map might be acquired, based largely on external information. With more experience, this hypothesized map can then be tailored to include relevant abstract hidden cognitive constructs. This might default to scalar value in situations where other attributes are minimized or largely irrelevant, whereas in richer tasks, the structure might continue to be represented, at least where relevant to behavior. Here we tested this prediction by recording single unit activity from the OFC and hippocampus in rats navigating an odor sequence task analogous to a spatial maze. Rats sampled one of 16 odors on each trial and made a "go" or "no-go" response to obtain reward or to avoid a prolonged ITI. The 16 odors were organized into two pairs of 6-trial odor sequences (S1a vs. S1b and S2a vs. S2b). In sequences S1a and S1b, the shared odors made identical reward predictions, whereas in sequences S2a and S2b, some made opposing predictions, depending on the context. The odor sequences provided a mappable state space, with 24 unique "positions" defined by sensory information, likelihood of reward, or both. Consistent with the hypothesis that the OFC represents a cognitive map suiting the subjects' intentions or plans, we found a close correspondence between how subjects' behavior suggested they were using the sequences, and the neural representations of the sequences in OFC. Further, these representations of task structure were robust to the removal of value selectivity. Thus, value and task structure are potentially dissociable components of the neural code in OFC. Our preliminary analyses have shown that the cognitive map represented by

the hippocampus also depends on task need and is value-dissociable. However, unlike OFC that showed stable discrimination of states along the sequence, hippocampus showed better state discrimination early in the sequence.

TU12. Modeling Motivational Influences on Sustained Attention

Harrison Ritz, Joseph DeGutis, Michael Frank, Michael Esterman, Amitai Shenhav*

Achieving our goals often requires sustained focus, such as ignoring distractions while writing a conference abstract. This focus is known to wane with time, a phenomenon called vigilance decrement. Recent studies suggest that this decrement is not a fixed limitation, as incentives can lead to overall performance improvements and/or diminished vigilance decrements. However, the cognitive mechanisms driving these motivational effects remain unclear, including how they influence sensory processing and strategic responding. Here, we test a process model of sustained attention in order to better characterize its constituent processes.

We re-analyzed Esterman and colleagues' (2014, 2016) experiments, in which participants performed 10-minute sustained attention task. Participants were incentivized with either no reward, performance-contingent reward on each trial (fixed reward), or a potential large loss on an unknown future trial (anticipated reward; n=30 per group). No-reward participants performed worse overall and exhibited a vigilance decrement. Fixed-reward and anticipated-reward participants performed better overall, though only the anticipated-reward group lacked a vigilance decrement. We modeled task performance with a novel time-varying drift diffusion model (DDM) in which the evidence accumulation (drift) rate varied with the visibility of the gradually morphing stimulus. We fit this model to behavior in each of the reward groups using hierarchal Bayesian estimation. Our time-varying model predicted behavior better than the standard (stationary) DDM across all groups, as well as in a large online sample (n=21,400, no reward; Fortenbaugh et al., 2016). Comparing incentive conditions, we found that drift rate and threshold were higher for rewarded groups than the no-reward group. Over time, drift rate and threshold decreased in the no-reward and fixed-reward groups, but these decrements were absent in the anticipated-reward group. Informing the debate on the control and constraints of sustained attention, we found that both sensitivity and caution increased with reward and that their decrement was attenuated in the anticipated reward condition. These results improve our understanding of the mechanisms and temporal dynamics underlying motivation-attention interactions.

TU13. A Toolbox for Modeling Instrumental Learning With the Reinforcement Learning Drift Diffusion Model

Mads Pedersen, Michael Frank*

The continuous development of computational models drives understanding of cognitive mechanisms and their neurobiological underpinnings. But this development can also create a gap between modelers and non-modelers as fitting data with complex computational models requires expertise and specialized knowledge. Luckily, during recent years, several groups have created software that simplify the process of fitting computational models. In the work described here, we extend HDDM, an open source python toolbox for Bayesian hierarchical parameter estimation of the drift diffusion model. Our extension lets users model two alternative forced choice instrumental learning data with the recently developed reinforcement learning drift diffusion model (RLDDM). The RLDDM simultaneously estimates parameters of learning and choice by assuming decisions are made by accumulating evidence of the difference in expected rewards between choice options until reaching a decision threshold. We show how users can structure data and run analyses including estimating the effect of neural regressors on learning and dynamic choice, and we validate the model through posterior predictive checks and parameter recovery. Lastly, we fit the model to pre-collected data on an instrumental learning task.

TU14. White Matter Connectivity Supports Brain State Transitions Underlying Working Memory

Eli Cornblath, Arian Ashourvan, Jason Kim, Richard Betzel, Rastko Ciric, Graham Baum, Xiaosong He, Kosha Ruparel, Tyler Moore, Ruben Gur, Raquel Gur, Russell Shinohara, David Roalf, Theodore Satterthwaite, Danielle Bassett*

A diverse white matter network and finely tuned neuronal membrane properties allow the brain to transition seamlessly between cognitive states. However, it remains unclear how static structural connections guide the temporal progression of large-scale brain activity patterns in different cognitive states. Here, we deploy an unsupervised machine learning algorithm to define brain states as time point level activity patterns from functional magnetic resonance imaging data acquired during passive visual fixation (rest) and an n-back working memory task from a large developmental sample (n=879). We find that brain states are composed of interdigitated functional networks and exhibit context-dependent dynamics. Using diffusion-weighted imaging acquired from the same subjects, we show that structural connectivity constrains the temporal progression of brain states. We also combine tools from network control theory with geometrically conservative null models to demonstrate that brains are wired to support states of high activity in default mode areas, while requiring relatively low energy. Finally, we show that brain state dynamics

change throughout development and explain working memory performance. Overall, these results elucidate the structural underpinnings of cognitively and developmentally relevant spatiotemporal brain dynamics.

TU15. Simulating the Benefits of Motivational Dopamine States in the OpAL Model

Alana Jaskir, Michael Frank*

Dopamine's (DA) role in both the striatal direct (D1) and indirect (D2) pathways suggest a more complex system than standard reinforcement learning models imply. Previous work of the Opponent Actor Learning (OpAL) model presented a more biologically plausible and interactive account, capturing both incentive and learning effects in one dual-actor framework. In OpAL, DA modulates the influence of each actor; one actor encodes the benefits of actions (D1 pathway when DA is high) while the other encodes the costs of the same actions (D2 pathway when DA is low). While OpAL accounts for a wide range of DA's effect on learning and choice, formal analysis of the benefits of different motivational states (the level of dopamine) is still needed. We present simulations to address the tradeoffs of learning according to benefits or costs in different contexts.

TU16. Microbes & Monoamines: Stepping Stones from Dysbiosis to Neuropsychiatric Disease

Stephen Skolnick, Nigel Greig*

In nature, certain features of the mammalian enteric microbiome are strongly conserved across generations, allowing the host to rely on symbiotic gut bacteria for metabolic pathways essential to healthy development and function. Here, we highlight several promising but largely overlooked mechanisms from the microbiome that may influence psychiatric and cognitive health. In particular, certain microbial taxa support the clearance of ubiquitous environmental neurotoxins, the elimination rate of which can vary by an order of magnitude depending on microbiome composition. Also discussed are microbial metabolites indirectly essential for the proper function of neurotransmitter systems involved in the regulation of mood, attention, memory formation, and anxiety. Disruption of the microbiome, leading to suppression or extinction of key taxa that provide these functions, could produce effects that parallel abnormalities observed in a variety of psychiatric, neurodevelopmental, and neurodegenerative conditions of uncertain etiology.

TU17. Milling With Ultraviolet Excitation (MUVE) for Brain Phenotyping

Jason Eriksen, Jiaming Guo, Camille Artur, David Mayerich*

Neurodegenerative disorders affect the surrounding tissue through complex changes that are impossible to quantify using traditional histology. Researchers and pathologists are currently in need of a comprehensive imaging method that allows them to routinely explore large tissue volumes at the cellular level. We propose an imaging technique, that we refer to as milling with ultraviolet excitation (MUVE), that realizes high-throughput multiplex imaging of large-scale three-dimensional samples. The proposed instrumentation overcomes several constraints inherent in current state-of-the-art three-dimensional microscopy, such as confocal microscopy and light sheet microscopy (LSM). MUVE offers throughput that is several orders of magnitude faster than confocal microscopy by collecting a two-dimensional array of pixels simultaneously. The proposed instrumentation also utilizes serial ablation, overcoming all depth limitations inherent in optical methods such as confocal and LSM and providing the opportunity for true whole-organ imaging at microscopic resolution. MUVE is significantly less expensive than existing methods and provides the potential for greater spatial resolution when acquiring images.

TU18. Regulation of 5-HT1B Serotonin Receptor Expression in the Striatum by Dopamine Depletion and L-DOPA Treatment

Heinz Steiner, Santanna Patterson, Feras Altwal, Fernando Padovan-Neto, Joel Beverley, Anthony West*

Serotonin and dopamine in the basal ganglia interact in a bidirectional manner. On the one hand, serotonin modifies dopamine transmission via specific serotonin receptor subtypes. For example, increasing serotonin action (by serotonin reuptake inhibitors) potentiates dopamine-induced gene regulation in the striatum, an effect that is mediated by the 5-HT1B receptor subtype. Conversely, there is evidence that indirect dopamine agonists (cocaine, methylphenidate) increase the expression of 5-HT1B in striatal neurons. In this study, we investigated the effects of dopamine depletion by 6-OHDA and subsequent L-DOPA treatment on the expression of 5-HT1B. Rats with a unilateral 6-OHDA lesion were treated for three weeks (5x/week) with either vehicle or L-DOPA (5 mg/kg) + benserazide (12.5 mg/kg). In week 4, the animals were killed 60 min after a final drug treatment, and gene expression in the striatum was assessed by in situ hybridization histochemistry. As shown in previous studies, the 6-OHDA lesion produced a decrease in the expression of the neuropeptide marker dynorphin (DYN, in direct pathway neurons)

and an increase in the expression of the marker enkephalin (ENK, in indirect pathway neurons) throughout the striatum. Repeated L-DOPA treatment prominently increased DYN expression and further elevated ENK expression, effects that were restricted to the sensorimotor (lateral) striatum. The 6-OHDA lesion produced a modest increase in 5-HT1B receptor mRNA levels evenly throughout the striatum. Treatment with L-DOPA markedly further elevated 5-HT1B expression, preferentially in the sensorimotor striatum. The 5-HT1B receptor is expressed by both direct and indirect pathway neurons and is situated presynaptically on their terminals and acts to inhibit GABA release. Our findings suggest that altered activity levels, as indicated by the changes in neuropeptide markers, in direct and indirect pathway neurons are associated with parallel changes in 5-HT1B receptor expression in these neurons, possibly as a compensatory mechanism to counteract these activity changes.

TU19. Chemogenetic Activation of Paraventricular Nucleus of the Hypothalamus Oxytocin Neurons Restores Oxytocin Release and Reduces Mortality, Cardiac Inflammation and Fibrosis, as Well as Improves Autonomic Balance and Cardiac Function in an Animal Model of Heart Failure

David Mendelowitz, Jhansi Dyavanapalli, Matt Kay*

Oxytocin (OXT) neurons in the paraventricular nucleus of the hypothalamus (PVN) are known to be involved in the short-term regulation of the autonomic nervous system and responses to stress. The overarching hypothesis of this project is that the release of oxytocin from oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN) that are essential for activating parasympathetic cardiac vagal neurons (CVNs) in the brainstem, is reduced in an animal model of heart failure (HF) and furthermore that this dysfunction can be restored or reversed with chronic activation of PVN OXT neurons. We report that, using CHO cells as sniffer assays for endogenous oxytocin release, in an animal model of heart failure (HF) the optogenetic synaptic release of OXT onto essential downstream autonomic targets was blunted, but was restored with chronic chemogenetic activation of PVN OXT neurons (PVN OXT treatment). We also found that PVN OXT treatment reduced mortality, cardiac inflammation and fibrosis, improved critical longitudinal indices of autonomic balance (such as heart rate recovery), and improved cardiac function (assessed using high resolution echocardiography for cardiac function measures such as cardiac output, stroke volume, ejection fraction and fractional shortening) when compared to untreated HF animals.

TU20. The Necroptotic Pathway is Involved in Seizure-Induced Neuronal Necrosis

Denson Fujikawa, Kung-Chiao Hsieh*

We investigated whether inhibiting the first enzyme in the necroptotic pathway, RIP1, with 7-Cl-O-necrostatin-1 (Nec-1) protects against neuronal necrosis induced by 3-h lithium-pilocarpine-induced status epilepticus (LPCSE). Male Wistar rats were implanted with EEG electrodes and i.c.v. cannulae. SE control rats received 5 μl of 20% DMSO i.c.v. (n=5), SE Nec-1 rats received 5 μl of 8 mM Nec-1 (n=4) and control rats received lithium and i.c.v. DMSO (n-3). All 3 groups received 3 i.c.v. injections: at the beginning, middle and end of the 3-h seizure period. SE was stopped with diazepam and phenobarbital i.p. After 3-h SE and a 6-h recovery period, rats had transcardiac perfusion-fixation of their brains with 4% phosphate-buffered paraformaldehyde, which were removed and processed for H & E staining. The unbiased stereological method, the optical fractionator, was used to estimate the numbers of normal and necrotic neurons in the hippocampal hilus. EEGs were analyzed with power spectrum analysis. The estimated numbers of acidophilic (necrotic) neurons in the hilus in the SE DMSO control group and the SE Nec-1 group were 10,699 ± 966 and 7,634 ± 760 respectively (mean ± SEM), while the total numbers of neuronal cell counts were the same in all three groups. The RIPK-1 inhibitor reduced neuronal death by 29% ($p < 0.025$). There was no significant difference in the EEG power spectrum of epileptiform discharges in the two SE groups. In addition to excitotoxicity, the necroptotic pathway contributes to seizure-induced neuronal necrosis.

TU21. Is TBI Susceptibility Related to Subject-Specific Brain Morphology and Biomechanics?

Francis Loth, Maggie Eppelheimer, Soroush Pahlavian, Dipankar Biswas, Phillip Allen, James Houston, John Oshinski, Rouzbeh Amini*

A force to the head appears to cause a traumatic brain injury (TBI) in some but not others and the reason behind this difference is unclear. Can one's individual brain morphology and biomechanics predispose them to TBI? Our center has pondered this question after years of research comparing brain morphology and biomechanics of healthy volunteers (HVs) to subjects with Type I Chiari malformation (CM). CM is a neuro-structural defect where part of the cerebellum is located below the foramen magnum and accompanied by a myriad of debilitating symptoms. Exactly why these subjects become symptomatic is not well understood and research has indicated that a traumatic event precipitated the onset of symptoms for some subjects. This is supported by our data from the Chiari1000 project. From a survey of 1,366 CM subjects, 436 (32%) cited a specific event that triggered their symptoms. Events most often reported are: car accident, fall, pregnancy, other head trauma, physical

exertion and sports injury. Mid-sagittal morphometric comparisons of 301 MR images of adult female CM patients and HVs yielded a multitude of reliable group differences between brain morphology measures. In a subgroup of CM subjects, the use of DTI and EEG were correlated to both cognitive function and self-reported pain. In a different subgroup, we quantified brain tissue deformation during normal cardiac induced forces using displacement-encoded stimulation echo MRI. We found cerebellum displacement and strain was significantly larger ($p<0.01$) for CM subjects compared to HVs (158±44 vs. 79±17 micron and 3.8 vs. 1.3%, respectively). In short, compared to HVs, CM subjects have significantly different morphometry and biomechanical measures and, for many, trauma was the trigger for their symptoms. Thus, we hypothesize that TBI susceptibility is also impacted by an individual's morphometry and biomechanics, warranting further examination.

TU22. Protection From TBI-Induced Vision Loss by the N-Acetylserotonin Derivative HIOC Through a BDNF/TrkB Receptor Mechanism

*P. Michael Iuvone**

N-Acetylserotonin activates BDNF/TrkB receptors but it's biological half-life following systemic injection is too short to be therapeutically useful. In this study we determined if HIOC, a structural analog of N-acetylserotonin with a longer half-life, prevents loss of visual function when administered after exposure to blast injury to the eye or head, examined HIOC's effect on optic nerve axon preservation, and investigated the role of BDNF/TrkB receptors in its neuroprotective effect. Mice were exposed to a single ~48psi blast directed at the eye or a 70 psi blast to the head. They were injected with vehicle or HIOC (40mg/kg, ip) 30 min before, or 0.25hr, 1hr, 3hr, or 24hr after exposure to blast. Injections continued daily for 6 days. Contrast sensitivity and visual acuity were measured 1 week, 1 month, and 4 months after exposure to blast by optokinetic tracking. Optic nerve axon counts were made 4 months after blast exposure in mice treated initially 15 min after blast. To test the role of BDNF/TrkB receptors, mice were treated with ANA-12, a selective TrkB antagonist, 2.5 hrs before each HIOC or vehicle injection. Results: In vehicle-treated mice, blast significantly reduced contrast sensitivity ($p<0.001$), but not visual acuity compared to naïve controls that were not exposed to blast. At 1 and 4 months after blast, both contrast sensitivity ($p<0.001$) and visual acuity ($p<0.001$) were reduced compared to naïve controls. In mice initially treated with HIOC 30 min before or 0.25hr, 1hr, or 3hr after blast, contrast sensitivity and visual acuity were significantly better than vehicle-treated mice ($p<0.001$), and not significantly different than naïve controls. If the initial treatment with HIOC was delayed by 24hr after blast, the protective effect on visual function was not observed. Four months after exposure to blast, axon numbers in the optic nerve

were significantly reduced in vehicle-treated mice ($p<0.001$), but in HIOC treated mice. Pretreatment with ANA-12 completely blocked the protective effect of HIOC against blast-induced vision loss. Conclusion: HIOC preserves vision in mice exposed to blast if the initial treatment is within a critical period (<3hr). Treatment with HIOC for 1 week preserves visual function for at least 4 months. The effect of HIOC is mediated by activation of BDNF/TrkB receptors.

TU23. Temporal Characterization of Neuroinflammation After Cranial Irradiation in the Mouse

Fredrik Kamme, Christine Cho, Curt Mazur, Holly Kordasiewicz, Eric Swayze*

Therapeutic cranial irradiation, as part of brain tumor therapy, can lead to chronic, progressive cognitive sequelae in pediatric patients. Cranial irradiation triggers long lasting neuroinflammation in humans and experimental animals. Pharmacological modulation of inflammation and microglia implicate neuroinflammation in the loss of neuronal progenitors in the hippocampus and impaired performance in novel object recognition testing (Monje, 2003, Acharya, 2016). Gene expression analysis of microglia post irradiation in mice have shown chronic elevations in phagocytic markers, type I IFN signaling and a similarity to aging (Li, 2015). We characterized neuroinflammation after cranial irradiation in mice with the goal to identify chronic processes that may underlie functional deficits in the model. C57Bl/6 mice were irradiated at 10 Gy in orthovoltage and allowed to recover for 1, 2, 4, 8 and 16 weeks. At each timepoint, microglia were isolated and analyzed by RNA sequencing.

After irradiation, microglial gene expression shows discrete inflammatory processes with different temporal profiles; a rapid onset but transient elevation in type I IFN response genes, a slow onset and progressive elevation in microglia priming genes and a rapid onset and chronic induction of p53-response genes. The neuroinflammatory response to cranial irradiation is dynamic and multifaceted, suggesting there may be several signaling events underlying the gene expression changes. The temporal correlation of specific subsets of inflammatory responses with the chronic nature of functional deficits highlight these responses as potential targets for therapeutic intervention.

TU24. Ahnak Scaffolds L-Type Voltage-Gated Calcium Channel and Modulates Depressive Behavior

Junghee Jin, Dionnet Bhatti, Ko-Woon Lee, Lucian Medrihan, Jia Cheng, Jing Wei, Ping Zhong, Zhen Yan, Cassandra Kooiker, Claire Song, Jodi Gresack, Paul Greengard, Yong Kim*

Genetic polymorphisms of the L-type voltage-gated calcium channel (VGCC) are associated with psychiatric disorders including major depressive disorder. Alterations of S100A10 (p11) level are also implicated in the etiology of major depressive disorder. However, the existence of an endogenous regulator in the brain regulating p11, L-type VGCC and depressive behavior has not been known. Here we report that Ahnak, whose function in the brain has been obscure, stabilizes p11 and Anxa2 proteins in the hippocampus and prefrontal cortex in rodent brain.

Protein levels of Ahnak, p11 and Anxa2 are highly and positively correlated in the brain. Together these data suggest the existence of an Ahnak/p11/Anxa2 protein complex. Ahnak is expressed in p11-positive as well as p11-negative neurons. Ahnak, through its N-terminal region, scaffolds the L-type pore-forming α1 subunit and, through its C-terminal region, scaffolds the β subunit of VGCC and the p11/Anxa2 complex. Cell surface expression of the α1 subunits and L type calcium current are significantly reduced in primary cultures of Ahnak knockout (KO) neurons compared to wild-type controls. A decrease in the calcium influx through the L-type channel is observed in both glutamatergic neurons and parvalbumin (PV) GABAergic interneurons of Ahnak KO mice. Constitutive Ahnak KO mice or forebrain glutamatergic neuron-selective Ahnak KO mice display a depression-like behavioral phenotype alike that of constitutive p11 KO mice. In contrast, PV interneuron-selective Ahnak KO mice display an antidepressant-like behavioral phenotype. Our results demonstrate that L-type VGCC is an effector of the Ahnak/p11/Anxa2 complex, revealing a novel molecular connection involved in the control of depressive behavior.

TU25. Elucidating Neural Circuits That Transmit Affective-Motivational Pain Signals to the Amygdala

*Sung Han**

Learning to avoid painful situations is critical for survival in all organisms. Association of a neutral stimulus (e.g., a tone) with a painful stimulus (e.g., a foot shock) results in a stable memory such that the tone alone will elicit a defensive response (immobility or freezing). In mammals, this form of associative aversive learning requires the amygdala. Although the pain is the main driver of aversive learning, the circuit-based mechanism by which pain information is conveyed and processed to the amygdala is not well-understood.

We found that neurons expressing calcitonin gene-related peptide (CGRP) in the brain are critical for relaying pain signals to the amygdala during aversive learning. Genetic silencing of these CGRP neurons attenuated pain responses and memory formation, and optogenetic stimulation of CGRP neurons produced robust aversive behaviors. These results provide compelling evidence that CGRP conveys pain signals to the amygdala during aversive learning.

TU26. CB2 Agonists Increase Ectopic Ovarian Tumor Growth Independent of Their Peripheral Antinociceptive Effect

*Henry Blanton, Isabel Castro, Jose-Luis Redondo, Jennifer Brelsfoard, Kevin Pruitt, Daniel Morgan, Josee Guindon**

The cost of ovarian cancer care is estimated to reach $173 billion in the US in 2020. Ovarian cancer is part of the deadliest gynecologic cancer among women. The first line of treatment for ovarian cancer pain and side effects of chemotherapy treatment (peripheral neuropathy) are mu opioid receptor agonists such as morphine. However, opioids offer short duration of pain relief, are ineffective in ~70% of patients and possess major unwanted side effects such as tolerance, addiction, and overdose death. And so there is an urgent need for novel analgesics to treat cancer and chemotherapy-induced chronic pain. The therapeutic use of cannabinoid-based therapies by cancer patients for their analgesic and antiemetic properties has been increasing, but the impact of long-term cannabinoid-based therapies on tumor growth in the context of chemotherapy-treatment and/or cancer remains to be determined. Preliminary data from our laboratory show that daily exposure to CB2 agonists causes female mice to exhibit elevated circulating estradiol resulting in an enhancement of ovarian tumor growth while the critical antinociceptive effects of these agonists are maintained. Therefore, this study addresses this gap in knowledge by testing the novel hypothesis that the elevation of estradiol and the enhancement of ovarian cancer growth by CB2 or mixed CB1/CB2 agonists, but not their antinociceptive effects, are mediated through neuronal and/or pituitary CB2 receptors. This innovative project has furthered our understanding of the mechanisms responsible for CB2 modulation of circulating estradiol levels, analgesia, and ovarian tumor growth and has the potential to improve the treatment of patients suffering from ovarian cancers.

TU27. Altered Sound Localization Ability in a Mouse Model of Fragile X Syndrome

Elizabeth McCullagh, Shani Poleg, Nathaniel Greene, Molly Huntsman, Daniel Tollin, Achim Klug*

Imagine a world where to sit in a noisy classroom is intolerable, and actually could be perceived as painful. In addition to the noise level being overwhelming, you also can't focus on the teacher because there is too much background noise. Hypersensitivity to sound and impaired sound localization are some of the most common sensory symptoms described by people with Fragile X Syndrome (FXS) and more broadly autism. However, it is difficult to determine the nature of people's impairments due to interactions with cognitive ability in most sound localization tasks. Sound localization processing occurs initially in the auditory brainstem, an area that has been underexplored in FXS. Here we present data using a sound localization prepulse inhibition (PPI) task. In this task, we use a mouse model of FXS and a reflexive behavior to determine if these mice have impairments in sound localization and spatial release from masking. As expected, FXS mice have hypersensitivity to sound, as illustrated by increased startle responses compared to control mice at low dB sounds. In addition, FXS mice have impairments in their ability to detect a gap in noise, suggesting alterations to temporal processing in these mice. Preliminary data also suggest that these mice have alterations in their minimum audible angle, and spatial release from masking all indicating the auditory brainstem as an important circuit that is altered in FXS. Additionally, these data present a novel task to access sound localization ability in this mouse model that could be extended to humans. Being able to address just auditory hypersensitivity and sound localization difficulties in Fragile X patients would be an important milestone in our ability to provide treatments for Fragile X patients.

TU28. Gut-Brain Axis in Hypertension: Role of the Afferents

*Jasenka Zubcevic**

Hypertension is a serious condition affecting forty six percent of Americans today. Despite life style changes and available therapeutics, around twenty percent of patients remain either resistant or refractory to anti-hypertensive therapy, thus categorizing as having resistant hypertension (R-HTN). A significant portion of R-HTN patients present with dysfunctional autonomic nervous system (ANS), while gut dysbiosis has also recently been linked with both rodent and human hypertension. Here, we investigated the effect of fecal matter transplant (FMT) from a rodent model of hypertension, spontaneously hypertensive rat (SHR), on the cardiovascular and ANS variables in its normotensive Wistar-Kyoto (WKY) control. Male adult WKY rats were gavaged with a cocktail of antibiotics daily for seven days, leading to depletion

of >90% of resident gut bacteria. Following a two-day rest from antibiotics, all rats were gavaged with fecal slurry from either WKY (WKY-WKY, n=6) or SHR (SHR-WKY, n=6), daily for seven days, then once a week for the duration of the study (seven weeks total). Blood pressure (BP) was measured in conscious unrestrained rats using radiotelemetry (DSI), and spectral analysis of waveform BP signal was used to mathematically derive autonomic variables. We observed a significant increase in BP starting at week five following the first FMT. This was associated with an increase in vasovagal ratio in SHR-WKY group, suggesting an imbalance in sympathetic and parasympathetic ANS variables following FMT from SHR to WKY. Real time PCR in proximal colon, nodose ganglia and the nucleus of the solitary tract (NTS), an important cardioregulatory brain region and a primary site for gastrointestinal afferent input, revealed changes in relative expression levels of glutamatergic and serotonergic neurotransmitter pathways, suggesting changes in vagal afferent input from the gut. Finally, surgical ablation of ventral subdiaphragmatic vagal branch increased BP in male adult WKY rats five weeks post-surgery. We propose that hypertension-associated gut dysbiosis contributes to increased BP via dysfunction in the vagal afferent feedback to the brain.

WEDNESDAY, JANUARY 30, 2019 • 3:30 P.M. – 4:30 P.M. • SALON A

W1. Headset VR Clinical Challenges Combined With Neuroscience Training to Enhance Clinician Action and Capability

*Mary Metcalf, Karen Rossie, Kimberly Workman, Bradley Tanner**

Chronic pain is common, affecting anywhere from 10% to 50% of the general population. The subsequent increased prescribing of opioids has resulted in the current U.S. epidemic of addiction to opioid pain medications leading to overdose deaths that outnumber automobile-related deaths, rising admissions to hospitals, and disrupted lives for both the patient and family. With support from NIDA, we have developed a clinical training experience involving a hybrid Oculus Rift VR Headset experience combining a patient encounter in a 3D virtual primary care clinic with an investigation of a 3D virtual brain. The learner first interacts with a virtual patient, then explores a 3D virtual brain to visualize reward pathways as well as the effect of opioids on these pathways. We postulate that science-minded physicians will enjoy building a more robust understanding of brain structures when the process is engaging and quickly yields a robust understanding of the neuroscience associated with the patient's condition and treatment. The approach is being modified to address the obesity epidemic. Patient encounters are similarly combined with an "inside the brain" experience to provide the needed neurobiological foundation for clinical treatment. The combination fosters and guides interaction with obese patients by linking skills development in the interview, assessment, and intervention

of overweight and obese patients with the exploration of the neuroscience associated with the regulation of energy, lipids, and glucose metabolism. Our Oculus Headset-based virtual 3D environment conveys brain components related to feeding behavior such as the ventral tegmental area (VTA), the nucleus accumbens (Nac), and the arcuate nucleus (Arc). We will also assess if once a basic understanding is established, physician learners seek more advanced knowledge of peptides such as NPY (neuropeptide Y) and AgRP (agouti-related gene product). Our research will assess if either experience enhances enthusiasm for seeking additional understanding of neuroscience and builds confidence in the ability to comprehend and apply the latest findings in neuroscience research. The novel approach can potentially enable the translation of neuroscience research to the science-based practice of medicine by neuroscience-informed clinicians.

W2. Enhancing Neuroscience Knowledge of Secondary School Children via a PlayStation VR Game

Bradley Tanner, Mary Metcalf, Elizabeth Tanner*

Research is rapidly unfolding the mysteries of the central nervous system. Unfortunately, elementary, middle, and high school students achieve minimal neuroscience understanding beyond simple discussions of the senses and neuronal communication. Although valuable, school visits by neuroscientists, teacher training in neuroscience, physical models, 2D diagrams, animations, and video are insufficient to confer a full understanding of neurobiology. At the same time, today's youth make critical decisions impacting their brain and health - including the foods they eat and their use or rejection of alcohol, cannabis, and other psychoactive substances. A robust model of brain functioning could guide these decisions and instill healthy behavior. In our immersive Headset-based PlayStation VR game, we are taking neuroscience education directly to the student as they play a game where they navigate inside a 3D brain. Game players utilize today's virtual reality technology to identify brain structures including components that connect: senses with perception, planning with muscle or cognitive action, and memory with emotions. They interact with chemical messengers affecting brain functioning and behaviors such as reward seeking and hunger. For example, the player reduces the impact of some chemicals (cortisol, ghrelin), attracts and enhances the positive effect of helpful chemicals (oxytocin), and repels others that may hijack the reward system (opioids). In the process, they build an understanding of brain structures, identify neurotransmitters, experience the impact of those chemicals on different areas of the brain, and see the importance of active participation in brain processes to assure whole-body health. In the future, the adolescent player will modulate additional chemicals and hormones and experience detailed linking of neurotransmitters to sub-components of the brain to win the game.

Game mechanics will emphasize decision making and challenges equivalent to those they face in the external world (e.g., food choices, substance use, peer bonding, stress, and anxiety). As the play progresses, the game builds a sufficiently robust brain image and neuroscience understanding for the learner to appreciate and utilize new research findings as neuroscientists further unravel the mystery of the brain.

W3. Neurophobia - What Causes It?

*Luke Hone, Stephen Bacchi, Sybil Stacpoole**

Neurophobia is a term used to describe a fear of clinical neurology and the basic neurosciences. This fear of clinical neurology is prevalent within medical student populations and numerous interventions have been trialled to assuage these fears (McColgan et al. 2013). Several studies have assessed the degree of neurophobia reported by medical students and doctors and the reasons they describe having this fear (e.g. knowledge of neuroanatomy, complex presentations and rare conditions) (Abushouk & Duc 2016). However, no studies could be identified that assessed which sources of information these opinions are being based upon. In practicing doctors and senior medical students, it would seem reasonable to hypothesize that these opinions may be based on personal experience. However, it is unclear what sources of information students are basing their preconceptions regarding neurology upon, when they have had no or very little personal experience in the field. We therefore set out to examine (a) the preconceptions of Cambridge University medical students regarding neurology at the beginning of the clinical course (b) the sources of information that students are basing these opinions on (e.g. doctors from other specialties, senior medical students, lecturers, family members, popular media, blogs, fictional/non-fictional books). We investigated this with a voluntary 30 question survey given to year 4 medical students, at the start of clinical school. 54% of the year group (141 individuals) completed the survey, with >70% indicating a degree of negative attitudes to clinical neurology, such as finding neurological patients difficult to assess. Factors affecting these opinions included peer medical students; popular media such as House and Grey's Anatomy and books such as the writings of Oliver Sacks; preclinical examinations and preclinical neuroscience teachers. Interestingly, preclinical neuroscience teachers had the greatest influence, in either a positive (60%) or negative direction (20%).

Understanding the means through which negative attitudes to clinical neurology develop should provide the opportunity to target interventions to assuage them. Further studies, examining whether these preconceptions are modifiable, and how strongly they persist after a rotation in clinical neurology, are warranted.

W4. H3.3 Barcoding of Nucleus Accumbens Transcriptional Activity Identifies Novel Molecular Pathways Associated With Cocaine Self-Administration in Mice

Mathieu Wimmer, Bruno Fant, Sarah Swinford-Jackson, Alexander Testino, Duncan Van Nest, Ted Abel, Chris Pierce*

Although numerous epigenetic modifications have been associated with addiction, little work has explored the turnover of histone variants. Uniquely, the H3.3 variant incorporates irreversibly and preferentially into chromatin independently of DNA replication at active sites of transcription and transcription factor binding. Thus, genomic regions associated with H3.3-containing nucleosomes are particularly likely to be involved in plasticity such as following repeated cocaine exposure. Here, we utilized a recently developed mouse line expressing a neuron-specific hemagglutinin (HA)-tagged H3.3 protein to track transcriptionally active sites cumulatively across a period of cocaine self-administration. RNA-seq and H3.3-HA ChIP-seq analyses were performed on nucleus accumbens collected following prolonged cocaine or food self-administration. RNA sequencing revealed five genes upregulated in cocaine relative to food self-administering mice: Fosb, Npas4, Vgf, Nptx2 and Pmepa1, which reflect known and novel cocaine plasticity-associated genes. Subsequent ChIP-seq analysis confirmed increased H3.3 aggregation at four of these five loci, thus validating H3.3 insertion as a marker of enhanced cocaine-induced transcription. Further motif recognition analysis of the ChIP-seq data showed that cocaine-associated differential H3.3 accumulation correlated with the presence of several transcription factor binding motifs including RBPJ1, EGR1, and SOX4, suggesting that these are potentially important regulators of molecular cascades associated with cocaine-induced neuronal plasticity. Additional ontological analysis revealed differential H3.3 accumulation mainly near genes involved in neuronal differentiation and dendrite formation. In summary, these results establish the H3.3-HA transgenic mouse line as a compelling molecular barcoding tool to identify the cumulative effects of long-term environmental perturbations such as exposure to drugs of abuse.

W5. Homecage Observation for Mouse Experiments (HOME) Device for Longitudinal and High-Throughput Measures of Physical Activity

Nanami Miyazaki, Alexxai Kravitz*

Obesity is a leading cause of preventable death in the United States, and is associated with physical inactivity. Despite the importance of physical activity levels to overall health, strategies to reliably increase physical activity in obese individuals remain challenging, in part due to a lack of understanding of how

obesity disrupts physical activity. Rodent models of obesity are also inactive; obese rodents show reduced locomotor activity characterized through open field mazes typically equipped with video tracking software, or with homecage running wheels. Open field maze assays, however, only capture a small portion of the animal's locomotor activity and requires costly specialized equipment, and in-cage running wheels offer information about a narrow type of activity and may alter or increase non-running wheel activity as well. To address these limitations, we developed the Homecage Observation for Mouse Experiments (HOME) device, an open-source and cost-effective device. The compact design allows for the HOME device to be placed in rodent homecages to collect longitudinal measures of locomotor activity. Ease and low cost of assembly allow for high-throughput studies. Our preliminary data shows that the device is able to reliably track circadian rhythms of mice and reflect differences in locomotor activity between wild-type and obese mice collected in a home cage over time, with minimal investigator interference. While the device we built for this experiment solely measures homecage activity, it is relatively easy to add sensors such as temperature, light and humidity to the HOME device for other studies. The HOME device provides a new platform on which to collect rodent physical activity data and will likely contribute to the understanding of how obesity affects activity over time.

W6. Effects of Nicotine and THC Co-Administration via Vapor Inhalation in the Rat

Michael Taffe, Mehrak Javadi-Paydar*

Electronic nicotine delivery systems (ENDS, e-cigarettes) are increasingly used for the self-administration of nicotine by various human populations, including previously nonsmoking adolescents. Studies in preclinical models are necessary to evaluate health impacts of ENDS including the development of nicotine addiction and the impact of co-administered psychoactive substances such as Δ9-tetrahydrocannabinol (THC). This study was conducted to determine possible interactive effects of nicotine and THC co-administration by inhalation of vapor created by ENDS in rats. Male Sprague-Dawley rats (N=8) were prepared with radiotelemetry devices for the reporting of temperature and activity. Experimental studies subjected rats to inhalation of vapor generated by an electronic nicotine delivery system (ENDS) adapted for rodent studies. Inhalation conditions included vapor generated by the propylene glycol (PG) vehicle, nicotine (1, 10, 30 mg/mL in the PG), THC (12.5, 25 mg/mL). Nicotine inhalation increased spontaneous locomotion and decreased body temperature of rats. Pretreatment with the nicotinic cholinergic receptor antagonist mecamylamine (2 mg/kg, i.p.) prevented stimulant effects of nicotine vapor inhalation and attenuated the hypothermic response. Combined inhalation of nicotine and THC resulted in apparently independent

effects which were either additive (hypothermia) or opposed (activity). These studies provide evidence that ENDS delivery of nicotine via inhalation results in nicotine-typical effects on spontaneous locomotion and thermoregulation in male rats. Effects were blocked by a nicotinic antagonist, demonstrating mechanistic specificity. This system will therefore support additional studies of the effects of nicotine and THC administered by ENDS.

W7. Serotonin 5-HT2A Agonist Facilitates Extinction of Incubated Palatable Food Memories

David Martin, Donna Calu*

Serotonin 5-HT2A agonists are promising pharmacotherapeutics that are currently the focus of clinical studies investigating their effectiveness in preventing relapse to alcohol, nicotine and cocaine addiction during abstinence. The preclinical 'Incubation of craving' model captures time-dependent increases in drug and natural reward seeking during abstinence, which translates to enhanced drug-associated cue-reactivity observed in human addicts. Here, we use the incubation of craving model to test if 5-HT2A agonists differentially facilitate extinction of recent and remote ('incubated') reward memories in rats. We trained rats to press a lever for palatable food pellets paired with a light cue on an FR1/20 s time out schedule for 10 days. In Exp. 1, we tested the effect of 5-HT2A agonist, DOI (0.2mg/kg, i.p.), on extinction of recent palatable food memories, giving a single injection before the first extinction session on day 1 of the abstinence period (day 1 incubation). In Exp. 2, we tested the effect of DOI (0.2mg/kg, i.p.) on extinction of remote palatable food memories, giving a single injection before the first extinction session on day 30 of the abstinence period (day 30 incubation). In both experiments, we examined extinction in three consecutive non-reinforced sessions (2h). We found that a single dose of DOI given before the first extinction session accelerated the rate of extinction for remote, but not recent, reward memories. The facilitatory effects of DOI on extinction were stably expressed in an additional extinction test 30 days later. These results suggest that a 5-HT2A agonist, DOI, has specific and lasting effects on extinction of remote appetitive palatable food memories. Ongoing pharmacology and electrophysiology studies explore the neural locus of 5-HT2A effects in facilitating extinction of remote memories.

W8. Self-Regulation of the Dopaminergic Reward Circuit in Cocaine Users With Mental Imagery and Neurofeedback

Matthias Kirschner, Ronald Sladky, Amelie Haugg, Philipp Stämpfli, Elisabeth Jehli, Martina Hodel, Etna Engeli, Sarah Hösli, Markus R. Baumgartner, James Sulzer, Quentin J.M. Huys, Erich Seifritz, Boris Quednow, Frank Scharnowski, Marcus Herdener*

Background: Enhanced drug-related reward sensitivity accompanied by impaired sensitivity to non-drug related rewards in the mesolimbic dopamine system are thought to underlie the broad motivational deficits and dysfunctional decision-making frequently observed in cocaine use disorder (CUD). Effective approaches to modify this imbalance and reinstate non-drug reward responsiveness are urgently needed. Here, we examined whether cocaine users (CU) can use mental imagery of non-drug rewards to self-regulate the ventral tegmental area and substantia nigra (VTA/SN). We expected that obsessive and compulsive thoughts about cocaine consumption would hamper the ability to self-regulate the VTA/SN activity and tested if real-time fMRI (rtfMRI) neurofeedback (NFB) can improve self-regulation of the VTA/SN.
Methods: Twenty-two CU and 28 healthy controls (HC) were asked to voluntarily up-regulate VTA/SN activity with non-drug reward imagery alone, or combined with rtfMRI NFB.
Results: On a group level, HC and CU were able to activate the dopaminergic midbrain and other reward regions with reward imagery. In CU, the individual ability to self-regulate the VTA/SN was reduced in those with more severe obsessive-compulsive drug use. NFB enhanced the effect of reward imagery but did not result in transfer effects at the end of the session. Conclusion: CU can voluntary activate their reward system with non-drug reward imagery and improve this ability with rtfMRI NFB. Combining mental imagery and rtfMRI NFB has great potential for modifying the maladapted reward sensitivity and reinstating non-drug reward responsiveness. This motivates further work to examine the use of rtfMRI NFB in the treatment of CUD.

W9. Fatal Overdose in Recently Detoxified HIV-Positive Persons With Opioid Use: The Role of Naltrexone in Prevention

*George Woody**

Persons with opioid addiction and HIV have increased risk of fatal overdose. This study presents data from two recent studies that were done around the same time and by the same local research team in St. Petersburg, Russia. One study randomized 200, detoxified, opioid-addicted persons seeking HIV treatment into a 12-month, double-blind, double-dummy study where they received an implant with 1000 mg naltrexone that blocks opioids for 3-months and daily oral naltrexone placebo; or to a placebo implant and 50 mg/day

oral naltrexone (NTX study). The other study randomized 349 persons with opioid addiction and HIV to detoxification with referral to HIV treatment, or to detoxification with case management by social workers and nurses to facilitate entry into HIV treatment over the next 6 months (LINC study). Participants in both studies were followed through month 12. About half of NTX study participants took naltrexone throughout the 12-month study period, and there were 2 overdose deaths (1.5%); in the LINC study, there were 18 overdose deaths (7.3%, $p<0.008$) over 12 months. Though naltrexone adherence was less than optimal, these findings emphasize its potential for preventing opioid overdose deaths.

W10. Role of HDAC3 in D1R- Vs D2R- MSNs in Regulating Cocaine-Induced Plasticity and Behaviors

Rianne Campbell, Eniko Kramar, Benjamin Gunn, Alberto Lopez, Om Chitnis, Jude Banihani, Lilyana Pham, Dina Matheos, Gary Lynch, Marcelo Wood*

Cocaine utilizes mechanisms of synaptic plasticity and transcription within the nucleus accumbens (NAc) to promote drug-seeking behaviors. Recent work from the field demonstrates that this occurs in a cell-type specific manner, often differentially affecting mechanisms of plasticity within the two major output cell types of the NAc: dopamine D1- (D1R) vs D2-receptors (D2R) medium spiny neurons (MSNs). Consistent with this, activation of D1R- and D2R-MSN drive opposing behavioral responses to cocaine. However, it is unclear how cocaine affects epigenetic mechanisms within D1R- vs D2R- MSNs to promote cocaine-associated behaviors. Prior work from our lab demonstrates that cocaine disengages histone deacetylase 3 (HDAC3) within the NAc to promote cocaine-induced gene expression and cocaine-associated memory formation. Here, we begin to examine the specific role of HDAC3's deacetylase activity in cocaine-induced synaptic plasticity within the NAc. In addition, we have investigated the role of HDAC3 within D1R- vs D2R-MSNs in regulating cocaine-induced gene expression and behaviors. Together, these results illustrate how cocaine alters mechanisms of histone acetylation to induce cell-type specific changes in gene expression and synaptic plasticity that promote drug-associated behaviors.

W11. Modulation of the Ventral Tegmental Area and Reward Seeking by Inhibitory and Excitatory Ventral Pallidum Output Pathways

Jessica Tooley, Lauren Marconi, Jason Alipio, Meaghan Creed*

The ability to appropriately integrate and respond to rewarding and aversive stimuli is essential for survival. The ventral pallidum (VP) is the primary output of the nucleus accumbens and projects to the lateral habenula (LHb) and

ventral tegmental area (VTA). The VP is thus poised to modulate the habenula-tegmental circuitry and contribute to processing rewarding and aversive stimuli. However, the VP is heterogeneous, and how VP subpopulations integrate into reward networks to modulate these behaviors is largely unknown. With neurochemical, genetic, and electrophysiology approaches, we identified a non-canonical population of glutamatergic VP neurons that play a unique role in responding to aversive stimuli and constraining inappropriate reward seeking. We performed patch clamp and in vivo electrophysiology recordings in the LHb and VTA to determine the effect of glutamatergic and GABAergic VP neuronal activation in these regions. We found that glutamatergic and GABAergic VP neurons are distinct populations. Glutamatergic VP neurons innervate and increase firing activity of the LHb, rostromedial tegmental nucleus (RMTg), and GABAergic VTA neurons. GABAergic VP neurons have a similar projection profile to glutamatergic VP neurons; however, activation of these neurons had complex and polysynaptic effects on downstream VTA neurons. We also investigated the behavioral role of glutamatergic and GABAergic VP neurons through optogenetic real time place preference tasks, operant conditioning, and conditioned taste aversion. While nonselective optogenetic stimulation of the VP induced a robust place preference, selective activation of glutamatergic VP neurons induced a place avoidance. Finally, selective ablation of glutamatergic, but not GABAergic VP neurons abolished devaluation of natural reward (sucrose) by pairing with an aversive stimulus (lithium chloride injection). Together, our results suggest that both excitatory and inhibitory VP neurons modulate activity of the LHb and VTA, which is necessary for expression of adaptive behavior in response to rewarding or aversive stimuli. Moreover, glutamatergic VP neurons play a unique role in aversion processing, while canonical GABAergic VP neurons promote reinforcement and encode the hedonic value of reward.

W12. Removal of Perineuronal Nets in the Medial Prefrontal Cortex Alters Cocaine Reinstatement and Excitability of Parvalbumin Fast-Spiking Interneurons

Emily Jorgensen, Travis Brown*

Our laboratory is interested in the molecular underpinnings that mediate pervasive drug memories. Perineuronal nets (PNNs) are specialized extracellular matrix structures that primarily surround parvalbumin-containing fast-spiking interneurons (FSI). Our research group previously published that removal of PNNs within the medial prefrontal cortex (PFC) attenuates cocaine-induced reinstatement of cocaine-conditioned place preference (cocaine-CPP) and increases the firing rate of pyramidal neurons within the prelimbic PFC. Our on-going research suggests that PNNs have a time-dependent effect on modulating firing activity of FSIs to influence pyramidal neuron activity. Rats

underwent cocaine-CPP training and extinction. After meeting extinction criteria, rats were microinjected into the prelimbic PFC 3d prior to cocaine-induced reinstatement with either vehicle or chondroitinase ABC (ch-ABC) to degrade PNNs. This procedure has shown to previously reduce cocaine-CPP. 2 hr following reinstatement, brain slices containing the mPFC were prepared for whole-cell electrophysiological recordings. PNN degradation resulted in an attenuation in the number of current-induced action potentials (APs) (vehicle: 99.0±7.31; ch-ABC: 53.33±1.43). In addition, we found significant changes in both the halfwidth and after-hyperpolarization potential (AHP) of APs in FSIs following ch-ABC treatment when compared to controls. Differences in these specific intrinsic properties suggest that there could be alterations in the currents responsible for the AHP and halfwidth. Through this work, we aim to further identify how PNNs are altering intrinsic and synaptic transmission following cocaine-associated learning, which contributes to persistent drug craving.

W13. Lack of GPR88 Alters Motivational Processing in Mouse Touchscreen Tests

Monica Langiu*, Michela H. Vermeulen, Greg Stewart, Christopher Langmead, Jess Nithianantharajah

GPR88 is an orphan G protein-coupled receptor expressed throughout the brain with high levels in the striatum, where it is localized in medium spiny neurons expressing D1 and D2 dopamine receptors. Human polymorphisms of the GPR88 gene have been linked to major psychosis in bipolar disorder and schizophrenia, and Gpr88 expression is regulated by antidepressant and mood-stabilizer treatments in both rodent models and humans. Work from Hamida et al. show that mice lacking the Gpr88 gene (Gpr88Cre/Cre) exhibit increased alcohol seeking behavior. In this study, we evaluated whether deletion of Gpr88 impacts motivational processing for appetitive stimuli using two rodent touchscreen tests, progressive ratio (with and without devaluation of the reward) and effort related choice. In these tests, animals are assessed for their ability to respond via nose-pokes to a stimulus displayed on a touchscreen for an appetitive liquid reward. Our findings suggest that Gpr88Cre/Cre mice have aberrant mesolimbic circuitry, consistent with Hamida's findings in alcohol consumption. Subsequently we analyzed gene expression and protein levels of key markers associated with production, metabolism and signaling of dopamine. Gpr88Cre/Cre mice displayed alterations in motivational processing however there were no detectable changes in the analyzed markers involved in the dopaminergic system, suggesting that non-dopaminergic pathways might be involved in this phenotype. These results extend that observed in alcohol seeking behavior and suggest GPR88 is important for the regulation of reward circuitry with a mechanism beyond dopaminergic signaling alteration.

W14. Genetic Dissection of Catecholaminergic Innervation of the Cognitive Cerebellum

Erik Carlson, Stefan Sandberg, Timothy Locke, Avery Hunker, Paul Phillips, Larry Zweifel*

Studies in primates have identified a region of the dentate nucleus of the cerebellum (DCN), or lateral nucleus in rodents (LCN), which is activated during performance of cognitive tasks. Previously, we showed that dopamine D1 receptor marks neurons in the LCN with similar spatial distribution and regulates cognitive performance on several tasks. Virtually nothing is known about the LCN's basic anatomical and functional organization. We hypothesized that the locus ceruleus (LC) is the source of both dopamine and norepinephrine release in LCN, that catecholamines are required for cerebellar enhancement of attention and working memory tasks, and act on LCN glutamatergic output neurons. Deletion of tyrosine hydroxylase (Th) expression in the LCN, results in abnormal performance on working memory behaviors, but not motoric ones. Thlox/lox mice (N = 7) were injected with CAV-Cre (retrograde virus) into LCN coordinates and trained on an FR1 schedule prior to starting either an impulsivity or a delayed alternation task. Littermate controls (N = 7) were injected with CAV2 encoding the fluorophore zsGreen (Cav2-zsGreen). Viral "hits" were verified by Western blot for Th protein from LCN tissue isolated by hole punch of a section of cerebellum. Th was reduced by 75% in the LCN with this manipulation. LCN Th knockout mice showed more impulsive pressing (or more failure to inhibit responses) than controls. LCN Th knockout mice showed a decreased rate of learning delayed alternation, and never achieved the same amount of success on the last day of testing. We found a remarkable parallel in that when we decrease neuronal excitability of glutamatergic LCN output neurons using DREADDs (N = 10 /group), learning of the working memory task is facilitated. Furthermore, we have mapped projections of the LC to LCN, and analysis has revealed distinct projections from the locus ceruleus, but no other nuclei known for producing catecholamines. When we injected DBH-IRES-Cre mice crossed with TdTomato mice with green retrobeads in LCN, we found overlap of the retrobeads and tomato staining, suggestive of LC projections to LCN. We did not see co-labeling in other noradrenergic or dopaminergic nuclei. When the LC is electrically stimulated, catecholamine release in the LCN is observed with fast scan cyclic voltammetry in anesthetized animals.

W15. Serotonin and Oxytocin Regulation of Social Approach/Avoidance Response After Social Defeat Conditioning

Luanne Hale, Maria Tickerhoof, Adam Smith*

Repeated social defeat (SD) can induce a chronic stress state, producing social avoidance behavior and heightened anxiety by dysregulating one of the major neuroendocrine stress pathways, the hypothalamic-pituitary-adrenal (HPA) axis. While current knowledge of the effects of SD on neurocognitive mechanisms is limited, studying the onset and persistence of defeat-induced effects in an animal model will allow insight to possible mechanisms that may play a role in socially avoidant behavior. In addition, selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants, are the most commonly prescribed drug treatments for individuals with social anxiety disorder, implicating that the neurotransmitter serotonin plays a role in symptomology or its relief. However, the effectiveness of SSRIs in treating anxiety disorders have been questioned. Oxytocin (OXT), a signaling peptide in the brain, can act to modulate the serotonin activity in both rodent and human brains. Our research group has developed an ethologically-relevant SD model in male and female prairie vole (Microtus ochrogaster) to study the effects of SSRI, OXT, and combination treatment on behaviors and neuroendocrine systems sensitive to defeat conditioning. By exposing male and female voles to repeated SD conditioning, we have characterized behavioral, hormonal, and neurochemical responses across various time points. The day following the last day of defeat, both males and females showed a strong social avoidance that persisted at least 8 weeks. When defeated voles were exposed to chronic peripheral treatment of an SSRI, there were no differences in social approach/avoidance behaviors. Animals that received a combination treatment of an SSRI and OXT displayed a statistical increase in social investigation when compared to vehicle treated defeated male and female voles. This treatment was effective in both male and female voles. This study demonstrates that males and females are sensitive to SD and that SSRI and OXT treatment is effective at alleviated the stress-induced social avoidance.

W16. Frontostriatal Circuit, Receptor and Neural Coding Mechanisms Underlying the Cognition-Improving vs. Cognition-Impairing Actions of Psychostimulants

Robert Spencer, Andrea Martin, Craig Berridge*

The prefrontal cortex (PFC) and extended frontostriatal circuitry play a critical role in higher cognitive function. Dysregulation of frontostriatal-dependent cognition is implicated in a variety of behavioral pathologies including addiction and ADHD. Psychostimulants are well known to exert

dose-dependent cognitive actions. Specifically, at higher doses associated with psychostimulant abuse, these drugs robustly impair frontostriatal-dependent cognition. In contrast, low-doses used in the treatment of ADHD, improve PFC-dependent cognitive function. Currently, our understanding of the neurocircuitry and neural coding bases for these diverse cognitive actions of psychostimulants are unclear. To address this, we infused various doses of MPH methylphenidate (Ritalin) into distinct nodes of the frontostriatal network. These studies revealed that MPH acts within the dmPFC to improve, but not impair working memory. Additional studies examined the MPH actions on task-related spiking activity of neurons in the dorsomedial PFC (dmPFC) and dorsomedial striatal (dmSTR) as well as changes in the power spectral density within these regions as measured with local field potentials (LFP). Cognition-impairing doses of MPH robustly suppressed the activity of dmPFC neurons strongly tuned to delay and reward, while activating neurons not tuned to correct tone. In contrast, in the dmSTR, cognition impairing doses of MPH had no effect on neurons strongly tuned to task events, while increasing firing of neurons not strongly tuned to these events. Interestingly, cognition-improving doses had a minimal impact on task-related firing of either PFC or striatal neurons. In terms of LFP spectral density during the delay, MPH elicited a dose-dependent decrease in theta (3-7 Hz) power in the PFC, but not the dmSTR. Cognition-impairing doses robustly increased high theta/alpha (7-12 Hz) and gamma (40-80 Hz) LFP oscillations in the PFC and dmSTR. These observations indicate that the cognition-improving vs. cognition-impairing effects of psychostimulants target different aspects of neuronal coding.

W17. EEG Correlates of Working Memory Gating: Link to Reinforcement Learning?

Rachel Rac-Lubashevsky, Yoav Kessler, Michael Frank*

Computational models of frontostriatal circuitry propose that the content of working memory (WM) is controlled through a selective gating mechanism which is modifiable by reinforcement learning. Information in WM is robustly maintained when the gate is closed; opening the gate enables updating. In the present study, a variant of the n-back task, the reference –back was used to learn about the mechanisms that underlie WM updating and gating in humans. The reference-back is composed of two trial-types: comparison trials, which require the maintenance of an item in WM, and reference trials, which require updating of this item. Switching between the two trial-types requires gating. EEG recordings were used to examine how the control functions involved in gating are mapped to different oscillatory activity. During gate-closing a relative increase in theta power was observed over mid-frontal electrodes. This mid-frontal theta response is a signature of cognitive control (Cavanagh & Frank; 2014) that is proposed here to reflect reactive updating conflict that is solved by

closing the gate to suppress updating irrelevant information. Conversely, during preparation time for gate-opening, a relative increase in posterior delta power was observed. These findings are reminiscent of reinforcement learning studies where posterior delta and mid-frontal theta power were correlated with negative and positive and prediction errors, respectively (Cavanagh, 2015; Cavanagh, Frank, Klein, & Allen, 2010). We propose that these analogous findings are suggestive of models and data in which WM gating strategies are learned by positive and negative prediction errors. Finally, preliminary multivariate decoding results of the EEG data, showing distinction between gate opening and gate closing will be presented and used to further test model predictions.

W18. Proactive Control, Reactive Control, and Impulsivity in the Imagen Data

Dan Scott, Michael Frank*

In this work we build on prior computational and empirical findings that identify two distinct contributors to impulsive behavior in frontostriatal circuitry. The first mechanism, elevated striatal dopamine, results in an imbalance in sensitivity to positive vs. negative decision outcomes. The second mechanism, dysfunctional communication between prefrontal cortex and subthalamic nucleus, results in a failure to adaptively pause or inhibit decision processes during difficult choices. We extend computational models of these phenomena and fit them to data from a large cohort (~2000 individual) longitudinal study (the IMAGEN data), to investigate control differences. Specifically, we fit a hierarchical Bayesian model of by-subject, reward-related reaction time speeding to data from a monetary incentive delay (MID) task, and a hierarchical Bayesian model (BEESTS) of response inhibition to data from a stop-signal task (SST). These models index striatal dopamine and inhibitory control, respectively, and the hierarchical Bayesian nature of the models optimizes the tradeoff between random and fixed effect analyses in capitalizing on group-level information. We use the parameter fits obtained to predict differences in neural data and impulsivity related questionnaire data, focusing on pre-established ROI's and subscales from the extensive literature in both tasks. The principal components of our stop task data index proactivity and established correlates of STN efficacy, as well as discounting and hyperactivity measures. We are also working to differentiate subjects with elevated ventral striatal reward prediction error signaling from subjects with reduced preSMA-IFC-STN activity during stop trials and to establish further links with task-based individual differences in proactive vs reactive control.

W19. Concussion Self-Management Concepts Among United States Air Force Academy Cadets

Michelle Weber, Brian Johnson, Johna Register-Mihalik, Karin De Angelis, Julianne Schmidt, Christopher D'Lauro*

Concussions have gained significant interest among neuroscience, medical, and lay communities. Service members are at a particular risk for sustaining concussions. The purpose of this study was to qualitatively examine factors that influence United States Air Force Academy cadets' decision to report or conceal a concussion, building off considerable prior quantitative work in the same population. Thirty-four anonymous interviews were conducted in April 2018 (18 with concussion history, 16 without concussion history). We followed a five-cycle analysis process of: topic review, performing a literature review, collecting data and summarizing the data utilizing a codebook developed by a four-person research team, linking findings to current research, and making final interpretations. Following this process, eight themes were identified. This abstract focuses on the self-management theme and subthemes. USAFA cadets frequently described aspects of self-management meaning they would try to treat the injury themselves before seeking care from a health care provider. Subthemes within self-management included delayed treatment, incorrect treatment, report to get better, the severity of the injury, who cadets could report to, and symptom duration. Cadets detailed that they would wait a period of time before seeking advice about a potential concussion first to a friend or advocate before seeking medical treatment from a health care provider. During that time, cadets described they would take medication, however medication mentioned is usually not prescribed immediately following injury and may be dangerous.

Education for cadets should include a focus on appropriate concussion treatment and benefits of seeking care. This focus should reinforce that all concussions require medical care, regardless of the duration of symptoms, and the sooner one obtains medical care the sooner they return to activity. Increasing concussion reporting can aid in decreasing prolonged recovery.

W20. Maternal Nicotine's Effects on Learning and Memory in Adolescent Mice

*Celina Mojica, Yu Bai, Shahrdad Lotfipour**

Maternal nicotine exposure influences over 314,000 adolescents per year in the United States alone. This accounts for over $100 million dollars in healthcare costs associated with maternal tobacco smoking during pregnancy. The long-term consequences of maternal tobacco exposure in offspring are related to hyperactivity, learning, memory and addictive disorders. The basic mechanisms mediating these effects are unknown.

Out of the 8000-plus constituents in tobacco smoke, nicotine is considered the primary psychoactive component mediating the long-term consequences of maternal tobacco exposure in offspring. Binding to a range of nicotinic acetylcholine receptors (nAChRs) (alpha1-10, beta1-4, encoded by the Chrna1-10 and Chrnb1-4 genes), nicotine can modulate the release of neurotransmitters to influence long-term neurobehavioral alterations in offspring. We have recently discovered that alpha2 nAChRs are necessary and sufficient for nicotinic-facilitation of synaptic and behavioral plasticity in adolescent rodents. These receptors are expressed in distinct regions of the brain, including the oriens lacunosum-moleculare GABAergic interneurons within the CA1 hippocampus. The objective of our current studies delineates whether the deletion of Chrna2 subunit eliminates the long-term cognitive effects of maternal nicotine exposure on learning and memory in adolescent offspring. The methods used in our current studies include: (i) wild type and genetically modified alpha2 nAChR null-mutant (Chrna2KO) mice and (ii) a learning and memory behavioral assay called pre-exposure dependent contextual fear conditioning. Our results demonstrate that maternal nicotine exposure delays extinction learning in adolescent wild type mice, which is abolished in Chrna2KO mice. These effects are not influenced by sensory, locomotor or anxiety-related behaviors. In conclusion, the findings provide evidence for a distinct molecular genetic target underlying the learning and memory effects of maternal nicotine exposure in adolescent offspring.

W21. Real-Time Striatal Measurements of Oxidative Stress and Dopamine in Hemiparkinsonian Rats Expressing L-Dopa Induced Dyskinesias

Leslie Sombers, Leslie Wilson, Catherine Mason, Christie Lee, Greg McCarty*

Parkinson's disease is a neurodegenerative disorder commonly treated with levodopa (L-DOPA), which eventually induces abnormal involuntary movements (A.I.M.s). The neurochemical contributors to these dyskinesias are unknown; however, evidence indicates interplay of dopamine (DA) and oxidative stress. Here, we simultaneously monitored real-time DA and hydrogen peroxide (H2O2) fluctuations with fast-scan cyclic voltammetry. This was done bilaterally in the dorsal striatum of control and hemiparkinsonian rats after L-DOPA administration. Infrared matrix-assisted laser desorption electrospray ionization mass spectrometry imaging validated the lesions. In hemiparkinsonian rats, DA and H2O2 tone increased during A.I.M.s after one week of treatment. This was abolished by the third week. However, rapid chemical fluctuations were precisely correlated with involuntary bouts of rotation induced by L-DOPA administration. H2O2 increased and DA

concentrations recorded at the same location simultaneously decreased with rotation onset. These results help clarify how oxidative stress can modulate nigrostriatal DA signaling, and the behavioral consequences of this interaction.

W22. (-)-Phenserine (Phen): Prevention of Pre-Programmed Cell Death (PPCD) in Mild Traumatic Brain Injury (mTBI) and Alzheimer's Disease (AD)

*Daniela Lecca, Miaad Bader, David Tweedie, Barry Hoffer, Chaim Pick, Robert Becker, Nigel Greig**

mTBI is a risk factor for AD. TBI-derived neuropathologies both initiate and are potentiated by inflammatory processes: chronic microgliosis/pro-inflammatory cytokine release promote neuronal dysfunction and loss. Herein, we evaluated the anti-apoptotic, anti-inflammatory and synapse sparring actions of (-)-Phenserine (Phen), an anticholinesterase originally developed for AD, in a weight drop mTBI model in wild type (WT) and AD APP/PSEN1 (AD) mice.

Clinically translatable Phen doses (2.5 & 5.0mg/kg, BID) mitigated mTBI-induced neurodegeneration in hippocampus (HIP) and cerebral cortex (CTX). mTBI-induced pre-programmed cell death, assessed by Fluorojade C cell counts, was fully mitigated by Phen in WT mice. Degenerating cell counts were greater across all experimental groups in AD vs. WT mice, and Phen likewise mitigated mTBI-induced elevations in AD mice. Anti-inflammatory changes in microglial activation (IBA1-immunoreactivity (IR)) and TNF-α were evaluated. mTBI increased IBA1-IR in mTBI vs. controls in WT and AD mice. In WT mice, Phen inhibited microglial activation throughout HIP/CTX. A similar trend was evident in AD mice; reaching statistical significance in HIP. TNF-α-IR was increased in IBA1+ cells by mTBI in WT and AD mice. Phen reduced levels of IBA1/TNF-α-IR co-localization across all areas in WT, with a strong trend in Phen-treated AD mice. Synaptic viability was evaluated by counting PSD-95-positive dendritic spines, which were significantly reduced by mTBI in both WT and AD mice. Phen fully counteracted this in WT, with a strong trend in Phen-treated AD mice.

Clinically translatable doses of Phen ameliorated mTBI-instigated pre-programmed cell death/neuroinflammation/synaptic loss in WT mice, consistent with fully mitigating mTBI-induced cognitive impairments (assessed at 7 days by novel object recognition and Y-maze paradigms in separate animals). Phen demonstrated positive actions in the more toxic brain microenvironment of AD mice. These pharmacological actions were not associated with anticholinesterase activity, which was washed out prior to the above evaluations. In the light of these results and Phen's tolerability and efficacy in AD subjects (Winblad et al., 2010), it can rapidly be repurposed for appraisal as a new mTBI treatment and warrants further evaluation in AD.

W23. Neuroimmune and Epigenetic Mechanisms Regulate Adult Loss of Cholinergic Neurons Following Adolescent Binge Ethanol Treatment

Fulton Crews, Ryan Vetreno, John Bohnsack, Subhash Pandey*

Binge drinking and alcohol abuse are common during adolescence and cause lasting pathology. Preclinical studies using adolescent intermittent ethanol (AIE; 5.0 g/kg, e.g., 2-day on/2-day off from postnatal day [P]25 to P55) rat exposure find decreased cholinergic (ChAT+IR, vChAT+IR) neuron populations that persist into adulthood, e.g. P56 to P220. Endotoxin mimics AIE induced loss of ChAT+IR and AIE combined with exercise or the anti-inflammatory drug indomethacin prevent loss of ChAT+IR. Recent studies have suggested persistent AIE neuropathology was linked to neuroimmune and epigenetic signaling. We report here that the AIE induced loss of cholinergic neuron markers (i.e., ChAT, TrkA, and p75NTR) and cholinergic neuron shrinkage, as well as neuroimmune marker pNF-kB p65+IR are reversed by exercise. Potential progenitor formation of new ChAT+IR cells was determined using BrdU and no new neurons were found following AIE and exercise. DNA methylation can silence gene expression. AIE caused a persistent increase in adult methylation of promoter regions of both the ChAT and TrkA gene. Wheel running following AIE restored the AIE-induced loss of ChAT, TrkA, and p75NTR levels as well as of reversal learning deficits on the Morris water maze. Together, these data suggest AIE induced adult neuroimmune signaling and cognitive deficits are linked to suppression of ChAT and TrkA gene expression through persistent epigenetic methylation that can be reversed by exercise. Exercise reversal of the persistent AIE-induced phenotypic loss of cholinergic neurons is a novel mechanism of neuroplasticity with new therapeutic targets.

W24. Characterization of the VPS35 p.D620N Knock-In Mouse Model of Parkinson's Disease

Stefano Cataldi, Jordan Follett, Igor Tatarnikov, Jesse Fox, Chelsie Kadgien, Jaskaran Khinda, Austen Milnerwood, Matthew Farrer*

Parkinson's Disease (PD) affects approximately 1% of the population by 65 years increasing to 4-5% by 85 years. PD is a multifactorial disorder that arises due to a combination of genetic predisposition, environmental factors, and failure of age-associated compensation. Vacuolar protein sorting 35 (VPS35) p.D620N is genetically linked to autosomal-dominant parkinsonism (Vilariño-Güell, 2011; Zimprich, 2011), a syndrome clinically indistinguishable from late-onset PD (Struhl, 2014). VPS35 is a core component of the retromer system which regulates sorting of proteins from endosomes to lysosomes, the trans-Golgi network, or the plasma membrane. Cargos include CIM6PR, β2 and AMPA receptors (Bhalla, 2012; Choy, 2014; Harbour, Breusegem,

& Seaman, 2012; Munsie, 2015; Tsika, 2014). To study the physiological consequences of VPS35 p.D620N we engineered the mouse genome to constitutively express the VPS35 p.D620N missense mutation. Characterization of gene expression and retromer components compared to their wild type C57BL/6J littermates shows the expression and stoichiometry of retromer core subunits is unperturbed. Mice were tested in standardized behavioral tests at 3 and 18 months. Motor activity, cognitive abilities, and fear-related behaviors were evaluated. At 3 months mutant mice exhibited increased fear-related behavior compared to wild type littermates, and show altered learning abilities, but do not show significant locomotion alterations. At 18 months, cognitive alterations are still present, yet without apparent motor changes. At 3 months ex vivo fast scan cyclic voltammetry was conducted to assess nigrostriatal dopamine (DA) function. Electrically stimulated DA release was significantly elevated in brain slices prepared from young mutant mice, and pharmacological responses to DA agonist were also altered. In vivo microdialysis, shows no differences in extracellular levels, suggesting alteration in fast release rather than DA activity over all. Dopamine transporters levels are altered at this age, while tyrosine hydroxylase (TH) appears unaltered. The differential synaptic-endosomal, DAergic, and behavioral phenotypes observed at early and late stages in this knock-in model of VPS35 parkinsonism provide insight into the underlying pathophysiology of prodromal PD.

W25. Diurnal Fluctuations of Perineuronal Nets in the Prefrontal Cortex

John Harkness, Priyanka Bushana, Angela Gonzalez, Vanessa Real, Barbara Sorg*

Extracellular matrix aggregations called perineuronal nets (PNNs) surrounding synapses of fast-spiking, parvalbumin-containing GABAergic interneurons 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. We have previously shown that PNN intensity fluctuates with memory, experience, and drug exposure. Here, we investigated whether PNN intensity also fluctuated throughout diurnal 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. In combination with previous results, these data indicate that PNN, PV, and oxidative stress intensity fluctuate throughout the sleep/wake cycle, and that

diurnal fluctuations in PNN intensity could be important to other effects of PNNs on learning, memory, and behavior. Grants: WSU Postdoctoral Alcohol and Drug Abuse Research Program grant, NIH DA 033404, and NIH DA 040965.

W26. ACEA Chronic Administration Failed to Prevent Tumor Growth in an Ectopic Ovarian Cancer Model

*Henry Blanton, Isabel Castro, Jose-Luis Redondo, Kevin Pruitt, Daniel Morgan, Josee Guindon**

Ovarian cancer is the fifth and deadliest leading cause of gynecologic cancer among women, with cancer care associated costs reaching $173 billion in the US as projected by 2020. And so there is an urgent need for novel analgesics to treat cancer and chemotherapy-induced chronic pain. The therapeutic use of cannabinoid-based therapies by cancer patients for their analgesic and antiemetic properties has been increasing, but the impact of long-term cannabinoid-based therapies on tumor growth in the context of chemotherapy-treatment and/or cancer remains to be determined. This translational project will investigate the role of cannabinoid agonist 1 (ACEA) therapy in alleviation of pain, estrous cycle and estradiol changes and tumor growth in a xenograft ectopic ovarian cancer model. Preliminary results from our laboratory suggest that xenograft ectopic inoculation of OVCAR-5 (1x106 cells per 1 ml subcutaneous) cancer cells grow (from 0 to 32 days) steadily and exponentially better in SCID relative to NuNu mice without development of mechanical (digital von Frey) and cold(acetone) allodynia. After 32 days of ectopic OVCAR-5 cancer cells growth, we administered daily a CB1 agonist (ACEA 0.5 mg/kg i.p.) in SCID mice shows increase in tumor volume (mm3) similar to vehicle treated animals. ACEA failed to prevent tumor growth in our ectopic ovarian cancer model in both SCID and NuNu mice. We also observed following chronic administration of ACEA changes in estrous cycle to the metestrus phase and decrease in estradiol levels in chemotherapy-induced pain. Further studies are needed to evaluate a potential time and/or dose-dependent effect in ACEA failing to prevent tumor growth. This study confirms the need for in vivo preclinical studies to improve our understanding and investigate further the role of cannabinoid agonists in tumor growth and changes in estrous cycle in ovarian cancer.

W27. Improving Outcomes for Treatment-Resistant Schizophrenia: The Efficacy of ECT in Clozapine-Refractory Patients

Sana Ali, George Petrides, Jian-Ping Zhang, Taylor Marzouk, Philip Watson, Raphael Braga, Miklos Argyelan, Anil Malhotra*

Background: Electroconvulsive therapy (ECT) is a remarkably effective treatment for depressive disorder but is less commonly utilized in psychotic disorders including schizophrenia. We recently conducted a systematic review (Ali et al, in press) and determined that ECT can also be an effective treatment with minimal cognitive side effects in treatment-resistant schizophrenia. Of note, our group found (Petrides et al. 2015) that, even in patients who had previously failed treatment with clozapine, there was a 50% response rate with the addition of ECT to clozapine. Therefore, we are now conducting a neuroimaging study of ECT in clozapine-resistant schizophrenia to determine biomarkers of treatment response to this novel strategy. Methods: To date, we have enrolled 13 subjects (4F, 9M; mean age = 37.1 yrs) into an 8 week clinical trial of the effectiveness of ECT augmentation in patients who had failed clozapine. Inclusion criteria require the subject to be currently treated with clozapine, with a documented plasma level of >350 ng/ml, and a rating of at least 4 on one of the 3 item Brief Psychiatric Rating Scale (BPRS) positive symptoms scale. Patients are then treated for 8 weeks with bitemporal ECT or until clinical response is achieved. Results: To date, eleven patients have completed the course of treatment. Mean baseline BPRS total score was 42.8; subjects had a mean of 13 ECT treatments; mean total BPRS rating at endpoint was 35.5. No significant effects were observed on the MATRICS composite index of cognitive function nor were any major adverse events observed. Preliminary neuroimaging data are currently being analyzed.

Conclusions: These data, coupled with the prior evidence from previous studies, suggest that ECT augmentation of clozapine treatment can be a remarkably effective treatment for severely ill patients with schizophrenia. However, these approaches are vastly underutilized; less than 3% of patients receive either treatment in the U.S. Our future aim is to use neuroimaging to identify biomarkers that may provide predictive biomarkers of response, in order to bring about a "precision medicine" strategy to the treatment of this underserved population.

W28. Anesthesia Alters Neuronal Interactions Across the Hierarchy of Rat Visual Cortex

Anthony Hudetz, Siveshigan Pillay, Shiyong Wang, Heonsoo Lee*

Introduction: Conscious perception may be supported by recurrent information processing across hierarchically organized regions of the cerebral cortex. Anesthetics may suppress consciousness by interrupting the feedback arm of long-range recurrent communication. Does this suppression also occur in local circuits of modality-specific sensory cortex? We investigated this question by taking advantage of the layer-specific anatomical segregation of feedforward and feedback pathways in visual cortex. Methods: Microelectrode arrays consisting of 32 microwires (33um diameter, 250um/375um spacing) were chronically implanted in the visual cortex of 10 rats. Recording sites targeted supragranular (shallow) and infragranular (deep) layers of both primary (V1) and secondary (V2) visual regions. Extracellular unit activity was recorded in wakefulness and during administration of the anesthetic desflurane at 2%, 4%, 6%, 8% inhaled concentrations (rats lose consciousness at 6% desflurane). Sorted spikes were binned at 1, 4 and 10 ms time bins and the coincident spike configurations (unitary patterns) were enumerated to calculate spike population entropy, mutual information (MI), and transfer entropy (TE) in and among regions. Results: Desflurane dose-dependently decreased MI between V1 and V2 and between shallow and deep layers. It also decreased TE from shallow to deep layers in V1 and from V2 to V1 at the deep sites (presumably layer 5) implying suppression of feedback. Conclusions: Desflurane anesthesia interferes with layer-selective local neuronal communication within the hierarchy of rat visual cortex. The findings are consistent with anesthetic suppression of cortical recurrent information processing that may contribute to loss of consciousness. Acknowledgments: Supported by the National Institute of General Medical Sciences of the National Institutes of Health, Bethesda, Maryland, USA, award number R01-GM056398, and by the Department of Anesthesiology, Center for Consciousness Science, U of M.

TH1. Incubation of Discriminative-Stimulus-Controlled Cocaine Craving During Abstinence

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Background: Environmental stimuli paired with drug use can provoke craving and relapse in humans, and elicit cocaine seeking in rats. Previous studies in rats have shown that drug seeking can incubate (i.e., increase over weeks of abstinence) in response to discrete cues, but not to the contextual cues. To our

knowledge, incubation of the response to discriminative stimuli (DSs) has not been evaluated. Methods: In experiment 1, using a trial-based discrimination procedure, we trained rats (8 male, 8 female) to self-administer cocaine (0.75 mg/kg/infusion) during a positive discriminative stimulus (DS+) signaling cocaine availability, and to suppress responding on the same lever during a negative discriminative stimulus (DS-) signaling cocaine unavailability. Drug infusions were not paired with discrete CSs. After discrimination training, DS-controlled cocaine seeking was assessed after 1, 21, 60, 120, 200, 300 and 400 days of abstinence, and finally, after noncontingent priming injections of cocaine (10 and 20 mg/kg). In experiment 2, we trained rats (8 male, 8 female) to self-administer palatable food pellets using a similar procedure and assessed DS-controlled food seeking after 1, 21, 60, 120, and 200 days of abstinence. Results: In experiment 1, we observed incubation of DS-controlled cocaine seeking, which peaked at 60 days and persisted up to 300 days of abstinence. Additionally, priming cocaine injections reinstated DS-controlled seeking after 400 days. In experiment 2, DS-controlled relapse to palatable food seeking peaked on day 1 of abstinence and progressively decreased over time. Conclusions: Reward seeking controlled by cocaine- but not food-DSs incubates during abstinence.

TH2. Impact of Gut Dysbiosis on Cocaine-Seeking in Adolescent and Adult Male Rats

Gregory Suess, Jennysue Kasiah, Benoit Chassaing, Kyle Frantz*

Research on the gut-brain axis has revealed that gut dysbiosis is associated with several psychiatric disorders, including substance abuse. We hypothesize that adolescent vulnerability to drug-related reward and reinforcement might also be related to gut dysbiosis. Using a cocktail of antibiotics in the drinking water of male Wistar rats, we sought to determine whether reduced abundance of bacteria in the gut heightens intravenous cocaine self-administration. Adolescent and adult male rats were given two weeks of antibiotic exposure, fecal samples were collected, DNA was extracted, and qPCR was conducted to assess changes in the gut microbiota. Simultaneously, animals acquired lever-pressing in operant conditioning chambers using a white noise training procedure, followed by cocaine self-administration under fixed ratio and progressive ratio schedules of reinforcement. Following forced abstinence, animals underwent extinction and cue-induced reinstatement testing. At sacrifice, peripheral organs were extracted to test for correlations between gross anatomy or inflammation with age, antibiotic treatment, and cocaine intake levels. Body mass and water intake were normal in both age groups, but the antibiotic cocktail decreased bacterial abundance to a greater degree in adolescents compared to adults. Cecum mass and size were greater in all antibiotic treated animals, compared to age-matched controls, and a further

increase was associated with cocaine intake in adults but not adolescents. Gut dysbiosis did not alter cocaine intake during acquisition, but several animals on antibiotics reached high levels of lever pressing during progressive ratio testing. We predict that lower rates of cue-induced reinstatement among adolescents reported previously may be raised closer to adult counterparts when antibiotics are introduced. Together, these results suggest new avenues for treatment of addiction through improved gut health.

TH3. Sexual Divergence in Reward and Immune Responses Following Experimental Adolescent Traumatic Brain Injury

Lee Anne Cannella, Allison Andrews, Roshanak Razmpour, Hannah McGary, Cali Corbett, Servio Ramirez*

The pathology of traumatic brain injury (TBI) adversely affects many brain regions, often resulting in the development of comorbid psychiatric disorders including substance use disorders (SUD). Although traditionally thought to be an epidemic that predominantly affects males, recent epidemiological studies report females have higher rates of concussions and longer recovery times than males. Yet, how neurotrauma-induced molecular changes affect brain structures essential for reward perception remains unknown. Importantly, the risk of TBI peaks during adolescence when neuronal networks that regulate reward behaviors are not fully developed. Previously, using the conditioned place preference (CPP) assay, we found that adolescent TBI increased the susceptibility to the rewarding effects of 2.5 mg/kg and 10 mg/kg cocaine in male mice. Further, we observed augmented inflammatory profiles, increased microglial phagocytosis of neuronal proteins, and decreased neuronal spine density in brain regions associated with reward. Thus, we hypothesize that adolescent TBI-induced neuroinflammation in areas such as prefrontal cortex and nucleus accumbens (NAc) results in remodeling of neuronal reward networks and affect how the rewarding effects of cocaine shift as a consequence of TBI. Notably, the extent of sex differences in SUD susceptibility following TBI has not be investigated. Thus, here we ask the central questions of whether adolescent TBI-induced neuroinflammation alters maturation of reward neurocircuits, leading to increased SUD vulnerability in a sex-dependent manner. We used the CPP assay after adolescent TBI in female mice and utilized vaginal cytology to measure estrous cycle at the time of injury. Adolescent TBI female mice did not demonstrate increased sensitivity to the rewarding effects of any dose of cocaine tested (1.25, 2.5, 10, 30 mg/kg). Interestingly, we also found significantly reduced microglial activation and phagocytosis of neuronal proteins within NAc of females. These studies begin to offer crucial insight into our understanding of how sex differences affect adolescent TBI-induced inflammatory responses and vulnerability to addiction-like behavior.

TH4. Sigma-1 Receptor Control of Extracellular Vesicle Release and Cocaine-Induced Endocannabinoid Signaling in the Ventral Tegmental Area (VTA)

Dilyan Dryanovski, Yoki Nakamura, Tsung-Ping Su, Carl Lupica*

Endogenous cannabinoids (eCB) are signaling lipids released from neurons to retrogradely activate cannabinoid CB1 receptors (CB1R) located on axon terminals of presynaptic cells to limit neurotransmitter release. The eCB associated with activity dependent modulation of synapses is 2-arachidonoylglycerol (2-AG). 2-AG synthesis is triggered by activation of Gα/q11-coupled metabotropic receptors through activation of phospholipase C-β (PLCβ), which hydrolyzes membrane phospholipids to form 1,2-dacylglycerol (DAG) and inositol triphosphate (IP3). DAG is converted to 2-AG via diacylglycerol lipase-α (DGLα), whereas IP3 can elevate cytosolic Ca2+ by stimulating its release from endoplasmic reticulum (ER). Increasing the cytosolic calcium concentration can further increase the synthesis of 2-AG. The Sigma-1 receptor (σ1R) resides on the mitochondria-ER interface membrane, serving as a protein chaperone, and conferring a conformation of the IP3 receptor that sustains Ca2+ signaling. Under basal conditions, the σ1R is bound to ADP-ribosylation factor 6 (ARF6), however, cocaine binds to σ1R and releases ARF6. Recent evidence suggests that cocaine stimulates synthesis of the endocannabinoid 2-arachidonoylglycerol (2-AG) in midbrain, increasing DA neuron activity via disinhibition. Although a mechanism for cocaine stimulation of 2-AG synthesis is known, our understanding of 2-AG release is limited. Here, we describe a mechanism whereby 2-AG is localized in non-synaptic extracellular vesicles (EVs) that translocate when cocaine binds to the σ1R. This occurs when the inhibition of EV release is relieved by dissociation of the σ1R from ARF6, leading to activation of myosin light chain kinase (MLCK). Eliminating the σ1R, inhibiting its activity, or blocking ARF6 or MLCK prevented the cocaine-induced EV release and cocaine-stimulated 2-AG modulation of inhibitory synapses in DA neurons. Our results implicate the σ1R-ARF6-MLCK pathway in control of EV release and demonstrate that cocaine-mediated 2-AG release occurs via this mechanism.

TH5. C-terminus Phosphorylation of Mu-opioid Receptor Regulates Acute and Chronic Sensitivity to Opioids

Sweta Adhikary, Stefan Schulz, John Williams, William Birdsong*

Opioids produce both pain relief and reward through agonist activity at the mu-opioid receptor (MOR). Long-term opioid use results in development of tolerance. Receptor tolerance can develop by decreasing signaling through opioid receptors and cellular tolerance can develop through downstream processes like the upregulation of adenylyl cyclase. Phosphorylation of

multiple serine and threonine residues leads to rapid MOR desensitization, but the initial molecular mechanisms underlying tolerance remain unsolved. Phosphorylation-deficient mice with alanine mutations to 10 serine (S) and threonine (T) residues in the C-terminus of MOR (10S/T-A) were used to examine the role of phosphorylation in mediating tolerance to presynaptic inhibition by opioid agonists. Glutamate projections from the medial thalamus to the dorsal striatum were isolated using an optogenetic approach in wild type and MOR 10S/T-A mice. Optically evoked thalamo-striatal EPSCs were recorded in brain slices containing the dorsal medial striatum following stereotaxic injection of AAV2 CsChR into the medial thalamus. Both the high efficacy agonist, [Met]5enkephalin and the partial agonist, morphine reduced EPSCs in both genotypes and the inhibition was greater in 10S/T-A mice. Full agonists like DAMGO and ME robustly desensitize MOR in the postsynaptic compartment resulting in decrease signaling, but less is known about desensitization in the presynaptic compartment. A saturating concentration of DAMGO (10 μM) produced presynaptic inhibition of EPSCs which was reversed by naloxone. There was no decline in the inhibition by DAMGO over 10 minutes suggesting that presynaptic MORs do not acutely desensitize in either mouse line. To investigate the role of receptor phosphorylation on tolerance to opioids, mice were chronically treated with morphine for six to seven days using an osmotic mini-pump. Chronic morphine treatment decreased morphine-induced inhibition in WT mice but not in 10S/T-A mice suggesting that phosphorylation mediates receptor tolerance after long term opioid use, even without acute desensitization.

TH6. Cell Type Specific Control of Basolateral Amygdala Plasticity via Entorhinal Cortex Driven Feedforward Inhibition

Ethan Guthman, Ming Ma, Philip Chu, Serapio Baca, Diego Restrepo, Molly Huntsman*

The basolateral amygdala (BLA) plays a vital role in associating specific sensory stimuli with salient valence information. Excitatory principal neurons (PNs) undergo plastic changes to encode this integrated sensory-valence information; however, local BLA inhibitory interneurons (INs) gate the plasticity of the PNs via feed forward inhibition (FFI). Despite extensive literature implicating parvalbumin expressing (PV+) INs in FFI in cortex and hippocampus, prior anatomical experiments in BLA implicate somatostatin expressing (Sst+) INs. The lateral entorhinal cortex (LEC), a brain region carrying information on odors projects to BLA where it drives FFI. In the present study, we asked whether input from LEC mediates plasticity in BLA and explored the role of interneurons in this circuit. We combined patch clamp electrophysiology, chemogenetics, unsupervised cluster analysis, and predictive modeling and

found that a previously unreported subpopulation of fast-spiking Sst+ INs mediate LEC-->BLA FFI and gate plasticity. Our study raises the question whether this novel Sst+ IN FFI circuit is involved in plasticity in olfactory learning, and future experiments will test this hypothesis in awake, behaving animals.

TH7. Dorsal Raphe Dual Serotonin-Glutamate Neurons Drive Reward by Establishing Excitatory Synapses on VTA Mesoaccumbens Dopamine Neurons

Huiling Wang, Shiliang Zhang, Jia Qi, Huikun Wang, Roger Cachope, Carlos Mejias-Aponte, Jorge Gomez, Gabriel Gabriel Mateo Semidey, Gerard Beaudoin, Carlos Paladini, Joseph Cheer, Marisela Morales*

Dorsal raphe (DR) serotonin neurons provide a major input to ventral tegmental area (VTA). In the present study, we examined the ultrastructural and molecular characteristics of the synaptic connectivity between DR serotonin neurons and VTA dopamine neurons, and determined the role of these synapses in behavior. (1) By ultrastructural studies, we found that DR serotonin neurons (expressing serotonin transporter, SERT) establish both symmetric and asymmetric synapses on VTA dopamine neurons. (2) Surprisingly, we found that axon terminals from DR-SERT neurons that make asymmetric (putative excitatory) synapses on VTA dopamine neurons co-express vesicular glutamate transporter 3 (VGluT3, transporter for accumulation of glutamate into synaptic vesicles). These findings suggest that a subset of DR dual SERT-VGluT3 neurons establish excitatory synapses on VTA dopamine neurons. (3) By tract tracing approaches, we found that dual SERT-VGluT3 neurons establish asymmetric synapses on VTA dopamine neurons that innervate the nucleus accumbens (nAcc), suggesting that release of glutamate from SERT-VGluT3 terminals have the capability to activate mesoaccumbens dopamine neurons. (4) By VTA photoactivation of fibers from DR-SERT neurons, we found that this activation elicits excitation of mesoaccumbens dopamine neurons, induces release of dopamine in nAcc, and promotes conditioned place preference (CPP). (5). Because we have previously demonstrated nAcc dopamine release and a robust reinforcing effect by VTA glutamate release from DR VGluT3-fibers (Qi et al., 2014. Nat Comm), we compared these effects with those mediated by DR SERT-fibers. We found that the amount of dopamine release and CPP induced by VTA activation of SERT-fibers are lower than those induced by activation of VGluT3-fibers. However, CPP induced by activation of SERTfibers is more resistant to extinction when compared to the CPP induced by activation of VGluT3-fibers.

TH8. Stress and Drugs of Abuse Alter GABAergic Transmission in the Ventral Tegmental Area via Chloride Cotransporter KCC2 Downregulation

Alexey Ostroumov, Alyse Thomas, Blake Kimmey, William Doyon, John Dani*

Stress and drugs of abuse trigger or modulate multiple forms of synaptic plasticity within the dopamine (DA) system, leading to maladaptive behaviors. Although glutamatergic synaptic plasticity is most commonly studied, there is a growing appreciation that inhibitory synapses also undergo plasticity and regulate circuit function and adaptability. Our findings indicate that exposure to acute stress or nicotine downregulates neuron-specific anion transporter, KCC2, leading to a depolarized GABAA reversal potential in ventral tegmental area (VTA) GABA neurons. The depolarized GABAA reversal potential results in a decreased synaptic inhibition or even paradoxical GABAergic excitation of GABA neurons. Compromised inhibition alters DA signaling in the VTA and the nucleus accumbens, linking synaptic plasticity to circuit-wide modifications. At the behavioral level, decreased KCC2 function and excitatory GABA signaling in the VTA mediate increased stress or nicotine-induced ethanol self-administration. Our most recent, unpublished data demonstrate that acute, in vivo injections of cocaine, morphine, and ethanol converge onto the GABAergic circuitry of the VTA. Like stress, these addictive drugs trigger KCC2-dependent depolarizing shift in the GABAA reversal potential in VTA GABA neurons. In summary, our studies demonstrate that exposure to stress or drugs of abuse trigger a currently understudied form of GABAergic synaptic plasticity in the mesolimbic circuitry.

TH9. Investigating Accumbal Encoding of Effortful Behavior

Bridget Matikainen-Ankney, Lex Kravitz*

NAc neural mechanisms are altered during obesity, a disease that is a leading cause of preventable death among Americans. Yet despite evidence from human imaging studies suggesting the NAc is involved in forceful behavior, rodent studies of the role of the NAc in physical activity have largely been limited to speed to initiate a response or frequency of lever presses to obtain a reward, a measure of persistence. Very few studies have examined the kinematics of motion itself, such as the force or speed with which a reward lever is pushed. Thus it is not known how the NAc encodes effort or vigor. Here we hypothesize that the NAc encodes effortful actions. To investigate how endogenous NAc activity may underlie this behavior, we use lines of transgenic mice expressing cre-recombinase in either direct- or indirect-pathway NAc neurons, and viral delivery of cre-dependent GCaMP6s (AAV-DJ-GCaMP6s), with fiber optics implanted into the NAc and cemented onto the skull. Mice are trained on a

behavioral device we developed to exert varying degrees of force to achieve a palatable reward. NAc GCaMP6s fluorescence and force output readings are recorded in tandem, and changes in force overtime are integrated with neural responses to delivery of reward. Preliminary data shows that average NAc GCaMP6s signal appears to increase during forceful interaction, suggesting NAc neurons encode force output, or effortful actions. These findings may provide a platform to investigate how this circuitry may be altered in obesity.

TH10. Adaptive Immune Signaling at the Meningeal Barrier: Neuroimmune Interactions Underlying Stress-Induced Mood Disruption

Miles Herkenham, Samuel Listwak, Virginia Sun, Elkahloun Abdel, Michael Lehmann, Kigar Stacey*

Major depressive disorder (MDD) is correlated with increased peripheral inflammation, but basic mechanisms by which the immune system influences the brain under these conditions remain largely unknown. The blood brain barrier (BBB) in particular prevents free exchange of peripheral immune signals with the brain; however, CD4+ T (Th) cell lymphocytes are found in human cerebrospinal fluid (CSF) under homeostatic conditions, indicating that they normally extravasate across the BBB to gain access to this brain compartment. Although present in the CSF, Th cells do not reside in healthy brain parenchyma and must therefore transmit information to parenchymal cells indirectly. Greater understanding of this process is critical to exploit peripheral immunity for MDD treatment. The meninges envelop the brain as part of the BBB, contain a large population of immune cells (monocytes, macrophages, lymphocytes, and granulocytes), and confine the CSF in subarachnoid spaces. They are therefore a key interface between the peripheral immune system and the brain. Our hypothesis, supported by flow cytometric, bioinformatic, and immunohistochemical analyses, is that Th cells are recruited to the meninges to facilitate the repair of neurovascular damage accumulated during stress. Once inside, they release signaling factors that alter neurobiology. To test this hypothesis, we used chronic social defeat (CSD) stress in mice, which induces depressive- and anxious-like behavior, elevates markers of peripheral inflammation, and produces scattered cerebral microbleeds. We found that CSD triggered increased infiltration of T cells into the meninges accompanied by skewing of T cells in immune organs towards a pro-inflammatory phenotype. Multicolor flow cytometry and single-cell RNA sequencing analysis were used to determine the immune cell variants most closely associated with CSD stress, what resident meningeal cells were responsible for their recruitment into the meninges, and what CNS-mediated events precipitated an immune reaction.

Preliminary data suggest that several immune cell populations are affected by stress, including Th cells and neutrophils. The basis for possible dynamic cellular interactions within the meninges is under investigation.

TH11. Shared and Dissociable Features of Apathy and Reward System Dysfunction in Bipolar I Disorder and Schizophrenia

Matthias Kirschner, Flurin Cathomas, Andrei Manoliu, Benedikt Habermeyer, Joe Simon, Erich Seifritz, Philippe N. Tobler, Stefan Kaiser*

Background: Bipolar disorder (BD) I is defined by episodes of mania, depression, and euthymic states. These episodes are among other symptoms characterized by altered reward processing and the clinical expression of apathy. However, the neural correlates of these deficits are not well understood. Methods: We first compared negative symptoms in 25 euthymic BD I patients compared to 25 healthy controls (HC) and 27 patients with schizophrenia (SZ). Then, we investigated ventral and dorsal striatal activation during reward anticipation in a Monetary Incentive Delayed Task and its association with negative symptoms. Results: In BD I patients the severity of apathy was comparable to SZ patients. Apathy scores in the BD I but not in the SZ group correlated with sub-syndromal depression scores. At the neural level, we found no group differences in striatal activation between BD I patients and HC as well as SZ patients. In contrast to SZ patients, apathy did not correlate with striatal activation during reward anticipation in BD I patients. Explorative whole brain analyses revealed reduced extra-striatal activation in BD I patients compared to HC and an association between reduced activation of the inferior frontal gyrus and apathy. Conclusion: This study found that in BD I patients' apathy is present to an extent comparable to schizophrenia, but is more strongly related to sub-syndromal depressive symptoms. The findings support the view of different pathophysiological mechanisms underlying apathy in the two disorders and suggest that extra-striatal dysfunction may contribute to impaired reward processing and apathy in BD I.

TH12. Oscillations in Basal Serotonin and Psychiatric Disorders

Yangguang Ou, Colby Witt, Melinda Hersey, Anna Marie Buchanon, Parastoo Hashemi*

Rapid measurements of changes in neurotransmitter concentrations are powerful; however, there is also a wealth of information in ambient levels of neurotransmitters. For example, both abnormally low and high levels of serotonin are toxic. Thus, the body must tightly regulate the ambient levels of serotonin to maintain it within a viable range. There has been a lack of tools

capable of measuring ambient neurotransmitter levels with good spatiotemporal resolution. We have in recent years developed a rapid voltammetric technique to perform such measurements. Preliminary data reveals that there are apparent oscillations in ambient serotonin, which we hypothesize are a mechanism by which the brain regulates the serotonergic system. This hypothesis is further evidenced by apparent changes in frequency, amplitude, and average basal concentrations with external and internal stressors. For the first time, the subtle and intricate workings of the ambient serotonergic system can be uncovered.

TH13. Medial Amygdala Dopamine Receptor Activity Regulates Social Avoidance Response Following Social Defeat Stress in Prairie Voles (Microtus Ochrogaster)

Maria Tickerhoof, Luanne Hale, Adam Smith*

Social stress is a major risk factor in the formation of multiple mental conditions, including depression, anxiety, and post-traumatic stress disorder. Social defeat stress (SDS) has been a rising animal model of social stress to investigate the connection between social stress experience and the onset of behavioral changes reflective of depressive-like and anxiety-like states. Mesolimbic dopamine signaling has been indicated to be an important factor in the behavioral response following experience of SDS. However, the ethological validity of SDS is limited in most rodent models since female aggression is not common. In this study, we utilized SDS to examine the effects of social stress on social interaction and dopamine receptor expression in the mesolimbic pathway in male and female prairie voles, which exhibit natural aggressive behavior following the formation of a pair bond. We discovered that, similar to other rodent species, SDS induced a social avoidance response in both males and females. In addition, prairie voles that experienced repeated sessions of defeat had increased levels of dopamine receptor D1 (DRD1) in the medial amygdala, a region implicated in avoidance and social behaviors. Pharmacological manipulation of DRD1 in this region induced social avoidance in non-defeated voles and trended towards reversing the social avoidance phenotype in voles that experienced SDS. These results indicate that DRD1 activity in the medial amygdala is sufficient to induce social avoidance and may be a necessary component in neurocircuitry governing stress-induced changes in social behavior.

TH14. Value-to-Choice Transformation in the Orbitofrontal Cortex and Midbrain Dopamine Neurons in Monkeys Performing an Economic Decision-Making

Mengxi Yun, Takashi Kawai, Masafumi Nejime, Hiroshi Yamada, Masayuki Matsumoto*

In economic choice behavior, animals first evaluate the value of an option and then decide to choose or not to choose that option. Although several cortical and subcortical areas are known to signal value information and contribute to decision-making, neural mechanisms that transform the value information into a decision command remains unknown. Here, we hypothesize that the midbrain dopamine (DA) system, a subcortical neuromodulatory system, transmits the value information while the orbitofrontal cortex (OFC), a cortical center for reward processing, encodes the value information and transforms such value signal to a decision command. To test this hypothesis, we recorded single-unit activity from DA and OFC neurons in monkeys performing a value-based decision-making task. In this task, only one option was presented, and the monkey was required to immediately decide to choose or not to choose it. Briefly, six visual stimuli were associated with different amounts of a liquid reward, and one of them was presented as an option. The monkey was required to decide to choose or not to choose that option within a limited time. After the animal's choice, another stimulus was presented. If the monkey had chosen the former option, the animal obtained the reward associated with that option at the end of the trial. If the monkey had not chosen the former option, the animal obtained the reward associated with the latter stimulus. We recorded the activity of 96 DA neurons and 285 OFC neurons from two monkeys. Of these, many DA and OFC neurons encoded the value of the option, consistent with previous work. Notably, we found that not only OFC neurons, but also DA neurons represented whether the monkey would choose the option or not. We then examined the time course of these value- and choice-related signals, and found that, shortly after the option presentation, the value signal rapidly emerged, and the choice signal appeared later in both DA and OFC neurons. Such value-to-choice signal dynamics were observed even in individual DA and OFC neurons. Thus, against our initial hypothesis, these findings suggest that not only OFC neurons, even subcortical DA neurons participate in the value-to-choice transformation during economic decision-making.

TH15. Effects of Adiposity on Postural Control and Cognition in Older Adults

Stacey Gorniak, Hao Meng*

Obesity has been associated with increased risk of developing cardiovascular diseases and metabolic syndrome. Despite this knowledge, the impacts of obesity persists in other health domains including cognitive and motor

functions. A number of studies have evaluated the relationship of increased body weight with postural control, however, most of them are focused on young adults or children. The purpose of this study was to examine the effects of adiposity on motor functions in older adults. Thirty healthy older adult participants (aged ≥ 60 years) were assigned to one of three Groups based upon their BMI at the onset of the study: healthy weight (BMI: 18.5–24.9 kg/ m2), overweight (BMI: 25–29.9 kg/m2), or class I/II obese (BMI: 30–40 kg/m2). The average age for each Group was 70.1 ± 6.87, 71 ± 8.52 and 68.5 ± 5.9 years old, respectively. Study participants had no known neurological, muscular, or metabolic diagnoses. Participants were required to perform anthropometric measurement, cognitive evaluation, posture evaluation, sensory assessments, and body composition assessment via dual energy x-ray absorptiometry (DXA). Increased body weight was associated with postural control deficits during cognitive-posture evaluations and sensory assessments. No significant cognitive deficits were found among different body weight groups in the current study. BMI was a better predictor of postural stability as compared to percentage of body fat in older adults. Waist to hip ratio presented some correlation with postural stability deficits, suggesting physical anatomy constraints may lead to postural instability in this population.

TH16. Mesoscale Wave Turbulence in the Hippocampus

Alex Sheremet, Andrew Maurer, Yu Qin, Jack Kennedy*

Of the three scales of brain activity generally identified in LFP recordings (micro-, meso- and macro-scale), mesoscopic activity is the least studied. In the cortex, mesoscopic collective action (MCA) manifests as propagating waves (e.g., Muller et al., 2018). Dismissed often as marginally-significant neuron synchronization (Buzsaki 2006), MCA may in fact be the main function of the cortex, as suggested by the non-hierarchical (isotropic and homogeneous) structure of cortical layers, which favors MCA over hierarchical microcircuit activity. This is consistent with the conjecture that physical structures underlying cognition resemble biological systems, with no design and no a priori function (Edelman and Gally, 2001). As such, collective action might play an essential role in the integration of brain activity (e.g., Freeman 2010). Despite a few initial insights (Wilson and Cowan 1973, 1974; and others) a consistent theory for MCA dynamics is still lacking. Because the mesoscale is macroscopic with respect to microscopic processes, the wealth of knowledge accumulated about microscopic physics cannot be directly extended to mesoscopic processes. We propose the "weak turbulence" theory (Zakharov, 1992) as a framework for studying MCA dynamics. Turbulence describes the internal energy balance in nonlinear multi-scale systems with a large number of components. Nonlinear interaction between scales results in cross-scale flows of energy and other conserved quantities, known as the "turbulent cascade" (Richardson, 1922; Kolmogorov, 1941). We show that

the observed evolution of MCA energy balance (LFP spectra and bispectra) in the hippocampus are consistent with mesoscopic weak turbulence. We derive the governing equations in a general conservation form, that generalize existing models (Wilson-Cowan, 1974, Wright and Liley 1995; and others). We derive dynamical equations for the evolution of the power spectral density and investigate their averaged (kinetic) behavior. The turbulent model predictions of the theta-gamma phase coupling characteristics are consistent with observations. Turbulence holds the promise to provide a consistent theoretical framework for modeling hippocampal energy processes, including the persistent question about the significance of power law spectra and their slopes.

TH17. Consider the Cascade- A Classical Physics Turbulence Description of LFP Energy Interaction in the Hippocampus.

Andrew Maurer, Alexandru Sheremet*

The brain is often equated to a computer, with the processing of different functions occurring in localized regions. In this description, sensory input is "encoded" in lower cortical regions and relayed up through parallel pathways. In higher associational cortices, where this activity converges, it has been suggested that simultaneous cognitive functions can occur in a multiplexed fashion. For example, it is tempting to assign distinct hippocampal oscillatory frequencies to different pathways that subserve unique cognitive processes (e.g., encoding versus recall). The virtue of analogies is to derive information about something we know little, the brain, from something we know a great deal, a computer. It has been noted, however, that "While brains do indeed perform something akin to information processing, they differ profoundly from any existing computer in the scale of their intrinsic structural and dynamic complexity" (Koch and Laurent, 1999). In light of this, it is necessary to consider another framework in which the heavy lifting of cognition is not relegated to multiplexed oscillations, but rather a consequence of an energy cascade. Energy enters the hippocampus at low-frequencies and re-purposed in smaller densely interconnected networks, which in turn result in gamma, epsilon and ripples. Simply, the brain supports cognition by moving activity on the macroscale and passing this energy into smaller scales. This framework, while sharing a similarity to the unitary slope 1/f power distribution observed in self-organized criticality, is more akin to the multi-sloped organization of power seen in wind, temperature, and water waves. The common theme is classical turbulence theory. Interestingly, this theory can explain why the integrity of hippocampal place cells and entorhinal grid cells require the theta paced input from the medial septum and the relationship between theta and gamma coupling to velocity (specifically, energy into the network). Moreover, it reinforces the idea that the LFP can often outperform behavioral decoding relative to multiple simultaneously recorded single units.

As the LFP is the result of coherent activity across a population of neurons, this theory connects single units to the macroscale offering the capability to relate physics to cognition.

TH18. OpenBehavior: Accelerating Behavioral Neuroscience With Open-Source Tools

Lex Kravitz, Samantha White, Linda Amarante, Mark Laubach*

Neuroscientists often invent new devices and methods to further their experiments. While open-source software has a long and productive history, open-source hardware is a more nascent development. Recent developments in prototyping and fabrication, such as 3D printing and production of custom printed circuit boards, have lowered the bar to entry for hardware design. In 2016, we launched a website, Openbehavior.org, to promote open source methods for neuroscience research. OpenBehavior.org is 100% non-commercial, meaning we don't take money for anything, and we don't pay for any services. Our mission is to accelerate behavioral neuroscience research through the promotion of open-source projects. We have two main goals with respect to this mission: (1) dissemination of open-source research methods, and (2) encouraging documentation and use of these methods. To achieve the first goal, OpenBehavior.org highlights innovative projects weekly on our site (>80 projects covered so far), and on social media. To achieve the second goal, we formed a collaboration with Hackaday.io to provide a place for hosting code, instructions, videos, etc. (>40 projects hosted so far). We encourage researchers to fully document their projects to facilitate replication and dissemination of their work. Sharing methods in this manner can reduce duplication of efforts between labs and can allow novel research methods to be tested and validated by multiple users. Finally, open-source methods can dramatically reduce the cost of setting up new behavioral experiments and can extend opportunities for research to educational environments which may not have the funds to purchase commercial research equipment. In this poster, we will highlight recent developments on OpenBehavior.org, and share a selection of promising projects for accelerating behavioral neuroscience.

TH19. Poster Withdrawn

TH20. Targeted Delivery of Two Transgenes to Modulate Protein Expression in the Brain Using MRI–Guided Focused Ultrasound

Kelly Markham-Coultes, Zeinab Noroozian, Kristiana Xhima, Fadl Nabbouh, Kullervo Hynynen, Anurag Tandon, Isabelle Aubert*

The use of immunoglobulins to treat neurodegenerative diseases remains a challenge due to the properties of the blood-brain barrier that limit therapeutic access to the brain. Protein modulating therapeutics possess great potential however the delivery of such therapies can be either invasive, requiring surgeries, or high dose, causing unwanted side effects. Here we demonstrate the functionality of MRI-guided focused ultrasound (MRIgFUS) using two gene therapy approaches to modulate protein expression in transgenic mouse models of Alzheimer's and Parkinson's diseases increasing expression of a single-chain variable fragment (scFv) against amyloid beta and using an siRNA to reduce expression of alpha-synuclein respectively.
Firstly, adeno-associated virus (AAV) serotype 6 with synapsin promoter (syn) was developed to express an scFv which binds amyloid monomers and oligomers. TgCRND8 mice were given AAV6-syn-scFv and microbubbles intravenously and treated with MRIgFUS targeted to the hippocampus. Amyloid beta plaque number was decreased in treated areas when quantified after two months of transgene expression. Secondly, AAV9 was rendered with a short hairpin RNA sequence targeting the alpha-synuclein gene. The construct was delivered to transgenic mice overexpressing human alpha-synuclein by tail vein in combination with microbubbles. MRIgFUS was used to target four brain regions of interest: hippocampus, substantia nigra olfactory bulb and dorsal motor nucleus. After one month of gene expression, alpha-synuclein immunoreactivity was decreased in targeted brain regions. This study demonstrates the advantages of using MRIgFUS for delivery of long-lasting therapeutic efficacy to the brain with regional specificity. Recent advances in gene therapy approaches combined with MRIgFUS delivery bodes well to open new avenues for treating neurodegenerative diseases.

TH21. Peptide Mediated Transport of SiRNA to the CNS Across the Blood-Brain Barrier

Brian Spencer, Anthony Adame, Jazmin Florio, Michael Mante, Eliezer Masliah, Robert Rissman*

Misfolded, aggregated proteins are characteristics of many neurodegenerative diseases of the aging population including Parkinson's Disease and Alzheimer's disease. Although much progress has been made at targeting accumulated

protein for degradation, the ability to regulate the expression at the gene transcription level would be beneficial for reducing the accumulation of these proteins or regulating expression levels of other genes in the CNS. Short interfering RNA (siRNA) oligonucleotides can bind specifically to target RNAs and target them for degradation via the RISC complex. This approach has shown promise as a therapeutic in vitro and in mouse models of PD and AD and other neurological disorders; however, delivery of the siRNA to the CNS in vivo has been achieved primarily through intra-cranial stereotaxic injection. Repeat stereo-taxic injections may not be amenable to clinical translation; therefore, a new approach for delivery of siRNAs to the brain is needed. We have identified a peptide for the transport of nucleotides across the BBB based on the apolipoprotein B (apoB) protein targeted to the family of low-density lipoprotein receptors (LDL-R). We used an 11-amino acid sequence from the apoB protein (ApoB11) that, when coupled with a 9-amino acid arginine linker, can transport siRNAs across the BBB to neuronal and glial cells. This peptide:siRNA delivery method was examined in the context of a-synuclein accumulation with a mouse model of Parkinsons/ Lewy Body disease expressing a-synuclein. Delivery of the siRNA effectively reduced accumulation of a-synuclein and improved neuronal and astrocytic numbers in the CNS of the model. Thus, we have identified a non-invasive, alternative delivery route for siRNA molecules for the CNS. Delivery of oligonucleotides to the CNS could be beneficial for neurodegenerative diseases, neuro-modulatory treatments, cancers of the CNS, gene targeted editing of the CNS or anti-microbial gene delivery of the CNS.

TH22. Evidence of Neuronal Dedifferentiation Following Spinal Cord Injury in Adult Zebrafish

Angelo Milli, Melanie Rojas Hammani, Taylor Schanel, Sebastian Mariategui, Michael Fernando, Martin Oudega, Jeffery Plunkett*

It is well established that amphibians and fish, in contrast to mammals, are capable of regenerating severed axons following central nervous system (CNS) trauma. In amphibians, CNS trauma causes phenotype reversion of fully differentiated cells (i.e., dedifferentiation) preceding their proliferation and (re-)differentiation and organization into new tissue. Although the zebrafish (Danio rerio), retains multiple proliferative neurogenic and stem cell niches throughout adult life, our research suggests that adult zebrafish are also capable of dedifferentiating fully differentiated neuronal cells in response to injury. We injured the spinal cord in adult zebrafish and studied how stem cell-related gene expression profiles in identified populations of differentiated brainstem neurons with an axon projecting into the spinal cord. Our data demonstrates that injured brainstem neurons express the putative stem and neural progenitor markers Sox-2, neuroD1 and the cell proliferation marker PCNA at various time points

from 1-21 days post-SCI. The expression profiles suggest that these neurons dedifferentiate following SCI. We are currently examining other time points, axonal growth associated genes and stem cell markers to correlate our findings to regenerative events seen typically in the spinal cord in adult teleost fish.

TH23. Development of a Novel Stem Cell-Based Culture System to Study Axonal Outgrowth and Neuronal Differentiation

Jeffery Plunkett, Scarlyn De Los Santos, Andrea Solano, Raul Banos, Angelo Milli, Martin Oudega*

Adult zebrafish (Danio rerio) have been shown to retain multiple proliferative neurogenic and stem cell niches to enable growth and repair of central nervous system (CNS) tissues. We initially developed cellular culture conditions that allowed for the in vitro growth of isolated brain cells that contained abundant stem populations. These cultures revealed, at 7 days in vitro (div), the presence of distinct populations of stem cell-derived neural progenitor cells that can differentiate into mature neurons and extend axonal processes across various substrate terrains. One terrain investigated was chondroitin sulfate proteoglycans (CSPGs). In mammals, CSPGs have been shown to prevent axonal regeneration following CNS injury. In contrast, certain axonal tracts within the zebrafish CNS can regenerate despite the presence of CSPGs. In the present study, we investigated a potential role for CSPGs in the phenotypic regulation of adult zebrafish CNS stem cells into neurons. We used substrate adhesion CNS cellular cultures to examine the role CSPGs play in axonal outgrowth and differentiation. Furthermore, using free-floating, rotating aggregate, CNS cellular cultures we examined neuronal differentiation in the presence of CSPGs. In analyzing various markers for axonal outgrowth and differentiation in both culture systems, our initial data indicate that CSPGs do play a role in both processes. We are currently using a combination of immunocytochemical and statistical analyses to gain a better understanding of the roles that CSPGs play in guiding stem cell fate and neuron axonal regeneration.

TH24. Sodium Channel Dysfunction in Dravet Syndrome is Mutation-Specific

Peter Ruben, Colin Peters, Laura Jones, Madeline Angus, Richard Rosch, Elise Brimble*

Dravet Syndrome (DS) is a severe, potentially life-limiting seizure disorder arising from mutations in the gene encoding the neuronal voltage-gated sodium channel, NaV1.1. We measured sodium currents from normal and mutated sodium channels expressed in HEK293 and CHO cells, and found a variety of

mutation-specific effects on channel gating and trafficking. Some mutations decrease protein trafficking to the membrane (e.g. M72Dup mutant). Other mutations destabilize both activation and fast inactivation (e.g. A1273V in NaV1.1; Peters et al., 2016) with increased temperature, a known trigger for DS. Still others increase persistent current (e.g. T782I) or shift the voltage dependence of only fast inactivation (e.g. Y1274H, left shift; A1685S, right shift). To further confirm temperature as a trigger and to validate an animal model for in vivo drug testing in DS, we used CRISPR to introduce the A1273V mutation into the Drosophila para channel. The mutant flies displayed seizure activity when exposed to increased ambient temperature. Overall, our results suggest that a patient-specific approach to treating DS is necessary because, although the patient phenotype has some similarities, severity and response to drugs varies widely. Thus, understanding differences in channotype may give us clues about how to better treat patients.

Funding for this work was provided by grants from the Rare Disease Foundation and Dravet Canada.

TH25. Ascot Identifies Key Regulators of Photoreceptor-Specific Splicing

Jonathan Ling, Christopher Wilks, Rone Charles, Devlina Ghosh, Abhinav Nellore, Ben Langmead, Seth Blackshaw*

Public archives of next-generation sequencing data are growing exponentially, with petabases added each year. The difficulty of marshaling this data means that it has been underutilized by scientists. We present ASCOT, a resource that enable researchers to summarize, visualize, and query alternative splicing patterns in public RNA-Seq data. ASCOT uses new methods to rapidly call splice-variants across tens of thousands of bulk and single-cell RNA-Seq datasets in human and mouse. Focusing on the nervous system, we identified many alternative exons that are only used by specific neuronal subtypes. Leveraging datasets from the ENCODE and GTEx consortiums, we then analyzed the unique splicing patterns of rod photoreceptors and found that PTBP1 knockdown combined with strong overexpression of MSI1 and PCBP2 could activate rod-specific exons in HepG2 liver cancer cells. Furthermore, we observe that MSI1 binds intronic UAG motifs proximal to the 5' splice site and interacts synergistically with PTBP1 downregulation. Our work exemplifies how large-scale analysis of public RNA-Seq datasets can yield key insights into cell-specific control of RNA splicing and underscores the importance of considering both annotated and unannotated splicing events. ASCOT data, software, and alternative splicing browser are openly available.

TH26. Subthalamic Nucleus Activity Associated With Freezing of Gait

Neil Mahant, Matthew Georgiades, James Shine, Moran Gilat, Brian Owler, Jacqueline McMaster, Simon Lewis*

Freezing of gait (FOG) can be a devastating problem for people with Parkinson's disease (PD), characterized by an inability to lift the feet as though 'frozen to the floor'. It greatly limits mobility and can cause falls and subsequent injuries. The neurobiological basis of FOG is unknown. The subthalamic nucleus (STN) is an important node of the motor circuit. STN activity, particularly oscillatory activity in the beta (β) frequency band (13-30Hz), is thought to inhibit movement and behavior. We therefore hypothesized that increased STN output may underlie FOG in PD. In order to confirm the location of the STN during deep brain stimulation (DBS) surgery, the surgical team records multiunit neuronal activity (MUA) via a microelectrode while the patient is awake. We applied a virtual reality (VR) paradigm – a validated model of FOG in humans – to study FOG during DBS surgery and analyzed the MUA. We studied recordings from 8 individuals with PD, yielding 19 episodes of FOG. There was greater MUA during FOG than volitional stops (12.6±6.8 v 7.6±5.2, p=0.006). This was also the case for β oscillation, where the amplitude exceeded the 99th centile of normal walking 0.9s before to 1s after FOG, whereas this only occurred at the moment of volitional stopping. There was a less robust increase in theta (θ) frequency (3-8Hz) in the peri-FOG period. As expected, there was 'tremor in place' muscle activity in the lower limbs associated with FOG, mainly in the θ band. Granger causality analysis demonstrated that STN β was unilaterally linked to STN θ, which was unilaterally linked to muscle tremor in place ($p<0.001$).
These findings suggest a causal link between abnormal STN activity and lower limb dynamics as the basis of FOG. This may assist with improving treatment for this debilitating symptom of PD, with possibilities including 'closed loop' stimulation to alter pathological STN β.

TH27. Cortical Transcriptome Analysis Reveals a Persistent Neuroinflammatory Phenotype in a Mouse Model of Gulf War Illness

Kimberly Kelly, Lindsay Michalovicz, Diane Miller, James O'Callaghan*

Gulf War Illness (GWI) is a multi-symptom, neuroimmune-based disorder that presents with features similar to sickness behavior. Unfortunately, current treatments for GWI tend to focus on managing symptoms as opposed to addressing the underlying cause of the illness. Using a preclinical mouse model, we have found that GWI is associated with an exacerbated neuroinflammatory response to immune challenge, like lipopolysaccharide (LPS) exposure, and the

activation of microglia. In this model, mice are exposed to the stress hormone corticosterone (CORT; 200 mg/L) in the drinking water for 7 days followed by a single injection of diisopropyl fluorophosphate (DFP; 4 mg/kg, i.p.) to model the "in theater" conditions of high physiological stress and potential nerve agent exposure. This is then followed by periodic administration of CORT for 7 days every other week to a total of 5 weeks with a systemic LPS challenge (0.5 mg/kg, s.c.) on the final day. Mice were sacrificed 6 hours after LPS challenge and brain cytokine mRNA expression was evaluated by qPCR and RNAseq. RNAseq analyses revealed 2430 statistically significant genes ±1.5-fold change over saline controls. A PCA plot of these findings illustrate good separation of groups confirming a difference between the GWI (CORT+DFP+LPS) and CORT+LPS groups. Of these genes, 114 were unique to the GWI group. Analysis of the gene list with DAVID revealed inflammatory related GO terms and KEGG pathways. Ingenuity Pathway Analysis of the significant genes reveals many inflammatory canonical pathways across the groups to be depicted in a heat map. Together these findings reveal the neuroimmune basis for Gulf War Illness.
Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

TH28. Controlling Receptor Trafficking by AAV Gene Therapy to Prevent Neuropathic Pain

Andreas Sørensen, Gith Noes-Holt, Nikolaj Riis Christensen, Mette Richner, Christian Bjerggaard Vægter, Kenneth Madsen*

Disease or tissue injury can give rise to chronic neuropathic pain. Treating such pain remains elusive, also mirrored by available therapies all targeting surface proteins that often lack efficacy and can lead to serious side effects. So, instead of aiming at surface membrane proteins, such as ion channels, we have by rational design and molecular engineering conceived an AAV-encoded recombinant peptide. It works by interfering with receptor trafficking, but only in disease states, hereby preventing key maladaptive plasticity to occur. With our AAV approach, we now demonstrate, through pan-neuronal expression of the recombinant peptide within the spinal dorsal horn, that mechanical allodynia is completely prevented in the mouse spared nerve injury (SNI) model. As the recombinant peptide is encoded by an AAV vector, the peptide product is released from within the neurons, implying that the therapy is focal and aimed specifically towards the disease area. These findings demonstrate that AAV gene therapy may prove useful for treatment of neuropathic pain.

F1. Cell Type Plasticity in the Nucleus Accumbens Core and Shell Following Remifentanil Self-Administration

Aric Madayag, Eden Anderson, Matthew Hearing*

Previous findings suggest cell type-specific plasticity at Infralimbic Cortex-to-nucleus accumbens shell but not Prelimbic cortex-to-nucleus accumbens core synapses following experimenter-administered morphine. It is unknown if these effects hold following contingent exposure to opioids. Mice expressing fluorescent proteins under the control of D1- or D2-dopamine receptor promoters were injected with channel rhodopsin-expressing viral vectors targeted at the prelimbic or infralimbic cortices, implanted with jugular catheters, then performed 14 self-administration sessions for remifentanil or saline. After 14-21 days withdrawal, we employed whole-cell electrophysiology recordings in acute brain slices to identify opioid-induced plasticity in NAc core and shell MSN excitatory signaling. LED-induced stimulation of presynaptic terminals in the core or shell was used to evoke EPSCs in D1- or D2-MSNs. Our findings indicate significant increases in mEPSC amplitude at D1MSNs in the core and shell and a significant increase in frequency at D1MSNs in the shell. D2MSNs appear to be less effected by remifentanil exposure as we only observe a significant decrease in mEPSC frequency at D2MSNs in the core. Increased mEPSC amplitude at D1MSNs points to heightened postsynaptic AMPAR current, however we observed decreases in AMPAR/NMDAR ratio; though possibly due to decreases in AMPAR rectification at these cell types. To further measure presynaptic regulation, we found that paired pulse ratio decreases at D1MSNs and increases at D2MSNs in the core following remifentanil self-administration. Following self-administration of remifentanil, plasticity was found at D1- and D2-MSNs in both the core and shell. These findings suggest that a self-administration model may be required to engage opioid-induced plasticity within the core and identify distinct and overlapping neuroplasticity generated by contingent and non-contingent opioid exposure. Future experiments will examine potential mechanisms underlying the cell-type plasticity and determine the relevance of this plasticity in relapse behavior.

F2. Inhibition of Nucleus Accumbens D1 Expressing Neurons Facilitates Extinction of Sign-Tracking

Rifka Derman, Jeffrey Pettibone, Elizabeth Bryda, Thomas Saunders, Wanda Filipiak, Michael Zeidler, Joshua Berke, Carrie Ferrario*

During Pavlovian appetitive conditioning, when discrete localized conditioned stimuli (CS) are used conditioned responding can manifest as behavior directed toward the site of US (unconditioned stimulus) delivery, otherwise known as goal-tracking, or toward the CS itself, referred to as sign-tracking

or autoshaping. These distinct forms of conditioned responses depend on separable, though overlapping neurocircuitry and neurotransmitter systems. Sign-tracking, but not goal-tracking, depends on dopamine transmission in the Nucleus Accumbens (NAc; 1,2). The principle neurons of this nucleus are medium-spiny-neurons (MSNs) that express either D1 or D2 dopamine receptors, in largely non-overlapping populations. The unique role of each of these subpopulations in the development, maintenance, and expression of conditioned responding has yet to be examined. Here we test the effect of selectively inhibiting NAc D1-MSNs on the maintenance of sign- and goal-tracking after acquisition and the expression of these behaviors during extinction training. To selectively target D1-MSNs we use newly developed transgenic rats in which iCre was knocked in downstream of the Drd1 gene. Cre-dependent virus that codes for the inhibitory DREADD, hM4Di, was delivered to the NAc of Cre+ and Cre- offspring of this transgenic line. After initial acquisition of Pavlovian conditioning, administration of CNO (the hM4Di activating ligand; 5mg/kg, ip) did not disrupt the maintenance of either sign- or goal-tracking conditioned responses, however administration of CNO during extinction training facilitated extinction of sign-tracking in Cre+ vs Cre- rats. These results suggest that inhibition of NAc D1-MSNs selectively enhances the extinction of sign-tracking. To fully explore this effect, rats were subsequently tested for reinstatement of conditioned responding under vehicle conditions. Consistent with the effects observed during extinction, Cre- rats showed stronger reinstatement than Cre+ rats suggesting that the facilitation of extinction in Cre+ was robust and long lasting. These data offer new insights into the divergent neurocircuitry underlying sign- vs goal-tracking by identifying D1-MSNs as one of the neuronal populations critical for the expression of sign-tracking under extinction conditions.

F3. Neuron Subtype-Specific Role of Methylated DNA Cytosine Dioxygenase TET1 in Cocaine Addiction

Haiyang Xu, Graham Kaplan, Amber Brown, Rachel Hedinger, Vanessa Joseph, Jian Feng*

The role of epigenetic mechanisms, such as DNA methylation, have been increasingly appreciated in drug addiction. Recently, additional forms of DNA epigenetic modifications have been identified through the oxidation of methylated DNA cytosine to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5-fC), and 5-carboxylcytosine (5-caC). This was accompanied by the recognition of their catalyzing enzymes, ten-eleven translocation proteins (TET), which may lead to DNA demethylation. Though the three members of the TET family are expressed in the adult brain, their role in drug addiction is still largely unknown. Previously, we found that TET1 in the nucleus accumbens (NAc) is implicated in cocaine action, suggesting a

functional role of DNA modifications in cocaine addiction. In the present study, we investigated the impact of Tet1 deletion in either dopamine D1 receptor-expressing medium spiny neurons (D1-MSN) or dopamine D2 receptor-expressing MSNs (D2-MSN) in mice on behavioral responses to cocaine in reward- and addiction-related behavioral paradigms. The rewarding effect of cocaine in mice with TET1 deficiency in D1- or D2-MSNs was evaluated using the conditioned place preference (CPP) paradigm. Operant intra-venous self-administration (SFA) of cocaine was also evaluated. We found that D1-MSN specific knockout of Tet1 in male mice enhances the rewarding value of cocaine, potentiates the vulnerability to cocaine binge, and amplifies the incentive motivation for taking cocaine. These findings suggest a neuron subtype-specific role of DNA epigenetic modifications in cocaine addiction.

F4. Hyperdopaminergic States Enhance Orbitofrontal-Striatal Pathway Function

Sebastiano Bariselli, Nanami Miyazaki, Ilona Sczcot, Alexxai Kravitz*

Dopamine, a neuromodulator released by midbrain axons innervating the striatum, seems to dichotomously regulate excitability and plasticity of glutamatergic inputs at direct (dMSNs) and indirect (iMSNs) medium spiny neurons ex vivo. However, its modulatory role on neuronal plasticity in vivo remains poorly understood. Here, by combining optogenetic-mediated stimulation of orbitofrontal cortex (OFC) with electrophysiological recordings in the dorsomedial striatum (DMS) of behaving mice, we investigated the role of dopamine in modulating OFC-striatal pathway function in vivo. We revealed that the psychostimulants amphetamine and cocaine both potentiate OFC-evoked local field potential (OFCe LFP), the latter attenuated by pharmacological blockade of dopamine receptors. Moreover, the cocaine-induced increase in OFCe LFP magnitude is associated with an increased firing rate and probability of OFCe firing of striatal neurons, pointing at an enhanced OFC synaptic efficacy during hyperdopaminergic states. Accordingly, optogenetic stimulation of Substantia Nigra pars compacta (SNc) neurons enhanced OFCe LFPs in DMS, mimicking the psychostimulant-induced effects. Finally, to assess the effects of hyperdopaminergic states on OFC stimulation-evoked MSN activity, we measured calcium population activity in response to OFC stimulation during hyperdopaminergic states in dMSNs and iMSNs, respectively. Altogether, these data unravel an unexpected role for dopamine as an enhancer of OFC input efficacy onto striatal neurons in awake animals.

F5. Wireless Near-Field Optogenetic Manipulation of the Paraventricular Thalamic Projection to Nucleus Accumbens in Heroin-Seeking Rats

Giuseppe Giannotti, Jamie Peters*

Relapse to heroin seeking is often driven by the aversive physiological and emotional states associated with opioid withdrawal and dependence. Many studies have focused on identifying the neural circuitry governing the reinforcing properties of heroin, but less is known about the circuitry responsible for the aversive mental states and physical dependence experienced during withdrawal. The paraventricular thalamus (PVT) projection to the nucleus accumbens (NAc) mediates aversion and opioid withdrawal symptoms after experimenter-administered chronic morphine (Zhu et al., 2016). We decided to test the hypothesis that optogenetic activation of this pathway might precipitate an aversive state capable of driving heroin seeking in a rat self-administration model. Using a wireless near-field optogenetic technology, and a combinatorial viral approach, we confirmed that photoactivation of PVT neurons projecting to the NAc generates a significant real-time place aversion during acute (24 h) withdrawal from heroin self-administration. At this same 24 h-withdrawal time point, we found that hyperalgesia is maximal compared to 12 h and 48 h. Finally, optogenetic activation of the PVT->NAc pathway during the first extinction session potentiated heroin seeking 24 h after the last heroin exposure but did not alter cued reinstatement of heroin seeking after extinction training (at 7d of withdrawal). These data confirm and expand previous studies showing that the PVT projection to the NAc is associated with aversion, and in our hands, optogenetic activation of this pathway was only capable of eliciting aversion during acute (24 h) heroin withdrawal. Furthermore, the same optogenetic stimulation pattern used to drive this aversive state is capable of driving heroin seeking under extinction conditions at this same time point. Future studies will explore different optogenetic stimulation patterns and test conditions to further delineate the role of PVT->NAc pathway in heroin seeking.

F6. Differences in Striatal Dopamine Release and Its Modulation by Nicotinic Acetylcholine Receptors in Adolescent and Adult Rats

Elizabeth Pitts, Lacey Sexton, Ashley Fennell, Mark Ferris*

Adolescence is a developmental period characterized by increased vulnerability to substance use and dependence. However, the mechanisms mediating this vulnerability are not well-understood. Acetylcholine, through nicotinic acetylcholine receptors (nAChRs), modulates striatal dopamine release and motivation of reward-seeking behavior. Previous work has shown that adult

rats with heightened vulnerability to drug taking have differential nAChR modulation of dopamine release in the nucleus accumbens (NAc) core. Specifically, blockade of nAChRs facilitates phasic dopamine release in drug use vulnerable, but not resistant, rats. We hypothesized that adolescent rats would have differential nAChR-mediated modulation of NAc dopamine release. Here we used fast scan cyclic voltammetry to examine striatal dopamine release and the effects of nAChR antagonism in adolescent and adult rats. We found that adolescents have significantly reduced dopamine release across a range of stimulation parameters used to model dopamine cell firing. We also found that selective antagonism of a6-containing nAChRs reduced dopamine release in adult rats but facilitated dopamine release to phasic-like stimulation in adolescents. This pattern is similar to the effects of nAChR antagonism in vulnerable adult rats. Finally, we have shown that glutamatergic receptors mediate a7-containing nAChR suppression of dopamine release in adult rats, but not in adolescents. Together, these findings suggest that nAChR receptor-specific modulation of dopamine release, and the mechanisms of this modulation, are different in adolescent and adult rats. Given the role of nAChRs in motivating drug-seeking behaviors, this difference in accumbal circuitry and dopamine modulation could underlie, in part, adolescent vulnerability to substance use disorders.

F7. Regulation of Nucleus Accumbens Core Dopamine to Differentially Mediate Drug-Taking and Drug-Seeking

Ryan Farero, Lauren Burgeno, Nicole Murray, Jennifer Steger, Antony Abraham, Charles Chavkin, Larry Zweifel, Paul Phillips*

Altered dopamine (DA) signaling is implicated in most contemporary theories of drug abuse. Cues that are repeatedly paired with delivery of drugs of abuse can become conditioned stimuli (CS) and are capable of driving DA release in the nucleus accumbens core (NAcc). Recent work from our lab indicates diametric changes in CS driven NAcc DA transmission mediate escalated drug consumption and cue induced drug-seeking in a divergent manner. We further support these findings with causal data utilizing optogenetics to elicit temporally precise NAcc DA release during context specific drug related CS presentation. We injected an AAV1 ChR2 containing viral vector (AAV1-CaMKIId-ChR2-mCherry) bilaterally into the VTA and implanted optic fibers in the NAcc of male Wistar rats. Our results show photostimulation paired with response-contingent CS decreases drug-intake in animals who previously escalated their daily drug consumption ($p<.05$), whereas photostimulation paired with investigator delivered CS increases drug-seeking behavior ($p<.05$). These results indicate an attenuation of dopamine transmission in the NAcc is at least partially responsible for escalated drug intake, and that potentiated dopamine signaling to non-contingent drug related CS

promotes drug-seeking behaviors. Thus, blocking the attenuation of dopamine through pharmacological intervention should decrease or prevent escalated drug consumption. One possible mechanism promoting the attenuation of dopaminergic transmission in the NAcc is dynorphin via action on Kappa opioid receptors (KOR). To test this, we locally injected the KOR antagonist norbinaltorphimine (norBNI) into the NAcc. Nor-BNI treated animals had no significant increase in drug intake across weeks ($p>.05$), whereas vehicle treated animals showed significant escalation ($p<.05$). Although, norBNI shows promising results in preventing escalation of drug intake, a more viable treatment would stabilize dopamine to help treat CS induced drug-seeking.

F8. FAAH Genetic Variation Enhances Mesolimbic Dopamine Function and Vulnerability to THC-Seeking Behavior in Female Adolescent Mice

Caitlin Burgdorf, Rui Rong Yang, Chienchun Huang, Matthew Hill, Ken Mackie, Deqiang Jing, Teresa Milner, Virginia Pickel, Francis Lee, Anjali Rajadhyaksha*

Cannabis dependence continues to increase in prevalence as a major world health problem with women demonstrating a quicker progression to cannabis dependence. However, little is known about the interaction of genetic variation within the endocannabinoid system with exogenous cannabinoid Δ9-tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis, and impact on mesolimbic reward circuitry. We recently developed a knock-in mouse that biologically recapitulates a common human mutation in the gene for fatty acid amide hydrolase (FAAH) (C385A; rs324420), the primary catabolic enzyme for the endocannabinoid anandamide. Using the genetic knock-in mouse, we show that the FAAH polymorphism in female adolescent mice results in an increased preference for THC, an effect not observed if exposure occurs in adulthood. Cellular studies reveal that the FAAH polymorphism induces an increase in cannabinoid 1 (CB1) receptors in the ventral tegmental area as determined by immunofluorescence and western analysis. In addition, the FAAH polymorphism induces an increase in tyrosine hydroxylase expression in the VTA, a marker for dopamine levels, as well as enhanced VTA-nucleus accumbens (NAc) connectivity as determined by tract-tracing studies. Furthermore, the variant allele results in an increase in c-Fos expression within the NAc following acute THC. Additional experiments are underway to determine if manipulation of the VTA-NAc pathway can reverse the enhanced THC preference observed in adolescent female mice with the polymorphism. This study suggests that female mice expressing the FAAH polymorphism demonstrate a gain in function of the mesolimbic pathway and increased vulnerability to THC-seeking behavior.

F9. Medial Septum Activation Enhances Reversal Learning via Actions on Ventral Tegmental Area and Substantia Nigra Dopamine Neurons

David Bortz, Anthony Grace*

The medial septum (MS) is involved in learning and memory processes, specifically response inhibition. For example, lesion of the MS increases perseverative responding and inhibits fear extinction; however, the mechanism by which this occurs is not well-understood. It was recently demonstrated that MS activation increases dopamine (DA) population activity in the ventral tegmental area (VTA) and decreases it in the substantia nigra pars compacta (SNc), via the ventral subiculum (vSub) and ventral pallidum. Therefore, one possibility is that the MS aids in response inhibition via its regulation of midbrain DA activity, possibly by attenuating SNc-driven habit-related responding in favor of VTA-driven goal directed responding. This was tested by infusing a DREADD-containing (hM3Dq) or control virus into the MS of Sprague Dawley rats. Eight to twelve weeks later, the effect of MS activation on midbrain DA activity and T-maze reversal learning was determined following systemic and intracranial (vSub) injection of CNO, with and without a co-injection of the D1 antagonist SCH23390. DREADD activation of the MS via systemic CNO reduced (32%) the number of trials to perform a reversal and the number of perseverative errors (37%) compared to controls. Infusion of CNO onto MS terminals in vSub increased (78%) the number of spontaneously active DA neurons in the VTA, and decreased (31%) the number of active DA neurons in the SNc, similar to what was shown previously via NMDA activation of the MS. Infusion of CNO onto MS terminals in the vSub also produced a similar enhancement in T-maze performance, suggesting that both effects were mediated via the direct projection from MS to vSub. Finally, co-injection of the D1 antagonist SCH23390 completely prevented the enhancement in reversal learning performance seen in the DREADD/CNO rats, indicating that the MS's effect on DA transmission is necessary for its enhancement of reversal learning. This suggests that the MS, via its regulation of the DA system, may be critical for response inhibition and cognitive flexibility, two functions central to higher order cognitive processing and disrupted in several psychological disorders. As such, manipulation of this pathway may prove to be beneficial in treating cognitive dysfunction in a range of diseases, such as schizophrenia and addiction.

F10. Excessive Alcohol Drinking Disrupts Stress Reactions Through Alterations in BNST Dynorphin in Mice

Lara Hwa, Sofia Neira, Melanie Pina, Dipanwita Pati, Emily Kokush, Daniel Bloodgood, Andrew Hardaway, Thomas Kash*

Chronic, excessive alcohol intake can lead to dynamic changes in stress coping behavior and stress-related neural mechanisms. We aim to explore how long-term intermittent alcohol (IA) changes how mice react to a variety of stressors and if the dynorphin (DYN)/kappa opioid receptor (KOR) system influences these aberrant behaviors. After six weeks of IA, C57BL/6J mice show reduced ability to cope with repeated forced swim stress, deficits in active coping in response to TMT predator odor and altered escape strategy when faced with an overhead looming disc threat compared to H2O-drinking mice. Further, we found that KOR antagonist norBNI could restore stress coping in the repeated forced swim and responses to predator odor, but not the looming disc. To next determine which DYN/KOR populations may drive these altered stress reactions, whole-brain c-Fos mapping in a transgenic DYN reporter line was conducted to reveal the dorsal bed nucleus of the stria terminalis (dBNST) contained the highest c-Fos interaction between alcohol history and stress. We next performed synaptic transmission experiments using whole cell patch clamp recordings of dBNST DYN neurons. IA robustly silenced synaptic drive while the combination of IA and stress significantly increased glutamatergic activity in DYN-containing cells in the dBNST. Knockdown of BNST DYN also partially restored the stress reaction in IA mice. Ongoing studies using Fos-inducible targeted recombination are in progress to locate which TMT-induced inputs to the dBNST may change after IA. Also, chemogenetic manipulations and genetic knockout of BNST KORs remain as future directions to further alter TMT coping behavior during protracted withdrawal after IA. Altogether, this research shows a behavioral representation of an allostatic shift of stress coping after long-term alcohol. The imbalance of stress neuropeptide signaling may ultimately underlie this complex relationship between alcohol and stress.

F11. Operant Social Interaction Inhibits Drug Self-Administration and Incubation of Drug Craving in Rat Addiction Models

Marco Venniro, Michelle Zhang, Daniele Caprioli, Sam Golden, Conor Heins, Marisela Morales, David Epstein, Yavin Shaham*

Background: Prevention and treatment of addiction have not been appreciably improved by neuroscientific research. One problem is that mechanistic circuit- or molecular-related studies using rodent models do not incorporate social

factors, which, for humans, play a critical role in addiction. Here we introduce an operant model of social choice in rats and demonstrate the profound impact of an alternative social reward on drug self-administration and relapse. Methods: We first determined whether rewarding operant social interaction would prevent extended access self-administration of methamphetamine or heroin; we also determined the boundary conditions for this effect. Next, we used the rat DSM-IV-based and intermittent access addiction models to determine whether operant social interaction would also prevent methamphetamine self-administration in the subpopulation of rats identified as "addicted." Finally, we determined whether social choice-induced voluntary abstinence would prevent incubation of methamphetamine craving (the time-dependent increases in drug seeking during abstinence) and investigated brain mechanisms underlying that effect. Results: Independent of sex, drug class, drug dose, training conditions, abstinence duration, housing conditions (including social housing), and "addiction score" in the DSM-IV-based and intermittent access models, operant social interaction prevented drug self-administration. Only when we introduced a long delay between lever-pressing and social interaction, or punished the operant response for social reward, did the rats resume drug self-administration. Social choice-induced voluntary abstinence prevented incubation of methamphetamine craving, an effect associated with selective activation of central amygdala PKCδ-expressing inhibitory neurons. Conclusion: Our results illustrate the profound impact of volitional social interaction on addiction and support wider implementation of social-based contingency-management programs to addiction treatment.

F12. Characterization of Activity-Dependent Neuronal Ensembles in the Prefrontal Cortex Following Cocaine Place Conditioning in Fos-tTa Mice

*Caitlyn Miller, Rosanna Marino, Courtney Cann, Sam Golden, Marco Venniro, Bruce Hope, Leslie Whitaker**

Learned associations between rewards and reward-predictive stimuli are critical to motivated behavior. Associative learning is thought to be encoded by functional alterations within activity-dependent neuronal ensembles. The stability of these activity-driven neuronal ensembles remains a critical question in determining how the brain encodes learning associations over time. The immediate early gene, Fos, can be used to identify activity-dependent ensemble neurons. We used a cocaine conditioned place preference (CPP) procedure to study the learned association between an environmental context and cocaine reward in Fos-tTa transgenic mice. To identify brain regions active during expression of cocaine CPP we used Fos immunohistochemistry and identified the prelimbic cortex as an active region. Using the Fos-tTa transgenic mouse system in conjunction with the AAV-TRE3G-H2BmCherry virus we were able

to label active neurons in the PFC following exposure to the cocaine paired context and compare this with the PFC ensemble labeled upon re-exposure to the paired context at a later time point. We re-exposed separate groups of mice to the saline-paired context, a separate novel context, or home cage exposure and examined the degree of overlap with the PFC ensembles labeled in the paired context. Our results suggest that there is greater overlap between PFC ensembles when mice are re-exposed to the cocaine-paired context. Future studies will determine the time course of functional alterations in Fos-expressing ensembles using the Fos-tTa system.

F13. Corticotropin Releasing Factor (CRF) Increases Excitability of Dorsal Raphe Glutamatergic Neurons

Jorge Miranda-Barrientos, David Barker, Flavia Barbano, Liu Bing, Marisela Morales*

The dorsal raphe (DR) is a heterogenous nucleus that contains serotonin, GABA and glutamate neurons that express the vesicular glutamate transporter 3 (VGluT3) (Gras et al., 2002; Herzog et al., 2004; Jackson et al., 2009; Qi et al., 2014). We had recently demonstrated that axons from DR VGluT3 neurons establish excitatory synapses on ventral tegmental area (VTA) dopamine neurons that innervate the nucleus accumbens, and that activation of DR VGluT3 terminals in the VTA is rewarding (Qi et al., 2014). To have a better understanding of cellular properties of DR VGluT3 neurons that may play a role in their regulation, we analyzed the electrophysiological and pharmacological properties of these neurons. By electrophysiological analysis of the membrane intrinsic properties of DR VGluT3 neurons, we found that DR VGluT3 neurons are a heterogeneous population that shares electrophysiological properties with their neighboring serotonin neurons. Given that the DR has high levels of expression of corticotropin releasing factor (CRF) receptor 2 (CRF-R2), by in situ hybridization we looked for expression of CRF-R2 within DR VGluT3 neurons. We detected expression of CRF-R2 mRNA in some DR neurons expressing VGluT3 alone or in combination with Tryptophan Hydroxylase (enzyme for the production of serotonin). Consistent with the presence of CRF-R2 mRNA in some VGluT3 neurons, by patch clamp recordings on genetically identified DR VGluT3 neurons, we found that CRF increased the excitability of a subpopulation of DR VGluT3 neurons in a CRF-R2 dependent manner. Given the role of CRF in increasing DR VGluT3 neurons excitability, we then tested the effect of stress exposure by foot shock in DR VGluT3 neurons excitability; consistent with our CRF data, we found that chronic stress exposure increased DR VGluT3 neurons excitability. These findings demonstrate that DR glutamatergic neurons are modulated by CRF and stress exposure.

F14. Poster Withdrawn

F15. Optogenetically-Induced Norepinephrine Release in the Bed Nucleus of Stria Terminalis is Altered Following Chronic Restraint Stress in Mice

Karl Schmidt, Viren Makhijani, Kriten Boyt, Elizabeth Cogan, Dipanwita Pati, Melanie Pina, Isabel Bravo, Joyce Besheer, Zoe McElligott*

Norepinephrine plays a critical role in the physiologic response to stress. The bed nucleus of the stria terminalis (BNST) is one brain region that acts as a hub, regulating anxiety, and upstream of stress responses. Furthermore, acute stress elevates norepinephrine release in this region. In order to determine how chronic stress alters norepinephrine release in the BNST, we exposed transgenic mice expressing channelrhodopsin selectively in norepinephrine neurons to two-hour restraint sessions. In accordance with the literature, we found acute restraint stress elevated plasma corticosterone, but this effect habituated following five consecutive days of restraint. In contrast, we saw equal activation of norepinephrine neurons in the A2 region of the nucleus of the solitary tract following a single, and repeated stress exposures. We then used ex vivo slice fast-scan cyclic voltammetry to determine whether the terminal release of norepinephrine differed following stress exposure. We optogenetically activated norepinephrine terminals in the BNST at physiologically relevant frequencies on the day following the final stress exposure and found that repeated stress increased norepinephrine release across multiple stimulation paradigms. The elevated norepinephrine levels seem to result from altered α2-adrenergic autoreceptor function following chronic stress. In conclusion, we have used a novel mouse line to illustrate selective changes in noradrenergic plasticity following repeated stress exposure.

F16. Stress Susceptibility Differentially Predicts Anxiety-Like Behavior in Male Versus Female Mice

Elizabeth Cogan, Shanaya Fozdar, Zoe McElligott*

Approximately 70% of adults in the United States have experienced a traumatic event, however, an estimate of 20% of these individuals will subsequently develop post-traumatic stress disorder (PTSD). Thus, it is important to not only study the neurobiology of anxiety and stress disorders, but it is especially crucial to research the differences between individuals that are differentially susceptible to the effects of trauma and stress. To begin to address these differences, recent animal model studies have focused on identifying stress 'resilient' and stress 'susceptible' populations. Here, we use an established novelty-induced hypophagia (NIH) paradigm to categorize mice into 'susceptible' versus 'resilient' phenotypes. Briefly, mice were habituated to liquid vanilla ensure and

were subjected to a baseline NIH session during which they were placed into a novel cage with a bottle filled with the vanilla ensure, and their latency to drink from the liquid was recorded. One week later, animals underwent Pavlovian fear conditioning with six 0.7mA tone-shock pairings. The following day, mice were given an NIH test session identical to the first. For each animal, the latency to drink from the vanilla ensure bottle during the baseline NIH session was subtracted from their latency during the NIH test to obtain an index score by which animals were categorized as "resilient" or "susceptible". Subsequently, we exposed mice to several anxiety assays including the elevated plus maze, light-dark box, and marble burying. Mice were then re-exposed to the context in which they underwent fear conditioning. Susceptible male, but not female, mice showed increased anxiety-like behavior both during anxiety assays, and during re-exposure to the fear context. These data suggest that the NIH paradigm predicts anxiety-like behavior in male, but not female mice.

F17. Dynamic Regulation of Cue-Triggered Reward Seeking by the Basolateral Amygdala and Orbitofrontal Cortex

Kurt Fraser, Patricia Janak*

While much is known about the ability of cues in the environment to serve as predictors of reward, the psychological and neurobiological mechanisms that regulate the predictive and motivational significance of reward-paired cues remains unclear. We investigated the regulation of conditioned reward seeking by discrete and phasic sensory events in the environment that inform whether a traditional conditioned stimulus will or will not be followed by reward delivery. We have demonstrated that these cues that resolve ambiguity, called occasion setters, are a unique class of Pavlovian cues that do not predict reward on their own, but are both motivationally desirable and their actions are resistant to extinction. To assess potential neural circuits underlying occasion setting we trained male Long-Evans rats in a task in which a conditioned stimulus was followed by sucrose reward only if preceded in time by the presentation of a different occasion setting cue. Presentation of either the occasion setting cue or the conditioned stimulus on their own was not followed by reward. As a result of this contingency, conditioned responding to the food cup was highest to the conditioned stimulus when preceded by the occasion setting cue. Using reversible inactivation with the GABA agonists baclofen and muscimol, we found that inactivation of either the basolateral amygdala or orbitofrontal cortex prevented rats from using occasion setters to produce adaptive conditioned reward seeking. These deficits were specific to occasion setting, as inactivation of either region in a simple Pavlovian task was without effect. These results are consistent with state value encoding theories of the basolateral amygdala and orbitofrontal cortex and suggest activity within this circuit is critical for flexibly updating the motivational significance of cues on a moment-to-moment basis.

F18. Stress Uncouples mGlu3 and mGlu5 Co-Signaling in the Hippocampus to Impair Contextual Fear

Branden Stansley, Max Joffe, Patrick Qain, Colleen Niswender, Jeff Conn*

Traumatic stress can result in the dysregulation of fear memory that leads to disorders such as post-traumatic stress disorder (PTSD). Our previous studies led to the discovery of a novel metabotropic glutamate receptor subtype 5 (mGlu5) mediated metaplasticity within the hippocampus, which is critical for the formation of fear extinction memory. Recently, we have discovered that mGlu5 maintains significant functional co-signaling with mGlu3 to influence synaptic plasticity and behavior. We therefore formed the hypothesis that this co-signaling between mGlu5 and mGlu3 could influence hippocampal dependent fear behaviors such as contextual fear extinction. We directly tested this hypothesis using contextually conditioned fear learning paradigms and acute slice electrophysiology. C57bl/6 mice or CaMKII-cre;mGlu5-/- mice were used in all studies. Results demonstrate that mGlu3 activation can enhance hippocampal long-term potentiation (LTP) as well as fear extinction retention. These enhancing effects of mGlu3 activation were dependent on mGlu5 activation. Furthermore, we found that acute stress uncouples mGlu3/5 co-signaling at the cellular and circuit level, as evidenced by impaired biochemical phosphatidylinositol hydrolysis and LTP in the hippocampus. These impairments corresponded to the impairment of behavioral fear extinction. Finally, stress-induced impairment of hippocampal plasticity and fear extinction behavior was rescued by potentiation of mGlu5 signaling, but not by mGlu3 activation. These results taken together demonstrate for the first time that mGlu3 activation can boost fear extinction behavior and related neural plasticity in mice. Additionally, these mechanisms are impaired by stress and can be rescued by mGlu5 positive allosteric modulation. These findings have implications for the treatment of stress disorders such as PTSD, as well as the mechanisms underlying such disorders.

F19. Inhibition of Matrix Metalloproteinase-9 Activity to Correct Auditory Hypersensitivity in Fragile X Syndrome

Patricia Pirbhoy, Jonathan Lovelace, Teresa Wen, Devin Binder, Iryna Ethell*

Most individuals with Fragile X Syndrome (FXS) and autism spectrum disorders (ASD) experience improper processing of sensory stimuli (McDiarmid et al., 2017). Auditory cortical neurons of fragile X mental retardation-1 gene knock-out (Fmr1 KO) mice exhibit abnormally sustained responses to sounds and impaired sound selectivity (Rotschafer et al., 2013). Notably, genetic reduction of matrix metalloproteinase-9 (MMP-9) rescued altered event-related potential (ERP) habituation responses in Fmr1 KO mice implicating MMP-9 as a target for reversing auditory processing deficits in

FXS (Lovelace et al., 2016). Both FXS patients and Fmr1 KO mice exhibit high levels of MMP-9, but how this impairs sensory processing and neuronal circuits remains unclear. To test the hypothesis that excessive activity of MMP-9 leads to increased degradation of perineuronal nets (PNNs) and altered parvalbumin (PV) interneuron development, the auditory cortex (AC) of Fmr1 KO C57BL/6 mice and their wild-type (WT) counterparts were treated with a selective MMP-2/9 inhibitor, SB-3CT (250 μM or 25mg/kg), or vehicle at P14 or P22. Immunohistochemistry was used to determine the density of PV-positive interneurons and PNNs in the AC one day after treatment. Results revealed enhanced PNN formation in layer 4 of the AC in Fmr1 KO mice treated with SB-3CT at P14 compared to saline-treated Fmr1 KO mice. To determine whether enhanced PNN formation following treatment of Fmr1 KO mice with the MMP-9 inhibitor reverses auditory processing deficits we measured resting state and evoked neuronal oscillations in freely moving mice implanted with electroencephalography (EEG) electrodes. Results show that acute treatment of SB-3CT (25mg/kg) reduces excessive resting gamma power and normalizes sound-evoked responses in Fmr1 KO mice compared to vehicle. Together, results reveal that inhibition of MMP-9 may serve as a potential therapeutic to ameliorate auditory cortical processing deficits in FXS.

F20. β-Amyloid Disrupts Synaptic CaMKIIα Signaling

Sarah Cook, Ron Freund, Susana Restrepo, Don Arnold, K. Ulrich Bayer*

Processes underlying synaptic plasticity, namely long-term potentiation (LTP) and depression (LTD) of synaptic strength, are required for memory and cognition. These brain functions are severely impaired in Alzheimer's disease (AD), the most common form of adult dementia. AD mouse models exhibit deficits in hippocampal LTP and similar LTP impairments are also found in acute hippocampal slices treated with soluble β-amyloid1-42 oligomers (Aβ, a major neuropathological agent in AD). However, processes mediating these Aβ-induced effects are unclear. LTP requires activation of the Ca2+/calmodulin(CaM)-dependent protein kinase II α (CaMKIIα) by Ca2+-influx through NMDA-type glutamate receptors (NMDARs). Additionally, LTP requires the regulated binding of CaMKIIα to NMDARs, which mediates rapid accumulation of CaMKIIα at excitatory synapses after LTP stimuli. My preliminary findings indicate that this CaMKIIα synaptic targeting is suppressed by acute Aβ application, suggesting a potential disruption in the CaMKIIα/NMDAR interaction. My results also show that this suppression of CaMKIIα translocation occurs in a dose and time-dependent manner that requires CaMKIIα activity. As CaMKII movement to excitatory synapses is required for normal LTP, its suppression provides a mechanism for the well-described Aβ-induced impairment of LTP. Notably, this project employs the use of intrabodies to monitor endogenous CaMKIIα targeting to excitatory and inhibitory synapses during plasticity. This innovative strategy allows for

the simultaneous imaging of multiple endogenous proteins in living cells, without impacting basal localization or cellular function. The results of this project provide insight into cellular and molecular mechanisms underlying Aβ-induced malfunctions in hippocampal plasticity, and may contribute to our understanding of AD-related memory and cognitive impairments.

F21. A Prefrontal-Bed Nucleus Circuit Coordinates the Suppression of Both HPA Output and Passive Coping Behaviors

Shane Johnson, Eric Emmons, Ryan Lingg, Sara Romig-Martin, Ryan Lalumiere, Nandakumar Narayanan, Jason Radley*

The prelimbic subfield (PL) of the medial prefrontal cortex has received considerable attention for its involvement in many facets of the stress response, yet the efferent pathways underlying these systems have yet to be elucidated. Our previous work has implicated the anteroventral subdivision of the bed nuclei of the stria terminalis (avBST) both as a site of integration for information from the limbic forebrain, and in the coordination of hypothalamo-pituitary-adrenal (HPA) and behavioral responses via divergent pathways. These observations indicate that avBST might act as a conduit for the prefrontal cortex to coordinate these responses. To assess this idea, we employed an optogenetic approach to manipulate PL-avBST pathway activity while measuring HPA and behavioral responses during acute challenges. Photoinhibition of halorhodopsin(Halo)-expressing PL terminals in avBST during tail suspension augmented both immobility and HPA output as compared with the YFP control group. Photoexcitation of the pathway diminished passive immobility behavior while HPA output was unaffected. Next, we examined the role of this circuit in the shock-probe defensive burying (SPDB) test which allows a broader behavioral repertoire, including both active (burying) and passive (immobility) coping responses. Animals receiving PL-avBST pathway photoinhibition spent more time immobile and buried less than YFP controls. Photoexcitation of the pathway diminished immobility but was insufficient to enhance burying relative to YFP counterparts. Given evidence from our group implicating the avBST-vlPAG pathway in passive behavioral output, we sought to determine whether this pathway might act downstream of the PL-avBST pathway to modulate coping behavior during the SPDB. Here, animals receiving photoinhibition of the avBST-vlPAG pathway spent more time immobile and buried less than YFP controls - effects that resemble those of PL-avBST photoinhibition. Our data identify a unique circuit that promotes the inhibition of both HPA output and passive coping responses. Withdrawal of top-down control in this pathway may provide a mechanistic link to perturbations of these responses found in stress-related disorders.

F22. Oligodendrocytes Contribute to Brain Glutamate Homeostasis

Wendy Xin, Yevgeniya Mironova, Rosa Anna Maria Marino, Hui Shen, Ari Waisman, Wouter Lamers, Dwight Bergles, Antonello Bonci*

Glutamate is the major excitatory neurotransmitter in the brain. Glutamate uptake and degradation are critical for neuronal signaling and prevention of excitotoxicity, and perturbations of these processes accompany numerous pathological states, including epilepsy, stroke, and ALS. Currently, glutamate uptake and degradation within the brain are thought to occur exclusively in astrocytes - ubiquitous glial cells that express glutamate transporters as well as the glutamate metabolizing enzyme glutamine synthetase (GS). However, a handful of studies have also reported GS expression by oligodendrocytes. Oligodendrocytes produce myelin and ensheath axons to provide electrical insulation, but they have largely been ignored in the context of glutamate regulation. Therefore, we set out to confirm the expression of GS by oligodendrocytes and determine whether they functionally contribute to glutamate processing. qPCR and fluorescent in situ hybridization revealed high levels of GS mRNA in oligodendrocytes, and immunostaining with validated GS antibodies confirmed expression at the protein level. Although they do not express their own glutamate transporters, approximately 90% of oligodendrocytes are structurally coupled to astrocytes via gap junctions. Most strikingly, animals in which GS was specifically deleted from oligodendrocytes have significant decreases in tissue levels of glutamate and glutamine, as well as a reduction in the size of electrically evoked glutamate currents onto midbrain neurons. These results represent a profound departure from the canonical view of glutamate metabolism in the brain and identify a novel, myelin-independent role for oligodendrocytes. As such, oligodendrocytes may represent a new target for treatment in diseases that involve glutamate dysregulation.

F23. Glutamatergic Innervations From the Parabrachial Nucleus to the VTA Produce Aversion

Smriti Mongia, Huiling Wang, Shiliang Zhang, Robert Juza, Marisela Morales*

Dopamine (DA) neurons of the ventral tegmental area (VTA) have been implicated in pain. Early tract tracing studies have shown that the VTA receives inputs from several brain areas known to play a role in pain, including inputs from the parabrachial nucleus (PBN). Here, we applied tract tracing, ultrastructural and optogenetics approaches to characterize the nature of the synaptic connectivity established by PBN neurons in the VTA and determined their role in behavior. We injected the retrograde tract tracer-Fluorogold (FG) in mice VTA, and phenotyped FG neurons in the PBN by combination of in situ hybridization [for the detection of vesicular glutamate transporter 2 (VGluT2), μ-opioid receptor (MOR) or Enkephalin (ENK) mRNA] and

immunohistochemistry for the detection of FG. We found that within PBN, the vast majority (95%) of FG neurons expressed VGluT2, 28% expressed MOR and 41% expressed ENK mRNA. These findings indicate that PBN provides a major glutamatergic input to VTA, which have the capability to co-release enkephalin or be regulated by opioids. Next, we determined the extent to which PBN VGluT2 neurons establish synapses on VTA DA neurons after tagging PBN VGluT2 neurons in VGluT2::Cre mice with a viral vector encoding Cre inducible channelrhodopsin tethered to mCherry. We found that within the VTA, axon terminals from PBN VGluT2 neurons expressing mCherry established asymmetric (excitatory type) synapses mostly (76%) on TH-negative dendrites (TH=tyrosine hydroxylase, DA neuronal marker), and fewer (24%) on TH-positive dendrites. These findings indicate that the PBN VGluT2 neurons provide a major glutamatergic input to non-dopaminergic neurons in the VTA. We found that VTA photostimulation of PBN VGluT2 fibers induced place aversion. Taken together the neuroanatomical and behavioral findings, we conclude that the pathway from PBN to VTA is glutamatergic and establishes synapses mostly on non-DA neurons. This pathway plays a role in aversion and may be regulated by opioids.

This research was supported by the intramural research program at NIDA/NIH.

F24. Behavioral and Synaptic Characterization of a Mouse Model of Syndromic Autism

Adam Harrington, Kayla Blankenship, Jennifer Cho, Ahlem Assali, Catherine Bridges, Duncan Nowling, Christopher Cowan*

Numerous genetic variants associated with MEF2C are linked to risk for a syndromic form of autism, termed MEF2C Haploinsufficiency Syndrome (MHS). These genetic variants range from point mutations within the MEF2C gene to chromosomal deletions of the 5q14.3 locus. The MHS patients have severe social and communication deficits, repetitive behaviors and stereotypies, intellectual disabilities, abnormal pain responses, and epilepsy. Therefore, we set out to create a mouse model of MHS. Previously, we showed that conditional embryonic deletion of Mef2c in Emx1-lineage populations (forebrain excitatory neurons) produces mice with numerous behavioral phenotypes with potential relevance to multiple human neurodevelopmental disorders, including autism and SCZ (Harrington et al., 2016. eLife). However, this genetic manipulation does not reflect MHS patient's genetic makeup. Therefore, we generated global Mef2c heterozygous (+/-) mice and behaviorally tested the offspring to explore autistic-like behaviors. Interestingly, the Mef2c+/- (MHS) mice display profound social and communication deficits, hyperactivity, and reduced pain sensitivity. Furthermore, we find changes in cortical synaptic transmission. Lastly, we show that MEF2C mutations identified in MHS patients disrupt

MEF2C binding to DNA. Together, our data supports that our mouse model of MHS may be a good animal model for studying brain and behavioral dysfunction in MHS and for testing candidate therapeutics for MHS symptoms.

F25. Mutations in the Dopamine Transporter Associated With Movement-And Neuropsychiatric Disease Drives Exploratory Behavior in Mice Through Altered Dopamine Release and Uptake Dynamics

Freja Herborg, Lisa Konrad, Benoît Delignat-Lavaud, Frida Berlin, Ciara Pugh, Louis-Eric Trudeau, Ulrik Gether*

Dysfunctional dopaminergic neurotransmission has long been implicated in the aetiology and symptomatology of both psychiatric disorders, such as ADHD, and movement disorders such as parkinsonism. The dopamine transporter (DAT) exerts a critical function in dopamine homeostasis by mediating reuptake of dopamine. We recently described the first patient, carrying two DAT missense mutations, who suffered from both adult early-onset parkinsonism and ADHD. We have generated a compound heterozygous knock-in (cHET KI) mimicking the patients genotype, and here evaluate the consequences of the mutations in vivo. Dopamine uptake into striatal synaptosomes demonstrated the disruptive effects of the mutations in vivo, showing approximately 75% reduction in uptake capacity in cHET KI mice compared to WT mice. The reduction in uptake capacity was confirmed with fast-scan cyclic voltammetry (FSCV) in striatal slices. FSCV also revealed pronounced reductions in evoked dopamine release that more severe in dorsal striatum (7% of WT) than ventral striatum (31% of WT), indicating regional differenced in impact of the mutations. In behavioral tests the cHET KI mice recapitulated core features of ADHD, including hyperactivity in open field testing and increased exploration in the elevated plus maze. Importantly, treatment with amphetamine lessened the hyperactive phenotype, supporting the predictive validity of the model for ADHD. No gross motor dysfunction was detected up until 6 months of age, but biochemical and immunohistochemical analysis showed that although the DAT mutants were expressed in target regions of dopamine projections, both DAT and TH expression levels were reduced in striatum, seemingly reflecting a combination of axonal loss and presynaptic adaptations in response to altered dopamine balance arising from impairments in DAT function. This novel model shows promising features as construct valid model of ADHD and as a potential tool to investigate putative links between neuropsychiatric diseases and movement disorders.

F26. Metabotropic Glutamate Receptor 1 Potentiation Enhances Prefrontal Cortical Inhibitory Transmission and Rescues Schizophrenia-Like Deficits Induced by NMDAR Hypofunction

James Maksymetz, Samantha Yohn, Max Joffe, Branden Stansley, Nellie Byun, Michael Bubser, Jordan Galbraith, Ellen Rieth, Brianna Li, Mark Moehle, Carrie Jones, Craig Lindsley, Jeff Conn*

Impaired GABAergic interneuron function in the prefrontal cortex (PFC) is one of the most consistent pathophysiological findings in schizophrenia. Deficits in PFC inhibitory transmission are thus hypothesized to underlie many of the cognitive and motivational deficits in schizophrenia that remain largely untreated by current antipsychotic medications. Therefore, enhancing inhibitory transmission may be a viable therapeutic strategy for the development of novel cognition-enhancing drugs for the treatment of schizophrenia. Recently, we demonstrated that a positive allosteric modulator (PAM) for the metabotropic glutamate receptor subtype 1 (mGlu1) exhibited antipsychotic-like efficacy in preclinical models of positive symptoms of schizophrenia. Based on previous work suggesting that mGlu1 is selectively expressed on PFC GABAergic interneurons, we hypothesized that mGlu1 PAMs could also ameliorate cognitive and motivational deficits by normalizing deficient inhibitory transmission in an NMDAR hypofunction model of schizophrenia. We found that the mGlu1 PAM VU6004909 enhances inhibitory transmission but not excitatory transmission onto layer V pyramidal neurons in the mouse PFC. Furthermore, mGlu1 enhances inhibitory transmission in the PFC primarily via actions on somatostatin-expressing, not parvalbumin-expressing, interneurons. Systemic administration of VU6004909 reversed cognitive as well as social and motivational deficits induced acutely by the NMDAR antagonist MK-801, suggesting mGlu1 PAMs may have utility in treating cognitive deficits and negative symptoms in patients with schizophrenia. Future experiments will explore the in vivo mechanism of mGlu1 PAM action using in vivo imaging and genetic approaches. Altogether, these data suggest that mGlu1 PAMs could restore proper inhibition in the PFC and provide pro-cognitive and pro-motivational efficacy in patients suffering from schizophrenia.

F27. Basal and Diet-Induced Differences in Intrinsic Excitability of Medium Spiny Neurons in the NAc Core of Female Obesity-Prone and Obesity-Resistant Rats

Yanaira Alonso-Caraballo, Helena Papacostas-Quintanilla, Carrie Ferrario*

The nucleus accumbens (NAc) plays critical roles in motivated behaviors, including food-seeking in response to Pavlovian cues. Studies from our lab have shown that selectively bred male and female obesity-prone (OP) rats fed a chow diet show stronger motivational responses to food-cues than obesity-resistant (OR), suggesting basal differences in NAc function in OP vs. OR populations. In addition, we found estrous cycle modulation of cue-triggered motivation in OP female rats. These effects in OP rats manifest as enhanced Pavlovian conditioned approach during metestrus/diestrus compared to proestrus/estrus. In addition to the role of the NAc in cue-triggered motivation, basal intrinsic excitability of medium spiny neurons (MSN) in the NAc core is enhanced in male OP vs. OR rats. However, whether differences in MSN excitability or "junk-food"-induced alterations occur in females is unknown. Here, we conducted whole-cell patch clamp recordings to examine basal and diet-induced differences in intrinsic excitability of MSNs in female OP and OR rats, during different estrous cycle phases. Briefly, rats were maintained on chow or given 10 days of a "junk-food" diet, followed by 1-2 days of "junk-food" deprivation prior to recording from the NAc core. MSNs were identified by a stable resting membrane potential around -75mV, marked rectification, and slow-rising ramp depolarization in response to current injections. Initial results show no baseline differences in firing rate, rheobase, action potential properties or I/V between OP and OR females during metestrus/diestrus. Furthermore "junk-food" did not alter the firing rate or I/V in either group compared to chow-fed rats. However, "junk-food" increased the action potential threshold and amplitude in both OP and OR rats. These results differ from data collected in males, where "junk-food" differences in excitability resulted from decreased in fast transient potassium current (IA) in OR, whereas OP rats had increased inwardly-rectifying potassium current (IKIR). Our results point to sex differences in intrinsic excitability and the underlying mechanisms within OP and OR rats. Ongoing studies are examining potential differences in NAc MSN intrinsic properties between the phases of the estrous cycle.

F28. Localization of Spillover-Mediated Glutamate Transmission Onto Cerebellar Molecular Layer Interneurons

Reagan Pennock, Jacques Wadiche*

Cerebellar molecular layer interneuron (MLI) activity is driven by excitatory inputs from conventional synapses with parallel fibers (PFs), as well as by spillover transmission from neighboring climbing fiber (CF) synapses. PF-mediated synaptic transmission occurs at spatially restricted sites along the length of MLI dendrites and can be localized using imaging of Ca2+ influx through Ca2+-permeable AMPA receptors (CP-AMPARs). However, the locus and extent of MLI glutamate receptor activation following CF-spillover transmission has yet to be determined. We used a combination of single CF stimulation, electrophysiological recordings, and two photon (2P) Ca2+ imaging from individual MLIs to localize CF-mediated spillover onto MLIs. We find that CF stimulation results in all-or-none spillover excitatory postsynaptic currents (EPSCs) characterized by slow rise and decay kinetics (relative to synaptic responses) and paired-pulse depression. Similarly, CF-evoked all-or-none Ca2+ transients exhibit long latencies and slow kinetics (relative to PF-evoked Ca2+ transients), as well as paired-pulse depression. Surprisingly, CF-evoked Ca2+ transients were principally localized to proximal dendritic branches of MLIs that project towards the Purkinje cell layer. This suggests that CFs may target portions of MLI dendrites segregated from canonical synaptic activity.

F29. Recycling Endosomes Mediate Local, Golgi-Independent Secretory Trafficking in Dendrites and Spines

Aaron Bowen, Matthew Kennedy*

Long-term storage of memories in the central nervous system depends on the local dendritic synthesis and membrane trafficking of new synaptic proteins such as AMPA-type glutamate receptors (AMPAR). While traditional cell biology dictates that newly synthesized integral-membrane proteins require processing and sorting by the Golgi apparatus (GA) for trafficking, the GA is notably absent from most neuronal dendrites. Consequently, whether secretory cargoes are locally trafficked in dendrites, and if so, the identity and spatial organization of the organelles responsible for trafficking them remain unclear. We have utilized an inducible-ER release system in combination with live-cell fluorescence microscopy to define the dendritic organelles involved in trafficking new AMPA receptors. We found that upon exiting the dendritic endoplasmic reticulum (ER), AMPARs initially undergo spatially restricted entry into nearby ER-Golgi intermediate compartment (ERGIC). AMPARs are subsequently forward trafficked through the recycling endosome (RE) network

which is often located in close proximity to dendritic ERGIC. This pathway is critical for biosynthetic protein trafficking, including to individual synaptic sites via spine-resident REs, as disrupting RE function drastically impairs the surface delivery of newly-released AMPARs. Surprisingly, RE-mediated surface delivery of AMPARs still occurred in the absence of normal GA function, indicating that locally translated proteins may be directly trafficked through this pathway without requiring processing by the somatic GA. Thus, in addition to its canonical role in recycling membrane proteins, the RE network also participates in the local, GA-independent trafficking of new synaptic proteins. Ultimately, this pathway could deliver newly synthesized proteins during translation-dependent forms of neural plasticity.

F30. Evolutionarily Conserved Site on Neurexin3-Alpha Modulates Balance Between Excitation and Inhibition

Susana Restrepo, Jason Aoto, Kylan Nelson*

Imperative for proper synapse formation, Neurexins are a group of evolutionarily conserved presynaptic cell-adhesion molecules whose mutations have been implicated in several neuropsychiatric disorders. Although Nrxns have been studied for decades, many of their functions have yet to be elucidated. In particular, the role of Neurexin3α, has only began to come to light. Little is known regarding how the extracellular portion of Nrxn3α governs synaptic function. We identified a point mutation in an evolutionarily conserved region of Nrxn3α. The patient with this mutation suffers from severe intellectual disability and epileptic seizures. We found that this mutation, has profound effects on ligand binding and alters presynaptic morphology. Moreover, excitatory transmission is altered in the mutant. Knockdown of endogenous Nrxn3α and replacement with WT or mutant Nrxn3α in vitro and in vivo brought to light the role of Nrxn3α's involvement in excitatory and inhibitory transmission. These data exemplify the distinct role of Nrxn3α as a molecule necessary for the balance between excitation and inhibition at the synapse, and how this molecule's dysfunction can lead to unfavorable phenotypes often associated with the E/I imbalance such as epilepsy.

F31. Engineering Photoactivatable Neurotoxins for Light-Dependent Synapse Silencing

Brooke Sinnen, Qi Liu, Emma Boxer, William Buchta, Emily Gibson, Jason Aoto, Chandra Tucker, Matthew Kennedy*

Regulated secretion is critical for diverse biological processes ranging from immune and endocrine signaling to synaptic transmission. Botulinum and tetanus neurotoxins, which specifically proteolyze vesicle fusion proteins involved in regulated secretion, have been widely used as experimental tools to block these processes. Genetic expression of these toxins in the nervous system has been a powerful approach for disrupting neurotransmitter release within defined circuitry, but their current utility in the brain and elsewhere remains limited by lack of spatial and temporal control. Here we engineered botulinum neurotoxin B so that it can be activated with blue light. We demonstrate the utility of this approach for inducibly disrupting excitatory neurotransmission, providing a first-in-class optogenetic tool for persistent, light-triggered synapse silencing. In addition to blocking neurotransmitter release, this approach will have broad utility for conditionally disrupting regulated secretion of diverse bioactive molecules, including neuropeptides, neuromodulators, hormones and immune molecules.

Presenter Disclosures

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