48TH ANNUAL WCBR

JANUARY 24–29, 2015

BIG SKY, MONTANA

WINTER CONFERENCE ON BRAIN RESEARCH

Welcome to the Forty-Eighth Annual Winter Conference on Brain Research

Welcome all to Winter Brain! The Winter Conference on Brain Research (WCBR) is about to celebrate its 50th anniversary but it is its first time in Big Sky, Montana! It all started in Lake Tahoe in 1968, initiated by neuroscientists from Brain Research Institute at UCLA. The WCBR has grown quickly from ~100 to 400-500 participants. With its sophisticated interdisciplinary program, casual atmosphere and superb skiing environments, the WCBR is praised by many as the best conference on brain research. Many participants confess that the ski lift rides in particular offer unique opportunities to make friends and initiate long-lasting collaborations. There are many more other occasions to network: breakfasts, receptions, mountain lunches, ski/snowboard racing, and of course the meetings and sessions.

This year we have a fantastic program. We begin the week with a **Welcome Reception** on Saturday, where you can meet with friends and welcome newcomers (they will wear light green badges) and Travel Fellows (they will have a light green dot on their badge).

On Sunday, we kick off with an **Opening Breakfast** during which we feature our keynote speaker, Dr. **Andres Lozano**, University Professor and Canada Research Chair, University of Toronto, whose lecture *"Adjusting the dials on the circuits in the human brain with deep brain stimulation"* highlights recent advances in the treatment of movement disorders, and disorders of memory and cognition. Dr. Lozano is a pioneer in the use of deep brain stimulation for treating Parkinson's Disease, depression, anorexia and Alzheimer's disease.

On Monday, we have a **Brain Talk Town Meeting** aimed as a dialogue between scientists and non-scientists with Dr. Andres Lozano presenting "Treating Brain Disorders Using Electricity". Attendance is open to all, so invite your family members and non-scientist colleagues. Light refreshments will be provided! The Town Meeting is a traditional component of WCBR Outreach Program; the target audience is students from local schools, and WCBR participants are welcome to join. I encourage everyone to check out and volunteer in our Outreach Program, in which we present sessions at local schools during WCBR. It is a way to return something to the communities that host us at the meetings and stimulate student's interest in science.

We will also have vibrant poster sessions, and as in recent years, the best posters from young investigators are shown during a **Special Poster Session** and Reception on Tuesday. Awards will be given to the best posters identified by the program committee.

Don't forget to visit the **Exhibits** during all poster sessions. Having them in such an informal meeting allows for more in-depth interactions.

On Wednesday, we will have the **Smitty Stevens Memorial Race** for skiers and snowboarders, followed by a **Mountain Lunch**. Please attend the **Business Meeting** on Wednesday after the afternoon sessions, as we will hold elections for Conference Chair-elect and board members. We will also discuss the program, budget and future sites for the meeting. Because board members are critical for WCBR, we encourage you to nominate yourself or a colleague for open board positions in clinical, cellular/molecular, or systems/behavioral neuroscience. We will close the week on Thursday night with the **Annual Banquet**, at which we will give the awards to the Best Posters and the Ski Race competition, and we will wrap up the week dancing to live music.

We are an all-volunteer organization, and this meeting has been possible with the great effort of all those serving in the board of directors and committees as well as by the generous donations of our sponsors who allowed the Fellowship Program to select such an outstanding group of young scientist. Special thanks to Gretchen Snyder, Program Chair; Elmer Yu, Facilities Chair; Kyle Frantz and Susanna Rosi for Travel Fellowships; Susan Ferguson, Outreach Chair; Lloyd Fricker, Town Meeting Chair; Denson Fujikawa, Exhibit Chair, as well as our longtime and tireless Treasurer Jacqueline McGinty. Finally, we thank Michelle Chappell, the heart and soul of the WCBR, for all her hard work and superb organization of the meeting.

We thank you all for your contributions.

Have a great time skiing and snowboarding, enjoy a fantastic scientific program and come back next year!

Barbara K. Lipska
Conference Chair

Contents

General Information

HEADQUARTERS is at the Yellowstone Conference Center, Firehole Lounge, which is conveniently located within walking distance of lodging rooms. All scientific activities will be held there.

WCBR INFORMATION DESK AND MESSAGE CENTER is at the Yellowstone Conference Center, Firehole Lounge

The desk hours are as follows:

	Morning	*Afternoon*
Saturday 1/24	8:00 a.m.–12:00 p.m.	3:30–8:30 p.m.
Sunday 1/25	6:30–10:00 a.m.	3:30–7:00 p.m.
Monday 1/26	7:00–10:00 a.m.	3:30–6:00 p.m.
Tuesday 1/27	7:00–10:00 a.m.	3:30–6:00 p.m.
Wednesday 1/28	7:00–10:00 a.m.	3:30–5:30 p.m.
Thursday 1/29	7:00–10:00 a.m.	

REGISTRATION PACKETS containing a conference badge; tickets for receptions, mountain lunch, and closing banquet; and program book should be picked up at the WCBR Information Desk.

POSTER SESSION 1, SUNDAY
Posters can be set up after 12:00 p.m. on Sunday

Posters will be available for viewing 3:30–10:00 p.m. on Sunday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Sunday.

POSTER SESSION 2, MONDAY
Posters can be set up after 8:00 a.m. on Monday

Posters will be available for viewing 3:30–10:00 p.m. on Monday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Monday.

POSTER SESSION 3, TUESDAY
Posters can be set up after 8:00 a.m. on Tuesday

This is a special session displaying the highest-ranked posters by young investigators. A grand prize and several other prizes will be given to the best posters. Presenters will be with posters from 3:30–4:30 p.m. and returning for the special session 6:30–8:30 p.m. Posters must be removed by 10:00 p.m. Tuesday.

POSTER SESSION 4, WEDNESDAY
Posters can be set up after 8:00 a.m. on Wednesday

Posters will be available for viewing 3:30–10:00 p.m. on Wednesday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Wednesday.

Please refer to pages 24–34 for a listing of poster sessions.

EXHIBITS AND LOUNGE are in Jefferson & Madison. Refreshments are provided 3:30 to 4:30 p.m., Sunday through Wednesday. Exhibitor setup is Sunday, January 25, 12:00–3:00 p.m. All exhibitors should be packed up by 10:00 p.m. on Wednesday, January 28.

BREAKFAST is served to all conference delegates on Sunday 7:00–8:30 a.m. in the Missouri Ballroom and Lobby. Tickets are not required for the Sunday breakfast.

Monday through Thursday breakfast will be available from 6:30–10:30 am, in Huntley Dining Room & Peaks Restaurant (Summit Hotel)

If you are staying in: Huntley, Shoshone, Village Center, or Summit, your breakfast vouchers will be provided upon check-in at the hotel. If you are staying in any other properties, please go to the WCBR information desk to pick up your breakfast vouchers.

DAILY LIFT TICKETS can be purchased at the following locations:

- Concierge Desks (Huntley/Shoshone and Summit) 8:00 am–9:00 pm
- Base Camp 8:00 am–8:00 pm
- Snowcrest Mountain Services (ticket windows) 8:00 am– 4:30 pm

BANQUET table sign-up sheets will be posted next to the Information Desk, Monday–Wednesday. Attendees will have the opportunity to reserve a table at the Thursday banquet. This will make it easier for you and your friends to sit together at the banquet without rushing to hold a table when the doors open. If you have any questions, please inquire at the Information desk.

Continuing Medical Education (CME)

Winter Conference on Brain Research (WCBR) has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of PeerPoint Medical Education Institute and Winter Conference on Brain Research. PeerPoint Medical Education Institute is accredited by the ACCME to sponsor continuing medical education for physicians.

PeerPoint Medical Education Institute designates this educational activity for a maximum of **28.5** *AMA PRA Category 1 credits*. Physicians should only claim credit commensurate with the extent of their participation in the activity. This CME activity was planned and produced in accordance with the ACCME Essentials.

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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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Don't forget to visit the posters & exhibits

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Special Events

SATURDAY, JANUARY 24

Welcome Wine and Cheese Reception • 6:00–7:30 p.m. • Huntley Dining Room

Newcomers, fellows, and mentors only from 6:00–6:30 p.m., all attendees from 6:30–7:30 p.m.

SUNDAY, JANUARY 25

Conference Breakfast and Plenary Address • Missouri Ballroom

7:00–8:30 a.m. • Breakfast

8:00–9:30 a.m. • Plenary Address

The plenary keynote address is presented by:

Andres Lozano MD, PhD, University Professor and Canada Research Chair, University of Toronto

Adjusting the dials on the circuits in the human brain with deep brain stimulation

Dr. Lozano, remembers the most satisfying case of his career—helping a boy with a genetic form of dystonia which had twisted his body to the point where he was only able to crawl on his stomach. While he didn't respond to drugs, he responded wonderfully to deep brain stimulation. Dr. Lozano is a pioneer in deep brain stimulation. His team has mapped out areas of the human brain and pioneered novel surgical approaches to treat disorders like Parkinson's disease, depression, dystonia, anorexia, Huntington's and Alzheimer's disease. Brain shrinkage, declining function and memory loss can now be possibly reversed by the technique known as deep brain stimulation (DBS)—applying electricity directly to regions of the brain. DBS is providing new insights into the function brain circuits leading to new hope for the treatment of neurologic and psychiatric disorders that continue to disable many patients.

Career Development • 2:30–3:30 pm • Lake

Lakshmi Devi, PhD., Dean for Academic Development and Enrichment, Icahn School of Medicine at Mount Sinai, New York

This round-table discussion session will focus on topics including developing individual development plan (IDP)s, mentoring and being mentored, balancing career and life, identifying and resolving conflicts. All travel fellows are encouraged to attend. The session is targeted towards junior investigators (including faculty and postdoctoral fellows).

MONDAY, JANUARY 26

First Meeting of the Board of Directors • 6:30–8:30 a.m. • Talus Room—Summit Hotel

Brain Talk Town Meeting • 7:00–8:30 p.m. • Talus Room—Summit Hotel

Attendance is open to all.

Treating Brain Disorders Using Electricity

Andres Lozano MD, PhD, University Professor and Canada Research Chair, University of Toronto

Deep brain stimulation is a neurosurgical procedure involving the implantation of a medical device that sends electrical impulses through implanted electrodes to specific parts of the brain. This procedure has been approved as a treatment for Parkinson's disease, dystonia (a neurological movement disorder), essential tremor, and obsessive-compulsive disorder. In addition, deep brain stimulation is showing remarkable success in clinical trials for many other disorders including treatment-resistant depression, chronic pain, Alzheimer's and Huntington's disease, and some forms of epilepsy. Disorders that were once incurable now can be treated.

TUESDAY, JANUARY 27

Breakfast for Travel Fellows Meeting • 6:30–7:30 a.m. • Chet's Bar & Grill

Look for the reserved signs

Special Poster Session • 6:30–8:30 p.m. • Jefferson & Madison

The 20 top-ranked posters submitted by junior investigators will be on display, Tuesday from 6:30 to 8:30 p.m. in a special session with wine and cheese provided. Awards will be selected, including a "Best Poster" award. A grand prize will be given to the best poster and several prizes will also be given to runners-up. The awards will be announced at the Closing Banquet on Thursday, January 29. Poster awards made possible by a generous donation by WILEY www.onlinelibrary.wiley.com.

WEDNESDAY, JANUARY 28

Smitty Stevens Memorial Ski Race • 10:00–11:30 a.m. • Chet's Knob

Registration waivers must be completed no later than Monday, January 26, 8:00 a.m. at the WCBR Information Desk. Skiers will access the race course using the Explorer lift and then skiing down Lone Wolf trail.

Mountain Lunch • 11:30 a.m.–2:00 p.m. • Huntley Dining Room

Skiers: lunch is at the Mountain Village area—at the end of the race hill

Required lunch ticket is in your registration packet.

Business Meeting • 6:30 p.m. • Gallatin

Attendees will vote on the Conference Chair-Elect, and new board members. They will also discuss future meeting locations, along with other business items. All are welcome and encouraged to attend.

THURSDAY, JANUARY 29

Second Meeting of the Board of Directors • 6:30–8:30 a.m. • Talus Room—Summit Hotel

Reception • 6:30 p.m. • Chet's Bar & Grill

Banquet and Dance • 7:30 p.m. • Huntley Dining Room

Required ticket is in your registration packet.

Don't forget
Special Poster Reception
Tuesday, 6:30–8:30 p.m.

Program

PREAMBLE TO THE PROGRAM

The 2015 WCBR Program consists of panels, mini-panels, mini-courses, and posters. Please consult the program book and posted announcement for details regarding the scientific presentations as well as information regarding the School Outreach program and the Brain Talk Meeting. **Please note: Special timings for mini-panels (4:30–5:30 pm & 5:30-6:30 pm). New times this year for evening sessions (7:00–8:30 pm.)**

SUNDAY, JANUARY 25, 2015

7:00 A.M.

Breakfast • Missouri Ballroom

8:00 A.M.

Plenary Address • Missouri Ballroom

Adjusting the dials on the circuits in the human brain with deep brain stimulation

Andres Lozano

2:30–3:30 PM

Special Session • Lake

Career Development

Lakshmi Devi, PhD., Dean for Academic Development and Enrichment, Icahn School of Medicine at Mount Sinai, New York

3:30–4:30 P.M.

Exhibits and Posters • Jefferson & Madison

4:30–6:30 PM

Panel • Amphitheatre

NMDAR-dependent synaptic plasticity in health and disease

***Karl Ulli Bayer(Chair)**, Haruhiko Bito, Jose Esteban, Steve Traynelis*

2. **Panel** • Lamar/Gibbon

The emerging roles of peptides in brain function

***Lloyd Fricker (Chair),** Lakshmi Devi, Lucy Vulchanova, Sarah Leibowitz*

3. **Panel** • Dunraven/Obsidian

First Tracks: Moving beyond the first FDA approved EEG biomarker for ADHD

*Stephen Morairty, **David Devilbiss (Chair),** Howard Merry, Sandra Loo*

4. **Panel** • Canyon

   Mouse Models of Genetic Susceptibility for Complex Psychiatric Disorders

   ***Amanda Law (Chair)**, Clare Paterson, Elizabeth Tunbridge, Mark Geyer*

5. **Panel** • Cheyenne

   Neuronal endocytosis in brain development, plasticity and disease

   *Avital Rodal, Rejji Kuruvilla, Subhojit Roy, **Jason Shepherd (Chair)***

6. **Panel** • Gallatin

   Genetic and environmental modulation of prefrontal cortex pathways in health and disease: from rodents to humans

   *Ofer Yizhar, Jeremy Seamans, **Francesco Papaleo(Chair)**, Daniel Weinberger*

7. **Mini-Panel** • Lake

   4:30–5:30 P.M.

   Amphetamine neurotoxicity: Beyond dopamine

   ***Denson Fujikawa (Chair)**, James Bowyer, James O'Callaghan, Diane Miller*

8. **Mini-Panel** • Lake

   5:30–6:30 P.M.

   The System xc- glutamate / cystine exchanger: Consequences of the revolving door

   ***Richard Bridges (Chair)**, Leah Chase, Sarjubhai Patel, Sandra Hewett*

7:00–8:30 P.M.

9. **Panel** • Amphitheatre

   Shared neurobiology of addiction and post-traumatic stress disorder

   ***Jonathan Morrow (Chair)**, Devin Mueller, Constanza Garcia-Keller, Lara Ray*

10. **Panel** • Lamar/Gibbon

    Experience-related plasticity in the mammalian brain: A tribute to William Greenough

    *Roberto Galvez, **Anna Klintsova (Chair)**, Brenda Anderson*

11. **Panel** • Dunraven/Obsidian

    New Perspectives on Inhibitory Neurotransmission: Location, Timing, and Epilepsy

    *Michael Higley, Christopher Ransom, **William Catterall (Chair)***

12. **Panel** • Canyon

    Translational insights into the functional integrity of the central nervous system

    *Alex Santos, Sambit Mohapatra, **Stacey Gorniak (Chair)***

13. **Panel** • Cheyenne

    Sex-dependent effects of adolescent social stress on anxiety- and depression-related behavior and neural circuits

    *Seema Bhatnagar, Jodi Lukkes **(Chair)**, Gretchen Neigh*

14. **Panel** • Lake

    Latent Sensitization to pain and μ-opioid receptor constitutive activity

    *Bradley Taylor, Wendy Walwyn, **Juan Carlos Marvizon (Chair)***

MONDAY, JANUARY 26, 2015

7:30–9:30 A.M.

15. **Panel** • Amphitheatre

    Getting off of benzodiazepines: New molecular targets for modulating GABA neurotransmission for neuropsychiatric disorders

    ***Thomas Hyde (Chair)**, Nicholas Brandon, Tarek Deeb, Gianluca Ursini*

16. **Panel** • Lamar/Gibbon

    Physical activity, obesity and the brain: Hot legs or hot brains?

    ***Catherine Kotz (Chair)**, Colleen Novak, Emily Noble, Jason Tregellas*

17. **Panel** • Dunraven/Obsidian

    Zinc in the brain: new tools and new biology

    ***Elias Aizenman (Chair)**, Thanos Tzounopoulos, Richard Dyck, Larry Benowitz*

18. **Panel** • Canyon

    Novel techniques for elucidating the role of corticotropin releasing factor (CRF) in extra-hypothalamic nuclei

    *Victoria Risbrough, Thomas Kash, Larry Zweifel, Julia Lemos **(Chair)***

19. **Panel** • Cheyenne

    Reward mechanisms across disease processes

    ***Jon-Kar Zubieta (Chair)**, Sara Weisenbach, Jill Becker, Harriet de Wit*

20. **Panel** • Gallatin

    Opto- and chemogenetic insights into natural and pathological motivation and reward

    *Kay Tye, Stephen Mahler, **Michael Stefanik (Chair)**, Kyle Smith*

21. **Panel** • Lake

    Steep slopes: understanding new sites and substrates for sleep and sedation

    ***Andrew Jenkins (Chair)**, John Huguenard, Dave Uygen, Ken Solt*

3:30–4:30 P.M.

Exhibits and Posters • Jefferson & Madison

4:30–6:30 P.M.

22. **Panel** • Amphitheatre

    Non-coding RNA in brain development and disorders

    ***Murray Cairns (Chair)**, Christopher Dayas, Xinyu Zhao, Timothy Bredy*

23. **Panel** • Lamar/Gibbon

    Cyclic Nucleotide Phosphodiesterases: Roles in Diverse Neurodegenerative, Psychiatric and Mood Disorders

    ***Gretchen Snyder (Chair)**, Michy Kelly, Jos Prickaerts, Ying Xu, Nick Brandon, Anthony West*

24. **Mini-Panel** • Dunraven/Obsidian

    4:30–5:30 P.M.

    Parkinson's disease genes, pathways, and therapeutics

    *David Park, Matt LaVoie, **Warren Hirst (Chair)**, Peter LeWitt*

25. **Mini-Panel** • Dunraven/Obsidian

5:30–6:30 P.M.

The ups and downs of gene therapy for CNS disorders; will ongoing clinical attempts in Parkinson's live up to its expectations?

Jude Samulski, Peter LeWitt, ***Krystof Bankiewicz (Chair)****, Howard Federoff*

26. **Panel** • Canyon

Controversies in Ictogenesis and Epileptogenesis

Angus Wilfong, Ed Dudek, ***Claude Wasterlain (Chair)****, Anne Anderson*

27. **Panel** • Cheyenne

Impairments Caused by Cocaine: Cells, Circuits, and Cognition

Caitlin Orsini (Chair)*, Michael Saddoris, Federica Lucantonio, Leslie Whitaker, Kyle Frantz*

28. **Panel** • Gallatin

Recent Findings in the Regulation of Depressed Mood by Glutamate Receptors

Gerard Sanacora, Salah El Mestikawy, Fritz Henn, ***Gustavo Turecki (Chair)***

29. **Panel** • Lake

Intracellular signaling mechanisms affecting alcohol actions and drinking behavior

Han-Ting Zhang (Chair)*, Dorit Ron, Leslie Morrow, Subhash Pandey*

7:00–8:30 P.M.

Brain Talk Town Meeting • Talus Room—Summit Hotel

All are welcome and encouraged to attend

Treating Brain Disorders Using Electricity

Andres Lozano MD, PhD, University Professor and Canada Research Chair, University of Toronto

7:00–8:30 P.M.

30. **Panel** • Amphitheatre

Timing, Training, Treats: How is dopamine related to reward expectation?

Kate Wassum (Chair)*, Erik Oleson, Matthew Wanat, Catharine Winstanley*

31. **Panel** • Lamar/Gibbon

Serotonin and the desire to ski

Kathryn Commons (Chair)*, Jeremiah Cohen, Olivier Berton*

32. **Panel** • Dunraven/Obsidian

Neurons that fire together expire together: Large-scale, network modeling via co-activation and co-atrophy patterns

Peter Fox (Chair)*, Nicolas Crossley, Amit Etkin*

33. **Panel** • Cheyenne

The Dark Side of Opioids: Novel Approaches to Attack Tolerance and Hyperalgesia

Tuan Trang, ***Howard Gutstein (Chair)****, Anna Taylor*

34. **Panel** • Lake

Illuminating dendrite and spine plasticity

Theresa Jones, ***Oswald Steward (Chair)****, Gary Bassell*

TUESDAY, JANUARY 27, 2015

7:30–9:30 AM

35. **Panel** • Amphitheatre

What on earth is the orbitofrontal cortex doing up there?

Christina Gremel, Peter Rudebeck, ***Geoffrey Schoenbaum (Chair)****, Erie Boorman*

36. **Panel** • Lamar/Gibbon

GPCRs and the regulation of synaptic transmission

Reagan Pennock, Nicholas Oesch, ***Christopher Ford (Chair)****, Mark Dell'Acqua*

37. **Panel** • Dunraven/Obsidian

Allosteric Modulation of Cannabinoid Receptor Signaling: The Promise of Nonpsychoactive Cannabinoid Therapeutics

Ruth Ross, Alex Straiker, Elizabeth Cairns, ***Andrea Hohmann (Chair)***

38. **Panel** • Canyon

How to manage cognitive decline in the aging population?

Arjan Blokland (Chair)*, Jos Prickaerts, Jeroen Schmitt, Kristine Hoffman*

39. **Panel** • Cheyenne

The double black diamonds of stress and drug abuse: Crossing trails in the mesocorticolimbic system

Ryan LaLumiere (Chair), *Jayme McReynolds, Matthew Hill, Jason Radley, Olivier George*

40. **Panel** • Gallatin

Genomic and neurobiological studies of RNA binding proteins in complex traits relevant to psychiatric disorders

Camron Bryant (Chair)*, Vivek Kumar, Christopher Cowan, Joseph Dougherty*

41. **Panel** • Lake

Neurotensin in the hypothalamus and ventral midbrain: signaling mechanisms and motivated behavior

Daniel S. Zahm, Gina Leinninger, Pierre-Paul Rompre, ***Mike Beckstead (Chair)***

3:30–4:30 P.M.

Exhibits and Posters • Jefferson & Madison

42. **Mini-Panel** • Amphitheatre

    4:30–5:30 PM

    What's your gut reaction?

    Minda Lynch (Chair), *Laura O'dell, Pietro Cottone, Ralph DiLeone, Devon Graham*

43. **Mini-Panel** • Amphitheatre

    5:30–6:30 PM

    Exploring individual variations in behavior to understand addiction

    Benjamin Saunders (Chair), *Donna Calu, Vedran Lovic, Catharine Winstanley, Jeremy Clark*

4:30–6:30 PM

44. **Panel** • Lamar/Gibbon

    Novel Molecular Pathways in Psychotic Illnesses

    Robert Sweet, ***Jeremy Koppel (Chair)***, *Katherine Burdick, Anil Malhotra*

45. **Panel** • Dunraven/Obsidian

    Interdisciplinary Approaches to the Study of Social Stress Effects on Brain and Behavior in Non-Human Primates

    Zachary Johnson, Mar Sanchez, Vasiliki Michopoulos, ***Gretchen Neigh (Chair)***

46. **Panel** • Canyon

    Plasticity of identified inputs to dopaminergic neurons

    Stephan Lammel, John Williams, DeNard Simmons, ***Carlos Paladini (Chair)***

47. **Panel** • Cheyenne

    Neurobiology of Cognitive Aging

    Peter Rapp, Sheri Mizumori, ***Jennifer Bizon (Chair)***, *Mark Baxter*

48. **Panel** • Gallatin

    Why do ion channels interact with RNA binding proteins?

    Gary Bassell, ***Leonard Kaczmarek (Chair)***, *Vitaly Klyachko, Laurent Ferron*

49. **Mini-Course 1** • Lake

    What's new in neurodegeneration research? A tale of four diseases

    Peter LeWitt (Chair), *Irene Litvan, Cristina Sampaio*

6:30–8:30 P.M.

Special Poster Session & Reception • Jefferson & Madison

WEDNESDAY, JANUARY 28, 2015

7:30–9:30 AM

50. **Panel** • Amphitheatre

    Molecular and Imaging Approaches to Understanding Obsessive-Compulsive Disorder (OCD)

    ***James Knowles (Chair)**, Chris Pittenger, Stephanie Dulawa, Andrew Jaffe*

51. **Panel** • Lamar/Gibbon

    Emerging Pharmacotherapeutics for Cocaine Use Disorder

    ***Kathryn Cunningham(Chair)**, Phil Skolnick, Noelle Anastasio, Carrie Jones, Kathryn Reissner*

52. **Panel** • Dunraven/Obsidian

    The learning brain: Cognitive neuroscience for the educational system

    *Laurie Cutting, Tanya Evans, Valerie Darcey, Susan Magsamen, **Kyle Frantz (Chair)***

53. **Panel** • Canyon

    I'm only sleeping: Regulation of dopamine receptor responsiveness in dopamine neurons

    *Mark Brodie, Brooks Robinson, **Kim Neve (Chair)**, Jennifer Whistler*

54. **Panel** • Cheyenne

    Shocking old/new world: moving towards the more selective stimulation of the human brain

    *Wilder Doucette, Marom Bikson, Christopher Abbott, **Miklos Argyelan (Chair)***

55. **Panel** • Gallatin

    Regulation of excitatory synaptic transmission

    *Jeff Diamond, **James Howe (Chair)**, Katherine Roche, Roger Nicoll*

56. **Panel** • Lake

    Role of flexible intrinsic firing properties in spinal neurons organizing locomotion

    ***Ronald Harris-Warrick (Chair)**, Laurent Vinay, Frédéric Brocard, Kimberly Dougherty*

10:00–11:30 A.M.

Smitty Stevens Memorial Ski Race • Chet's Knob

11:30 A.M.–2:00 P.M.

Mountain Lunch • Huntley Dining Room

3:30–4:30 P.M.

Exhibits and Posters • Jefferson & Madison

4:30–6:30 PM

57. **Mini-Course 2** • Amphitheatre

    Illuminating the Brain

    *Matt Cater, **Lakshmi Devi (Co-Chair)**, **Susan Ferguson (Co-Chair)**, Krystof Bankiewicz*

58. **Panel** • Lamar/Gibbon

    Treatment Targets for Stress and Substance Use Disorders

    ***Jacqueline McGinty (Chair)**, Chantelle Ferland, Foster Olive, Nicholas Gilpin, Nicholas Goeders*

59. **Panel** • Dunraven/Obsidian

    Why do we eat too much? Corticostriatal circuits and feeding behaviour

    Robyn Brown, Christina Gremel, ***Stephanie Borgland (Chair)****, Alain Dagher*

60. **Panel** • Canyon

    An integrative approach probing putative mechanism(s) contributing to injury-induced cognitive impairment

    Edward Hall, Herb Geller, Catharine Winstanley, ***Akiva Cohen (Chair)***

61. **Panel** • Cheyenne

    The dark side of dopamine: Negative reinforcement and aversion

    Kay Tye, Erik Oleson, ***Kimberly LeBlanc (Chair)****, Mary Kay Lobo*

62. **Panel** • Gallatin

    Are you SERTain it's DAT?

    Amy Newman (Chair)*, Anders Kristensen, Habibeh Khoshbouei, Sara Jones, Ulrik Gether*

63. **Panel** • Lake

    Molecular Signaling Pathways that Regulate Excitatory Synapses

    Elva Diaz, Geoffrey Swanson, A Villu Maricq, ***David Bredt (Chair)***

6:30 P.M.

Business Meeting • Gallatin

THURSDAY, JANUARY 29, 2015

7:30–9:30 AM

64. **Panel** • Amphitheatre

    Green circles or black diamonds? Cue discrimination and generalization in fear and reward

    John Howland, ***Joshua Gordon (Chair)****, Larry Zweifel, Lilliane Mujica-Parodi*

65. **Panel** • Lamar/Gibbon

    From GWAS to brains to models: Inflammation in Schizophrenia

    Lisa Boulanger, ***Patricio O'Donnell (Chair)****, Cynthia Weickert, Elliot Hong*

66. **Panel** • Dunraven/Obsidian

    Understanding human brain development and disease through transcriptomics

    Ed Lein (Chair)*, Michael Oldham, Dan Geschwind, Andrew Jaffe*

67. **Panel** • Canyon

    Variety is the spice of the life: Adding flavor to neural function

    Paul Katz (Chair)*, Ralf Sommer, Akira Sakurai, Timothy O'Leary*

68. **Panel** • Cheyenne

Neurobiology, bad decisions and drug seeking

Paul Phillips, Heather Trantham-Davidson, ***Fulton Crews (Chair)****, Jacqueline McGinty*

69. **Panel** • Gallatin

Recent developments in NMDA receptor research: From structure-function to physiology

Ehud Isacoff, ***Kasper Hansen (Chair)****, Stephen Traynelis, Michael Kavanaugh*

70. **Panel** • Lake

The science of intractable epilepsy: When small molecules fail

Thomas Swanson (Chair)*, Detlav Boison, Bruce Ransom, Josh Lawrence, Dave Poulsen*

3:30–4:30 P.M.

Refreshment Break • Lower Atrium

4:30–6:30 PM

71. **Panel** • Amphitheatre

New insights into the role of immune cells in brain function and pathology

Carol Colton, Kim Green, Jonathan Godbout, ***Miles Herkenham (Chair)***

72. **Panel** • Lamar/Gibbon

Early cortical circuits–from function to dysfunction

Patrick Kanold (Chair)*, Anna Hoerder-Suabedissen, Patrick McQuillen, Matthew Colonnese*

73. **Panel** • Dunraven/Obsidian

Androgens, androgen receptors and motoneurons: Relevance to injury and disease

Kathryn Jones (Chair)*, Dale Sengelaub, Ashley Monks, Diane Merry*

74. **Panel** • Canyon

Rethinking how mu opioid receptors in the ventral tegmental area produce reinforcement: Count the ways

Derek van der Kooy, Leslie Sombers, Kevin Wickman, ***Elyssa Margolis (Chair)***

75. **Panel** • Cheyenne

Vasopressin/Oxytocin and the development of mammalian social behavior

Elliott Albers (Chair)*, Elizabeth Hammock, Matthew Paul, Alexa Veenema*

76. **Panel** • Gallatin

Composition and Regulation of AMPA Receptors

Johannes W. Hell (Chair)*, Hey-Kyoung Lee, Bernd Fakler, Richard L. Huganir*

77. **Panel** • Lake

Novel therapies for brain disease in those patients that are going downhill fast

Detlav Boison, Jacci Bainbridge, Pavel Klein, ***Thomas Swanson (Chair)***

6:30 P.M.

Reception • Chet's Bar & Grill

7:30 P.M.

Banquet and Dance • Huntley Dining Room

POSTER SESSION I

SUNDAY, JANUARY 25, 2015 • JEFFERSON & MADISON

Posters will be available for viewing 3:30–10:00 p.m. on Sunday. Presenters will be with posters 3:30–4:30 p.m.

Posters must be removed by 10:00 p.m. on Sunday. Posters can be set up after 12:00 p.m. on Sunday.

P1. Effects of exercise on brain intrinsic network connectivity in overweight/obese adults

Kristina McFadden, Korey Wylie, Marc-Andre Cornier, Edward L. Melanson, Jamie L. Bechtell, Jason R. Tregellas*

P2. Visual influences on intermuscular coherence during the control of postural sway

Adriana Degani, Charles Leonard, Alessander Danna-dos-Santos*

P3. Mild traumatic brain injury increases fear behaviors that are accompanied by increased cortical GABA levels

Alana Conti, Brandy Schneider, Farhad Ghoddoussi, Jennifer Charlton, Robert Kohler, Shane Perrine*

P4. A Novel Mouse Model of Genetic Risk for Excessive Alcohol Drinking

John Crabbe, Nick Grahame*

P5. Gene expression clusters in the central nervous system characterize the estrous cycle in the rat

Sonsoles de Lacalle, Robert Schmidt, Lonnie Welch, Paul Micevych*

P6. GABAergic bouton vesicular GABA transporter and GAD67 relative protein levels in the prefrontal cortex of subjects with schizophrenia

Kenneth Fish, Brad Rocco, David Lewis*

P7. Modulation of the IL-1ß effect on Hippocampal LTP by MK-801

Tammy Ivanco, Katrina Zmavc*

P8. ALK regulates binge ethanol consumption, ethanol reward and dopamine receptor sensitivity in the ventral tegmental area

Amy Lasek, John Dutton, Hu Chen, Chang You, Mark Brodie*

P9. Cellular mechanisms of serotonin regulation of orbitofrontal cortex function following cocaine self-administration.

Carl Lupica, Alexander Hoffman, Agustin Zapata, Andrew Wright*

P10. Deficits in tactile learning in a mouse model of Fragile X Syndrome

Aaron McGee, Megan Arnett, David Herman*

P11. Expression of CHRNA7 and CHRFAM7A and binding properties of the α7 nicotinic acetylcholine receptor show large inter-individual differences in human cortex

Jens Mikkelsen, Majbrit Jensen, Mads Dyrvig, Søren Christiansen, Lars Pinborg, Morten S Thomsen, Jacek Lichota*

P12. Decoding neural circuit components in compulsive sucrose-seeking

Edward H. Nieh, Gillian A. Matthews, Stephen A. Allsop, Kara N. Presbrey, Craig P. Wildes, Rachael Neve, Kay M. Tye*

P13. The pharmacological studies of mGlu5-GABA B receptor interplay in animal models of psychosis

Andrzej Pilc, Joanna Wieronska, Natalia Kleczek*

P14. Brain Banking for Modern Research on Mental Illness

Jonathan Sirovatka, Brent Harris, Robin Kramer, José Apud, Stefano Marenco, Barbara Lipska*

P15. A voltammetric characterization of serotonin and histamine during Parkinson's disease and therapies

Aya Abdalla, Parastoo Hashemi*

P16. Exposure to dietary high-fat modifies reward processing in the brain

Travis Brown, Rebecca Darling, Paige Dingess*

P17. Juvenile onset of stereotypy with loss of BDNF signaling in D1R expressing striatal neurons

Michel Engeln, Ramesh Chandra, Ashley La, T. Chase Francis, Mary Kay Lobo*

P18. CaMKII binding to GluN2B is differentially affected by macromolecular crowding reagents

Dayton Goodell, Tatiana Eliseeva, Steven Coultrap, K. Ulrich Bayer*

P19. Activation of hypothalamic oxytocin neurons blunts obstructive sleep apnea-mediated cardiovascular dysfunction

Heather Jameson, David Mendelowitz*

P20. Dopaminergic neuromodulation of the subthalamic nucleus

Asha Lahiri, Hong-Yuan Chu, James Surmeier, Mark Bevan*

P21. Comparison of neural ensembles engaged by novelty and cocaine

Christopher Olsen, Natalie Nawarawong, Matthew Muelbl, Hu Zhu, Yi Wei Lim, Bryan Roth*

P22. Behavioral deficits and serotonin reductions in rats after chronic L-dopa

Branden Stansley, Bryan Yamamoto*

P23. Cognitive Impairment in a Rat Model of TBI: The Role of Individual Differences

Cole Vonder Haar, Frederick Lam, Wendy Adams, Catharine Winstanley*

P24. Single neuron coding of fairness in the human anterior midcingulate cortex

David Devilbiss, Rick Jenison*

P25. Conditional Reprogramming and Immortalization of Rat Primary Astrocytes

Brent Harris, Lanier Heyburn, Saed Sadeghi, Galam Khan, Jamie Hollowman, Robert Walker*

P26. Functional Analysis of the Schizophrenia- and Autism-associated Gene, Transcription Factor 4 (TCF4) During Cortical Development

Brady Maher, Matthew Rannals, Stephanie Cerceo-Page, Andrew Jaffe, Morganne Campbell, Ryan Gallo, Thomas Hyde, Joel Kleinman, Daniel Weinberger*

P27. The search for LRRK2 kinase inhibitors: A selective and brain available compound to probe the function and safety of LRRK2 as a target for PD

Jaclyn Henderson, Matthew Hayward, Bethany Kormos, Paul Galatsis, Ravi Kurumbail, Elie Needle, Stephen Noell, Harry Samaroo, Warren Hirst*

P28. The Big Sky Brain Project: Bringing experiential neuroscience to Montanans

Amanda Duley, Jessie Herbert, Hannah Motl, Holly Truitt and Michael Kavanaugh*

POSTER SESSION 2

MONDAY, JANUARY 26, 2015 • JEFFERSON & MADISON

Posters will be available for viewing 3:30–10:00 p.m. on Monday. Presenters will be with posters 3:30–4:30 p.m.

Posters must be removed by 10:00 p.m. on Monday. Posters can be set up after 8:00 a.m. on Monday.

P29. Cognitive Control Network Function in Alcohol Use Disorder Before and During Treatment with Lorazepam

Claire Wilcox, Andrew Mayer, Josef Ling, Michael Bogenschutz, Charlene Dekonenko, Rose Bigelow*

P30. Individual Differences in Eye Movements During Speech Perception

Michael Beauchamp, Nathan Doyle*

P31. Ghrelin inhibits GABAergic neurotransmission to cardiac vagal neurons in the nucleus ambiguus

Ned Cauley, Valerie Amann, Jhansi Dyavanapalli, David Mendelowitz*

P32. "Autonomous" CaMKII mediates NMDAR-dependent LTP, LTD and cell death

Steven Coultrap, Ronald Freund, Kelsey Barcomb, Isabelle Buard, Guiying Deng, Tim Benke, Mark Dell'Acqua, Paco Herson, K. Ulrich Bayer*

P33. LPS-induced changes in SOCS-3 are reversed by the cannabinoid agonist CP-55,940 in nodose ganglia

Gaylen Edwards, Juliane Johnston, Kimberly Freeman*

P34. Imaging presynaptic proteins that may contribute to defects in synaptic transmission in a Drosophila model of amyotrophic lateral sclerosis

Hong Fei, Irwin Levitan*

P35. Insensitivity to outcome devaluation in sign-tracking rats

Kimberly Fiscella, Yu-wei Chen, Alex Kawa, Donna Calu*

P36. Activation of neuronal cotransporters as possible molecular mechanism of spreading depolarization-induced dendritic beading

Sergei Kirov, Annette Steffensen, Jeremy Sword, Deborah Croom, Nanna MacAulay*

P37. Activation of metabotropic glutamate 7 receptors decreases nicotine taking and nicotine-seeking in rats

Athina Markou, Astrid Stoker, Xia Li*

P38. Visualization of oxytocin release in the brainstem upon photoactivation of ChR2 expressing fibers originating from parvocellular neurons in the paraventricular nucleus of the hypothalamus

David Mendelowitz, Ramon Pinol, Heather Jameson*

P39. Changes in neuronal dopamine homeostasis following MPP+ exposure

Eugene Mosharov

P40. Intellectual abilities, memory, and behavioural problems in children and adolescents previously treated with glucocorticoids

Olaf B Paulson, Sara Krøis Holm, Martin Vestergaard, Kathrine Skak Madsen, William FC Baaré, Trine Bjørg Hammer, Alfred Peter Born, Hartwig T Siebner, Peter V Uldall*

P41. Disruption of relative reward value by reversible disconnection of orbitofrontal and rhinal cortex using DREADDs in rhesus monkeys

Richard Saunders, Mark Eldridge, Walter Lerchner, Takafumi Minamimoto, Yuji Nagai, Barry Richmond*

P42. Alterations of ESCRT protein CHMP2B contribute to the pathogenesis of PD/DLB by impairing α-synuclein clearance

Brian Spencer, Kori Kosberg, Christina Patrick, Edward Rockenstein, Anthony Adame, Seung-Jae Lee, Changyoun Kim, Paula Desplats, Eliezer Masliah*

P43. Dissecting the mesocortical dopamine pathway and its role in aversive motivation

Caitlin Vander Weele, Gillian Matthews, Romy Wichman, Craig Wildes, Kay Tye*

P44. Adolescent social behavior, social defeat, and housing conditions impact cocaine self-administration in adulthood

Andrew Burke, Klaus Miczek*

P45. Neto proteins: Exploring kainate receptor functional modulation

Theanne Griffith, Geoffrey Swanson*

P46. Associations between Gender Identity and Traditional Gender Roles in Indian and British Women

Samuel Kane, Meenakshi Menon*

P47. Human Postmortem Brain Collection: Brain Donations from a Diverse Population

Michelle Mighdoll, Amy Deep-Soboslay, Daniel Weinberger, Joel Kleinman, Thomas Hyde*

P48. Delineation of rostromedial tegmental nucleus (RMTg) in rats and mice via nociceptin/OFQ expression and anatomical connectivity

Rachel J. Smith, Thomas C. Jhou*

P49. Examining protein synthesis in the nucleus accumbens after withdrawal from extended-access cocaine self-administration

Michael T. Stefanik, Mike Milovanovic, Marina Wolf*

P50. Synphilin-1 in neuronal housekeeping- targeting protein inclusions to the lysosomes

Esther Wong, Sijie Tan*

P51. The neurophysiology of stress-related impairment of prefrontal cognitive function

David Devilbiss, Craig Berridge*

P52. MDMA reduces markers for GABAergic neurons in the hippocampus and increases seizure susceptibility: Role of cyclooxygenase-dependent glutamate release

Gary Gudelsky, Courtney Huff, John Anneken, Jacobi Cunningham, Stuart Collins, Bryan Yamamoto*

P53. The phosphodiesterase-4 (PDE4) inhibitor roflumilast decreases ethanol intake in C57BL/6J mice

Xin Liu, Pi-da Hao, Ming-feng Yang, Da-wei Li, Zong-yong Zhang, Han-ting Zhang, Bao-liang Sun*

P54. Cognition and hippocampal gene expression changes in mice challenged with mild physical- and blast-traumatic brain injury—models for drug development

Nigel Greig, David Tweedie, Lital Rachmany, Barry Hoffer, Chaim Pick*

P55. Anti-methamphetamine vaccine induces robust antibody response and attenuates the behavioral effects of methamphetamine in mice

Colin Haile, Kosten Therese, Xiaoyun Shen, Ramakrishnan Muthu, Berma Kinsey, Arora Reetakshi, Frank Orson, Kosten Thomas*

POSTER SESSION 3

TUESDAY, JANUARY 27, 2015 • JEFFERSON & MADISON

This is a **special session** displaying the highest-ranked posters by young investigators. A Grand prize and several other prizes will be given to the best posters. Presenters will be with posters from 3:30–4:30 p.m. and retruing for the special session 6:30–8:30 p.m.

Posters must be removed by 10:00 p.m. Tuesday. Posters can be set up after 8:00 a.m. on Tuesday.

P56. Alcohol triggers dopamine D1 receptor- and mTORC1-dependent synaptic plasticity in a subset of nucleus accumbens neurons

Jacob Beckley, Khanhky Phamluong, Scott Wegner, Dorit Ron*

P57. Effects of maternal opioid maintenance therapy on neonatal outcomes: Methadone vs. Buprenorphine

Laura Brandt, Stephanie Fischberger, Reinhold Jagsch, Gabriele Fischer*

P58. Cell subtype transcriptional regulation of mitochondrial biogenesis by chronic cocaine

Ramesh Chandra, T. Chase Francis, Prasad Konkalmatt, Michel Engeln, Ariunzaya Amgalan, Leah Jensen, Ashley La, Amy M. Gancarz, Sam A. Golden, Gustavo Turecki, Scott J. Russo, David M. Dietz, Mary Kay Lobo*

P59. Varenicline improves motor, cognitive and psychiatric symptoms in the YAC128 mouse model of Huntington's Disease

Gary D'Souza, Malcolm Tingle, Ailsa McGregor*

P60. Disruption of relative reward value by reversible disconnection of orbitofrontal and rhinal cortex using DREADDs in rhesus monkeys

Mark Eldridge, Walter Lerchner, Takafumi Minamimoto, Yuji Nagai, Richard Saunders, Barry Richmond*

P61. Egr3 Expression in Nucleus Accumbens Medium Spiny Neuron Subtypes Alters Outcomes to Social Defeat Stress

T. Chase Francis, Ramesh Chandra, Michel Engeln, Mary Kay Lobo*

P62. Characterizing subsecond dopamine during ethanol self-administration

Andrew Haack, Sharif Taha*

P63. Establishing a role for the paraventricular nucleus of the thalamus in Pavlovian conditioned approach behavior

Joshua Haight, Kurt Fraser, Huda Akil, Susan Ferguson, Shelly Flagel*

P64. Posttraining optogenetic control of basolateral amygdala projections to the ventral hippocampus modulates the consolidation of emotional, but not contextual, learning in rats

Mary Huff, Ryan LaLumiere*

P65. Corticotropin-releasing factor (CRF) signaling in the prefrontal cortex impairs cognitive function

Sofiya Hupalo, Robert Spencer, Craig Berridge*

P66. Neurokinin 1 receptor signalling from endosomes: a key source of pain signalling

Dane Jensen, TinaMarie Lieu, Michelle Halls, Nicholas Veldhuis, Quynh Mai, Nicholas Barlow, Christopher Porter, Meritxell Canals, Nigel Bunnett*

P67. Identification of human SLC1 transporters that mediate transmembrane flux of D-serine

Genevieve Lind, Jill Farnsworth, Brent Lyda, Nicholas Natale, Alan Foster, Michael Kavanaugh*

P68. Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy

Witold Lipski, Tom Wozny, Vincent DeStefino, Scott Stanslaski, Arun Antony, Donald Crammond, Judy Cameron, Mark Richardson*

P69. Underlying mechanisms and functional consequences of autonomous firing loss in the parkinsonian subthalamic nucleus

Eileen McIver, Jeremy Atherton, D. James Surmeier, Mark Bevan*

P70. Interactions between chronic stress and methamphetamine on the blood-brain barrier: Role of neuroinflammation

Nicole Northrop, Amy Ferng, Nicole Harless, Reka Natarajan, Bryan Yamamoto*

P71. Doxazosin XL reduces Post-traumatic stress disorder (PTSD)checklist-military-scored(PCL-M) ratings in veterans with PTSD

Christopher Rodgman, Christopher Verrico, Manuela Holst, Francisco Franco, Daisy Thompson-Lake, Colin Haile, Richard De La Garza, II, Thomas Newton*

P72. Brain mapping of neurons with a dual glutamatergic-GABAergic phenotype

David H Root, Shiliang Zhang, Hui-Ling Wang, Marisela Morales*

P73. Neurocircuitry and Receptor Mechanisms Underlying the Differential Sensitivity of Prefrontal Cognitive Processes to Psychostimulants

Robert Spencer, Jed Shmusky, Barry Waterhouse, Craig Berridge*

P74. Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala.

Joseph Stujenske, Ekaterina Likhtik, Mihir Topiwala, Joshua Gordon*

P75. Lateral habenula excitatory activity as a neural mechanism underlying ethanol-induced aversion

Shashank Tandon, Sharif Taha*

POSTER SESSION 4

WEDNESDAY, JANUARY 28 • JEFFERSON & MADISON

Posters will be available for viewing 3:30–10:00 p.m. on Wednesday. Presenters will be with posters 3:30–4:30 p.m.

Posters must be removed by 10:00 p.m. on Wednesday. Posters can be set up after 8:00 a.m. on Wednesday.

P76. Sign- and goal-tracking rats learn differently in the face of changing reward value

Sam Bacharach, Alex Kawa, Donna Calu*

P77. Site specific knockdown of D2 autoreceptors alters dopamine kinetics, behavior and sensitivity to dopamine based drugs

Caroline Bass, Kimberly Bernosky-Smith, Brian M, Michael J, Evgeny Budygin*

P78. Optogenetic and pharmacogenetic dissection of STN-GPe in vivo network activity in experimental Parkinson's disease

Joshua Callahan, Ryan Kovaleski, Mark Bevan*

P79. Novel mGluR5 positive allosteric modulator attenuates neurodegeneration and alters microglial polarization after TBI

Alan Faden, Bogdan Stoica, Jeffrey Conn, Alok Kumar, Boris Sabirzhanov, David Loane*

P80. A Clinical Trial of Gene Therapy to Prevent Neuropathy

David Fink, Marina Mata*

P81. Calcium Flux is associated with Synaptotagmin-1's Promotion of the Formation of Axonal Filopodia in developing Neurons

Karen Greif, Anna Brandtjen, Claire Weichelsbaum, Nikitha Ashok*

P82. Estrogen increases cocaine choice under concurrent reinforcement in castrated male rats

Tod Kippin, Jared Bagley, Kyle Ploense, Lana Bubalo*

P83. Understanding the neural dynamics of motivational encoding in the subthalamic nucleus and premotor cortex of the Parkinsonian brain

Mark Richardson, Witold Lipski, Donald Crammond, Michael Randazzo, Stathis Kondylis, Ahmad Alhourani, Robert Turner*

P84. Characterization of c-Jun N-terminal kinase (JNK)-mediated mechanisms of cannabinoid and opioid tolerance

Daniel Morgan, David Marcus, Michael Zee, Ken Mackie*

P85. Hot and cold: Temperature effects on neural circuits from therapeutic hypothermia to febrile seizures.

David Naylor

P86. The role of putative stem and neural progenitor cell populations in adult zebrafish axon regeneration following injury

Jeffery Plunkett, Haydee Torres, Abdiel Badillo, Aileen Hernandez, Alcides Lorenzo Gonzalez, Martin Oudega*

P87. Dependence receptors and retrograde neuronal death after spinal cord injury

Michael Shifman, Cynthia Laramore, James Shahoud, Jie Chen*

P88. Tonic vs. phasic retrograde synaptic modulation by endocannabinoids: differential astrocytic control of anandamide and 2-AG

Jeffrey Tasker, Shi Di*

P89. Sex and species differences in effects of chronic intranasal oxytocin

Karen Bales

P90. Differentiated antidepressant-like profiles of ketamine, fluoxetine and vortioxetine in Flinders Sensitive Line rats depleted of endogenous 5-HT—An approach to gain new mechanistic insights?

Kristian Gaarn du Jardin, Nico Liebenberg, Heidi Müller, Gregers Wegener, Connie Sanchez, Betina Elfving*

P91. Cocaine-induced alterations in calcium signaling in the striatum

Aaron Garcia, Susan Ferguson*

P92. From GWAS to function in schizophrenia: The role of Akt3 in neurocognitive development and conditioned learning

Kristy Howell, Amanda Law*

P93. Parkinsonian subthalamic nucleus-external globus pallidus network activity during stereotyped cortical activity states

Ryan Kovaleski, Joshua Callahan, Mark Bevan*

P94. Chronic stress causes behavioral deficits and decreases serotonin afferents to the medial prefrontal cortex

Reka Natarajan, Nicolas Chiaia, Nicole Northrop, Bryan Yamamoto*

P95. High yields of oligodendrocyte lineage cells from human embryonic stem cells at physiological oxygen tensions for evaluation of translational biology.

Sybil Stacpoole, Sonia Spitzer, Bilada Bilican, Alastair Compston, Ragnhildur Karadottir, Siddharthan Chandran, Robin Franklin*

P96. Phosphodiesterase inhibition and Impulsivity

Marlies van Duinen, Pim Heckman, Arjan Blokland, Jan Ramaekers, Jos Prickaerts*

P97. Circadian variation of alertness and subjective sleep quality in a brain trauma patient

Diane B. Boivin, Jenny Guo, Ari Shechter*

P98. Diet-induced increases in NAc CP-AMPARs and enhanced sensitivity to cocaine in obesity-prone vs. obesity-resistant rats

Carrie Ferrario, Cameron Nobile*

P99. The neural chaperone proSAAS blocks synuclein fibrillation and neurotoxicity

Iris Lindberg, Hua Lam, Michael Helwig, Akina Hoshino, Nikolai Lorezen, Daniel Otzen, Nigel Maidment*

P100. Huntington's disease CSF seeds mHTT aggregation

Steven Potkin, Zhiqun Tan, Charles Glabe, Jane Paulsen, Leslie Thompson, Wah Chiu*

P101. Allosteric regulation of phosphodiesterase-2 controls dopamine-induced GluA1 membrane insertion in medium spiny neurons

Susana Neves

P102. Sensory neuron-induced CSF1 triggers microglial DAP12-dependent neuropathic pain

Allan Basbaum, Zhonghui Guan, Julia Kuhn, Xidao Wang, Smitha Vaman, Andrew Guan, Carlos Solorzano, Joao Braz, Zoe Evans, Brad Colquitt, Sherry Werner, Stavros Lomvardas*

Session Abstracts

SUNDAY, JANUARY 25, 2015

SPECIAL SESSION • SUNDAY, 2:30–3:30 PM • LAKE

Career Development

Presenter: Lakshmi Devi, PhD., Dean for Academic Development and Enrichment, Icahn School of Medicine at Mount Sinai, New York

This round-table discussion session will focus on topics including developing individual development plan (IDP)s, mentoring and being mentored, balancing career and life, identifying and resolving conflicts. All travel fellows are encouraged to attend. The session is targeted towards junior investigators (including faculty and postdoctoral fellows).

PANEL • SUNDAY, 4:30–6:30 PM • AMPHITHEATRE

1. NMDAR-dependent synaptic plasticity in health and disease

Chair: Karl Ulrich Bayer
Presenters: Karl Ulli Bayer, Haruhiko Bito, Jose Esteban, Steve Traynelis

Depending on the precise pattern of stimulation, Ca2+-influx through the NMDA-type glutamate receptor (NMDAR) can induce either long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength, two forms of synaptic plasticity thought to underlie learning, memory and cognition. Additionally, defective or maladaptive plasticity causes detrimental effects in many neurological diseases. This panel will present advances in our understanding of NMDAR-dependent plasticity in health and disease. Ulli Bayer (University of Colorado Denver) will show that "autonomous" CaMKII mediates not only LTP, but also NMDAR-dependent LTD. The underlying mechanisms and implications in neurological diseases will be discussed. Haruhiko Bito (University of Tokyo) will consider two parallel pathways downstream of the NMDAR, Ca2+/calmodulin-dependent phosphorylation and dephosphorylation, and show that both play critical roles in consolidation of long-term memory through regulation of activity-dependent gene expression. Jose Esteban (Centro de Biologia Molecular Severo Ochoa) will show how membrane lipid composition and the endosomal trafficking machinery are regulated upon NMDAR activation during synaptic plasticity.

This regulation will be related to the transport of AMPA-type glutamate receptors into the synaptic membrane. Steve Traynelis (Emory University) will describe the effects of positive allosteric NMDA receptor modulators on GluN2B-containing receptors at hippocampal synapses. These compounds prolong the time course of the GluN2B-mediated component of the synaptic current, thereby increasing the charge transfer, which holds implications for synaptic plasticity.

PANEL • SUNDAY, 4:30–6:30 PM • LAMAR/GIBBON

2. The emerging roles of peptides in brain function

Chair: Lloyd Fricker
Presenters: Lloyd Fricker, Lakshmi Devi, Lucy Vulchanova, Sarah Leibowitz

Peptides are amazing molecules. Some peptides function as neuropeptides, the largest and most diverse class of cell-cell signaling molecules in brain. A number of hormones, including many that influence the brain, are peptides. Peptides also function as chemokines, affecting migration of neurons and expression of classical neuropeptides. Emerging evidence suggests that peptides can also function within the cytosol, affecting numerous physiological processes. This panel will bring together a diverse group of investigators to discuss the latest concepts. Lloyd Fricker will introduce the numerous roles for peptides in brain, ranging from well-studied neuropeptides to newer concepts such as indirect neuropeptides (which function by blocking peptidase activity, and do not directly interact with receptors). He will also present evidence that peptides function within the cytosol and nucleus to regulate protein function. Lakshmi Devi will discuss the function of peptides in the synapse and after internalization into neurons. She will present recent data that supports the concept that peptides continue to signal their receptors even after the receptors are internalized and the peptide has been cleaved by peptidases. Lucy Vulchanova will discuss the field of bioactive peptides that are derived from non-typical precursors, focusing on the protein named VGF. She will present data on interactions and signaling mechanisms of peptides generated from the C-terminal region of VGF in the context of pain signaling. Sarah Leibowitz will present her recent work on the chemokine CCL2—a peptide that binds to the CCR2 receptor and regulates cell migration and expression of neuropeptides such as enkephalin and galanin. She will also discuss the function of these neuropeptides in controlling ingestive behavior. Collectively, the presentations will highlight the multiple and diverse functions of peptides in brain under normal conditions as well as in CNS disease pathologies.

PANEL • SUNDAY, 4:30–6:30 PM •

DUNRAVEN/OBSIDIAN

3. First Tracks: Moving beyond the first FDA approved EEG biomarker for ADHD

Chair: David Devilbiss

Presenters: Stephen Morairty, David Devilbiss, Howard Merry, Sandra Loo

More than 200 years have elapsed since attention deficit hyperactivity disorder (ADHD) was first documented. In addition, nearly a century has passed since the first use of electroencephalography (EEG) to record neural activity. During this time, a number of spectral features of the EEG have been identified that correlate with subgroups of those with ADHD. Last year the US food and drug administration finally cleared the use of an EEG biomarker to aid in the assessment of ADHD. Based on the EEG theta/beta ratio during quietly resting conditions, this diagnostic advancement represents a milestone in general acceptance of using EEG as a quantitative assessment of brain function. However, multivariate signatures of EEG features are being developed that likely will provide a translatable EEG biomarker of ADHD with enhanced diagnostic utility. Stephen Morairty (SRI Director in the Center for Neuroscience) will open by presenting recent work on the use of functional EEG to provide translatable signatures of therapeutic efficacy. David Devilbiss (Univ. Wisconsin - Psychology) will present recent work on the neurophysiology underlying the efficacy of ADHD therapeutics. The effects on neural activity from individual neurons to EEG in animal models will be presented as a translational bridge to clinical findings. Howard Merry (NEBA Health) will overview the process and challenges that were faced in clearing an EEG biomarker to aid in the diagnosis of ADHD. The importance of this milestone for further development of translational diagnostics and personalized medicine will also be highlighted. Sandra Loo (UCLA - Director of Pediatric Neuropsychology) will conclude by presenting evidence that supports an emergent view that multivariate diagnostic signatures are the next steps in developing translational markers of disease and therapeutics.

PANEL • SUNDAY, 4:30–6:30 PM • CANYON

4. Mouse Models of Genetic Susceptibility for Complex Psychiatric Disorders

Chair: Amanda Law
Presenters: Amanda Law, Clare Paterson, Elizabeth Tunbridge, Mark Geyer

The validation and biological translation of susceptibility genes for psychiatric and other complex brain disorders requires novel approaches to rodent model design. This panel will present data on innovative strategies focused on modeling genetic-risk and disease related changes in genes associated with schizophrenia and bipolar disorder, along with assessment of the impact on neurodevelopment and behavior. Prof. Law will present novel evidence that the genome-wide significant schizophrenia risk gene, AKT3, impacts selective aspects of learning and memory in a novel AKT3 hypomorphic mouse. Dr. Paterson will describe findings from a mouse peripheral injection model of NRG3 and NRG1 perinatal overexposure, as a biological model of schizophrenia risk and its impact on cognitive and social development. Dr. Tunbridge will present recent data using a transgenic mouse model of COMT to explore the mechanisms underlying gene-environment interactions involving THC and provide evidence on their convergence with human data. Prof. Geyer will present evidence of developmental, anatomical, behavioral, electrophysiological, and biochemical abnormalities in a Sp4 hypomorphic mouse, a transcription factor associated with schizophrenia and bipolar disorder and a key regulator of brain embryogenesis. The creation of biologically relevant models of genetic susceptibility for complex human brain disorders is critical to understanding the mechanistic basis of disease and for the development of novel therapeutics.

PANEL • SUNDAY, 4:30–6:30 PM • CHEYENNE

5. Neuronal endocytosis in brain development, plasticity and disease

Chair: Jason Shepherd
Presenters: Avital Rodal, Rejji Kuruvilla, Subhojit Roy, Jason Shepherd

Trafficking of proteins to and from the surface of the cell is a highly regulated process and essential for normal cellular physiology. Neurons, due to their highly elaborate morphology and synaptic network, have evolved sophisticated machinery to traffic proteins. Moreover, fast synaptic transmission and synaptic plasticity pose unique cellular challenge for neurons to solve. This panel will concentrate on how neuronal endocytosis contributes to brain development, function and how these processes go awry in disease. Avital Rodal (Brandeis

University) will discuss how the endocytic machinery controls membrane deformation and signaling in Drosophila. Rejji Kuruvilla (The Johns Hopkins University) will examine the role of neurotrophin-dependent endocytic signaling in the developing nervous system. Subhojit Roy (University of California, San Diego) will discuss the role of endocytosis in axonal trafficking and Alzheimer's disease. Finally, Jason Shepherd (University of Utah) will elaborate on the role of post-synaptic endocytosis in synaptic plasticity and memory formation.

PANEL • SUNDAY, 4:30–6:30 PM • GALLATIN

6. Genetic and environmental modulation of prefrontal cortex pathways in health and disease: from rodents to humans

Chair: Francesco Papaleo
Presenters: Ofer Yizhar, Jeremy Seamans, Francesco Papaleo, Daniel Weinberger

The prefrontal cortex (PFC) plays a central role in modulating higher-order cognitive functions, impacting many domains of mammals behaviors such as flexibility, information processing, control and planning, thoughts and emotions. Moreover, impairment of PFC-dependent executive functions typifies many forms of psychopathology, including schizophrenia, autism, ADHD, mood/anxiety disorders and addiction. A growing literature from preclinical and clinical studies demonstrates that the PFC not only plays a major role in orchestrating the behavioral responses to environmental demands, but that neurons in the PFC are highly sensitive to environmental changes. The central goal of this panel is to compare and contrast the physiological and behavioral effects of genetic, environmental and pharmacological alterations of PFC functioning with a strong translational emphasis from rodents to human studies. First, Ofer Yizhar (Weizmann Institute of Science, Israel) will describe experiments using optogenetic techniques for mapping the impact of neuromodulation on PFC microcircuits at the cell and circuit level. Then, Jeremy Seamans (University of British Columbia, Canada) will discuss how amphetamine, at clinically relevant doses, affects PFC attractor ensemble dynamics associated with the performance of a rodent working memory task. Francesco Papaleo (Istituto Italiano di Tecnologia, Italy) will present data on an example of genetic*pharmacological modulation of PFC-dependent cognitive functions and how mouse data can predict behavioral performances in healthy subjects and patients with schizophrenia. Finally, Daniel Weinberger (Lieber Institute for Brain Development, USA) will present data showing associations of GWAS significant loci implicated in schizophrenia with PFC activity studied with fMRI.

MINI-PANEL • SUNDAY, 4:30–5:30 PM • LAKE

7. Amphetamine neurotoxicity: Beyond dopamine

Chair: Denson Fujikawa
Presenters: Denson Fujikawa, James Bowyer, James O'Callaghan, Diane Miller

Methamphetamine (METH) abuse is a major health problem in this country. Until relatively recently, animal studies of the neurotoxic effects of amphetamine (AMP) and its substitutes (AMPs), including METH, MDMA and MDA, have focused on damage to dopaminergic nerve terminals in striatum and underlying neuronal mechanisms that produce terminal damage. Non-striatal regions, non-neuronal cell types and non-CNS organs that participate in AMPs neurotoxicity have not been focused upon. Beyond the dominant role that body temperature plays in AMPs neurotoxicity, few other environmental or physiological factors have been examined that contribute to the neurotoxicity profile of AMPs. In this panel the potential interactive effects of seizures, vascular damage, stress and immune function on the neurodegeneration produced by AMPs will be reviewed. Denson Fujikawa will present evidence that METH produces morphologically necrotic neurons in brain regions in which they occur in chemically induced status epilepticus, in mice with subclinical electrographic seizure discharges. John Bowyer will present evidence that blood-brain barrier leakage/breakdown and cerebral surface vascular dysfunction may be what is responsible for the development of behavioral status epilepticus and neuronal damage. James O'Callaghan will discuss the similar neurotoxicity and neuroinflammatory effects of substituted amphetamines, and will provide data that neuroinflammation is a consequence, not a cause, of neurotoxicity. Finally, Diane Miller will discuss the paradoxical differences between in vivo stressor vs. exogenous corticosterone pretreatment on the neurotoxic effects of AMPs.

MINI-PANEL • SUNDAY, 5:30–6:30 PM • LAKE

8. The System xc- glutamate / cystine exchanger: Consequences of the revolving door

Chair: Richard Bridges
Presenters: Richard Bridges, Leah Chase, Sarjubhai Patel, Sandra Hewett

The System xc- transporter (Sxc-) is an obligate exchanger that couples the import of L-cystine into cells with the export of L-glutamate. Sxc- function is particularly critical in the CNS, as it mediates the uptake of a vital sulfur-containing amino acid needed for glutathione synthesis and oxidative protection, while simultaneously producing an efflux of an excitatory neurotransmitter well known for its contributions to fast and slow synaptic

signaling, synaptic plasticity and excitotoxic pathology. The goal of this panel will be to provide an overview of four topical areas of study on this antiporter. Dr. Bridges (University of Montana) will discuss the molecular pharmacology of Sxc- and describe recent efforts to develop specific inhibitors of the transporter. Dr. Chase will discuss the mechanism by which oxidants regulate the activity of Sxc- in glioma cells. Her data suggest that oxidative stress leads to an increase cell surface expression of Sxc-, while also triggering covalent modification of the transporter that attenuates function. Dr. Patel (University of Montana) will provide an overview of the regulation of Sxc- expression and its potential value as a biomarker for CNS injury. Dr. Hewett (Syracuse University) will present recent work investigating the seemingly paradoxical contribution of astrocyte Sxc- to neural cell death and protection. Each of the presenters will describe how these approaches provide tools and insight into the biological and pathophysiological roles of this transporter in the CNS.

PANEL • SUNDAY, 7:00–8:30 PM • AMPHITHEATRE

9. Shared neurobiology of addiction and post-traumatic stress disorder

Chair: Jonathan Morrow
Presenters: Jonathan Morrow, Devin Mueller, Constanza Garcia-Keller, Lara Ray

Psychiatric disorders such as addiction are most often studied in isolation, even though the majority of patients in actual clinical practice have at least two co-occurring psychiatric illnesses. This approach makes it difficult to identify psychological and neurobiological factors that may be common to different psychiatric disorders. Addiction and post-traumatic stress disorder (PTSD) are highly comorbid in clinical populations, and shared pathophysiological mechanisms between these two disorders may help to explain the frequency with which they co-occur. This panel will discuss evidence of overlapping neurobiological mechanisms of addiction and PTSD emerging from studies of clinical samples and pre-clinical animal models. First, Jonathan Morrow (University of Michigan) will discuss the neurobiology of individual differences in specific behavioral traits in rats that may confer vulnerability to both addiction and PTSD. Devin Mueller (University of Wisconsin-Milwaukee) will discuss converging preclinical evidence that the infralimbic medial prefrontal cortex mediates extinction consolidation across fear and drug paradigms. He will highlight the role of neurotrophic factors in extinction-related plasticity in this brain region. Constanza Garcia-Keller (Medical University of South Carolina) will describe stress-induced adaptations in ventral striatal glutamatergic synapses that predispose animals to cocaine self-administration. She will also discuss a recent clinical trial examining the effects of restoring glutamatergic activity with n-acetylcysteine on comorbid PTSD and addiction

in veterans. Finally, Lara Ray (University of California, Los Angeles) will discuss how experimental psychopathology approaches can be used to test hypotheses derived from preclinical models of addiction (e.g. the allostatic model and the incentive sensitization theory of addiction), as well as to propose studies that combine learning and fear conditioning and addiction vulnerability.

PANEL • SUNDAY, 7:00–8:30 PM • LAMAR/GIBBON

10. Experience-related plasticity in the mammalian brain: A tribute to William Greenough

Chair: Anna Klintsova
Presenters: Roberto Galvez, Anna Klintsova, Brenda Anderson

Experience-dependent plasticity was a central theme throughout the career of William Greenough (Bill). Bill was a leading investigator in the field, and strongly believed that dendritic and synapse growth, retraction and remodeling supported learning and memory. He persisted in demonstrating plasticity at a time when the adult brain was considered to be structurally static. Bill, an enthusiastic and consistent attendee of WCBR, passed away in December of 2013. This session consisting of Bill's former graduate and post-doctoral researchers seeks to pay tribute to his work in this area. Roberto Galvez (University of Illinois at Urbana-Champaign) will present his extension of Bill's research on the Fragile X Mental Retardation Syndrome (FX), a topic of great interest and passion for Bill. Galvez's recent analyses have demonstrated that FX mice exhibit elevated vascular endothelial growth factor (VEGF) expression that when blocked alleviates many FX abnormalities. The current talk will discuss recent analyses utilizing an FDA approved drug to block VEGF in conjunction with molecular, anatomical, and behavioral analyses to elucidate VEGF's role in mediating FX abnormalities. Anna Klintsova (University of Delaware) will talk about extending the use of environmental enrichment to other behavioral stimulating approaches and their potential as rehabilitative tools. She will describe the successful use of complex motor training ("Acrobat learning") and a combination of voluntary exercise with environmental complexity as rehabilitative tools applied to animals exposed to alcohol during the third trimester equivalent, the period when developing brain is vulnerable to the effects of alcohol. Brenda Anderson (Stony Brook University) will describe efforts to develop environments that allow precise control over parameters such as prediction and control over harm. She will discuss how threat without harm shifts behavioral tendencies and alters metabolic plasticity.

PANEL • SUNDAY, 7:00–8:30 PM •

DUNRAVEN/OBSIDIAN

11. New Perspectives on Inhibitory Neurotransmission: Location, Timing, and Epilepsy

Chair: William Catterall

Presenters: Michael Higley, Christopher Ransom, William Catterall

A rich variety of interneurons with unique biophysical and molecular properties exist in the brain. GABAergic interneurons expressing the molecular markers parvalbumin, somatostatin, and the 5-HT3a ionotropic serotonin receptors stand out in abundance and in their potent inhibitory input to dendritic and perisomatic areas of excitatory principal neurons. Recent work sheds new light on the mechanisms of GABAergic neurotransmission onto dendritic spines and shafts, dynamic regulation of tonic inhibitory transmission, and roles of different interneuron types in epilepsy and co-morbidities. Catterall will provide an overview to introduce these different classes of interneurons. Higley will present his work using high-resolution calcium imaging methods that defines the location, timing, and functional significance of GABAergic inhibitory transmission onto dendritic spines and shafts. Ransom will present results showing that tonic inhibition is not truly tonic but can be rapidly regulated by factors associated with ongoing neural activity, including postsynaptic depolarization, nonvesicular GABA release produced by GABA transporter type 1 (GAT1), and postsynaptic GABAB receptor activation. Catterall will present results on a mouse model of Dravet Syndrome (DS), a devastating childhood epilepsy caused by loss-of-function sodium channel mutations. His work demonstrates preferential impairment of action potential firing in specific classes of GABAergic interneurons in mutant mice and defines their differential roles in the phenotypes of epilepsy, premature death, hyperactivity, autistic-like behaviors, and cognitive deficit in DS. Altogether, the results illustrate the roles of unique types of GABAergic interneurons in controlling electrical excitability through phasic and tonic inhibitory mechanisms. Alteration of interneuronal behavior, as occurs in DS, has distinct functional consequences, including epilepsy, autistic-like behaviors, and cognitive impairment.

PANEL • SUNDAY, 7:00–8:30 PM • CANYON

12. Translational insights into the functional integrity of the central nervous system

Chair: Stacey Gorniak
Presenters: Alex Santos, Sambit Mohapatra, Stacey Gorniak

Current demand for translational research in the neurosciences and rehabilitation sciences have increased interest the application of computational approaches to behavioral research. The use of computational analyses on sensory, motor, and cognitive data have recently been used in conjunction with clinical gold-standard evaluation techniques as a means to better evaluate the functional integrity of the central nervous system in human subjects. The application of different computational techniques, originating in physics and engineering sciences, to evaluation of sensory, motor, and cognitive behaviors across several neurological diseases will be the focus of this interdisciplinary panel. Alex Santos (University of Montana) will present electrophysiologic analysis of common neural inputs as a means to understand multi-muscle control changes in patients with mild traumatic brain injury. Sambit Mohapatra (University of Montana) will discuss non-invasive techniques to investigate cortical disruption paradigms, the role of non-lesioned hemisphere, and the associated implications regarding recovery in cerebrovascular accident patients. Stacey Gorniak (University of Houston) will discuss detection and measurement of fine sensory, motor, and cognitive deficits in patient populations with central (eg. Parkinson's disease) and peripheral (eg. diabetic peripheral neuropathy) nerve damage. The panel will finish with a discussion of new research directions and collaborations with neurology-focused clinicians that could arise from these new forms of data analysis with respect to central nervous system functionality.

PANEL • SUNDAY, 7:00–8:30 PM • CHEYENNE

13. Sex-dependent effects of adolescent social stress on anxiety- and depression-related behavior and neural circuits

Chair: Jodi Lukkes
Presenters: Seema Bhatnagar, Jodi Lukkes, Gretchen Neigh

Sex differences in depressive illnesses emerge during adolescence, a time when females are more sensitive to stress and exhibit a higher rate of depression than males. Adverse experiences during adolescence increase susceptibility to develop anxiety and depression through unknown neural mechanisms. This panel will present different rodent models of adolescent social stress to demonstrate sex differences in subsequent anxiety- and depressive-like

behavior and underlying neural substrates. Dr. Bhatnagar (Children's Hospital of Philadelphia) will discuss the immediate and long-term effects of social isolation and chronic social defeat during adolescence in both male and female rats. Dr. Bhatnagar will present results suggesting that the impact of adolescent social stress on behavior is both sex- and stress-specific, and that different neural substrates are engaged in males compared to females by adolescent social stress. Dr. Lukkes (McLean Hospital/HMS) will discuss the sex-dependent, long-term effects of adolescent isolation-rearing on anxiety- and depressive-like behavior. Additionally, Dr. Lukkes will describe a potential link between estrogen, isolation-rearing, and alterations in raphe corticotropin-releasing factor-serotonin interactions during adolescent development. Dr. Neigh (Emory) will discuss the role of the glucocorticoid receptors and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) in sex differences following chronic adolescent stress exposure. She will discuss how these two transcription factors play a role in precipitating a depressive-like phenotype and HPA axis dysregulation in females following chronic adolescent stress, whereas, the same stress exposure elicits an enhanced inflammatory response in males. Together, these talks will summarize effects of adolescent social stress on the neural mechanisms underlying anxiety and depression in both males and females.

PANEL • SUNDAY, 7:00–8:30 PM • LAKE

14. Latent Sensitization to pain and μ-opioid receptor constitutive activity

Chair: Juan Carlos Marvizon
Presenters: Bradley Taylor, Wendy Walwyn, Juan Carlos Marvizon

Latent Sensitization (LS) is a new concept developed in animal models that reproduces the episodic and stress-sensitive nature of many chronic pain disorders. LS is induced by most injuries that trigger persistent pain, including the intraplantar injection of inflammatory agents like Complete Freund's Adjuvant (CFA), surgeries involving skin incision or nerve injury. Typically, these forms of tissue damage produce a period of hyperalgesia lasting from a few days to a couple of months. Afterwards there is an apparent return to normal pain sensitivity; however, administration of a μ-opioid receptor (MOR) inverse agonist such as naltrexone produces a robust reinstatement of the hyperalgesia for a couple of hours in both the ipsilateral and the contralateral paws. In contrast, naltrexone does not induce hyperalgesia when given to animals without LS. Importantly, stress also produces reinstatement in animals with LS but not in control animals, which is reminiscent of the ability of stress to induce pain episodes in chronic pain patients. After a brief introduction by Dr. Marvizon, Dr. Taylor will discuss the properties and signaling pathways involved in LS in mice and will present preliminary data indicating the presence of LS in humans. Dr. Walwyn will show that LS is mediated by the constitutive

activity of MOR receptors using data from mice lacking genes encoding for opioid peptides and MORs. She will also demonstrate MOR constitutive activity in patch-clamp recordings from primary afferent neurons. Lastly, Dr. Marvizon will discuss LS induced by nerve injury in rats, the ability of stress to induce pain reinstatement, the involvement receptors other than MOR and the role of medullary descending pathways in maintaining pain remission during LS. Taken together, our results show that LS involves the modulation of pain at opioid receptors located within multiple levels of the neural axis.

MONDAY, JANUARY 26, 2015

PANEL • MONDAY, 7:30–9:30 AM • AMPHITHEATRE

15. Getting off of benzodiazepines: New molecular targets for modulating GABA neurotransmission for neuropsychiatric disorders

Chair: Thomas Hyde
Presenters: Thomas Hyde, Nicholas Brandon, Tarek Deeb, Gianluca Ursini

Benzodiazepines, through their facilitation of GABA neurotransmission, have been a mainstay of the treatment of neuropsychiatric disorders since their introduction in 1960. Due to sedative side effects, their clinical utility is compromised. There is an alternative route to modulate GABA neurotransmission, through the cation chloride cotransporters KCC2 and NKCC1. In adult brain, KCC2 activation leads to hyperpolarization, while NKCC1 activation has the opposite effect. In multiple CNS disorders there may be a deficit in KCC2 function. Presenter One will provide an overview of KCC2 and NKCC1, including their roles both in human brain development and adult brain function. Presenter Two will review new data around KCC2 function in various models of CNS disorders including Autism Spectrum Disorders and describe possible ways of protecting and regaining KCC2 activity. In particular he will describe emerging data around PKC-dependent phosphorylation of serine 940 on KCC2 as a key modulatory site. Presenter Three will review data demonstrating the critical role of KCC2 as an inhibitor of neuronal excitability and a determinant of the efficacy of GABAA modulators. Specifically, he will show data obtained with a new selective KCC2 inhibitor and data from a KCC2 point-mutant mouse in cell-based and hippocampal slice-based assays of hyperexcitability. Finally, Presenter Four, using RNA sequencing analysis of post-mortem brain human samples, will discuss the regulation of expression of NKCC1. He will show that the promoter of NKCC1 also originates noncoding RNA (ncRNA) transcription and can initiate transcription bi-directionally. One ncRNA partially overlaps the 5' region of the coding NKCC1, and likely plays

a role in regulating the levels of NKCC1 protein. In summary, the development of a new class of drugs specifically targeting KCC2 or NKCC1 is promising and novel approach to normalize GABA neurotransmission across a spectrum of neuropsychiatric disorders.

PANEL • MONDAY, 7:30–9:30 AM • LAMAR/GIBBON

16. Physical activity, obesity and the brain: Hot legs or hot brains?

Chair: Catherine Kotz
Presenters: Catherine Kotz, Colleen Novak, Emily Noble, Jason Tregellas

Physical activity is universally accepted as a means of reducing body weight and as being beneficial for brain health, but there is little understanding about how the brain exerts control over the drive to be physically active, or the mechanisms underlying the reciprocal benefits of exercise on brain and energy balance. To explore this topic, Dr. Catherine Kotz will talk about her work on brain orexin mechanisms regulating physical activity in rodent models and how this influences the propensity for obesity. Dr. Colleen Novak from Kent State University will discuss the role of brain melanocortins and physical activity levels, and the 'hot-legs' project examining how brain melanocortins modulate activity energy expenditure independent of activity level. Physical activity and obesity are inversely linked to learning and memory and cognitive disorders. Dr. Emily Noble from the University of California Los Angeles will discuss the metabotrophic actions of brain derived neurotrophic factor and the opposing effects of exercise and over-nutrition on cognitive function and appetite (rodent models). The panel will close with Dr. Tregellas from the University of Colorado discussing his work in humans investigating neuronal mechanisms of obesity, including exercise effects on brain.

PANEL • MONDAY, 7:30–9:30 AM •
DUNRAVEN/OBSIDIAN

17. Zinc in the brain: New tools and new biology

Chair: Elias Aizenman
Presenters: Elias Aizenman, Thanos Tzounopoulos, Richard Dyck, Larry Benowitz

Since the surprising discovery that Zn2+ is present in large amounts within synaptic vesicles in many areas of the brain, numerous investigators have studied the possible roles of this metal during synaptic transmission. Nonetheless, the physiological roles of Zn2+ during synaptic transmission remain largely unknown. The inability to resolve such fundamental questions of synaptic zinc transmission is largely due to the paucity of zinc–selective biological tools optimized for neurobiological studies. Here, we will present the latest, exciting

new developments in the field that have come about as new tools and models have become available. Elias Aizenman (University of Pittsburgh) will chair and introduce the panel as he summarizes the current status of the field of zinc neurobiology, raising the key questions that need to be answered in future work. Thanos Tzounopoulos (University of Pittsburgh) will discuss recent findings that reveal a novel neuromodulatory role of zinc at inhibiting extrasynaptic NMDA receptors. This modulation was uncovered by the development of a fast, high affinity zinc chelator as well as a novel ratiometric zinc indicator. Richard Dyck (University of Calgary) will present behavioral data using a mouse model of synaptic zinc deficiency demonstrating that vesicular zinc is critical for vibrissae texture discrimination. In addition, he will reveal the impact of synaptic zinc in hippocampal neurogenesis in response to environmental enrichment. Finally, Larry Benowitz (Harvard Medical School) will present his exciting new findings revealing the novel role of synaptic zinc as a suppressor of optic nerve regeneration. He will present data from mouse genetic models and zinc chelator-treated mice that squarely place the metal at a critical juncture of retinal ganglion cell survival and axonal regrowth following optic nerve damage.

PANEL • MONDAY, 7:30–9:30 AM • CANYON

18. Novel techniques for elucidating the role of corticotropin releasing factor (CRF) in extra-hypothalamic nuclei

Chair: Julia Lemos
Presenters: Victoria Risbrough, Thomas Kash, Larry Zweifel, Julia Lemos

Corticotropin releasing factor (CRF) is a stress-associated neuropeptide that is strongly localized in the paraventricular nucleus (PVN) of the hypothalamus and was first characterized as the initiation factor for the activation of the hypothalamic-pituitary-adrenal axis. However, in addition to being localized to the PVN, it has been acknowledged for several decades that CRF as well as its two receptors CRF-R1 and CRF-R2 are widely distributed throughout central nervous system. Yet, understanding how CRF functions in these extra-hypothalmic regions to modulate stress and non-stress related behavior has remained elusive. To date dissecting the actions of CRF in distinct nuclei with spatiotemporal precision has been difficult using conventional pharmacologic, genetic and behavioral techniques. This panel will discuss the use of novel viral and genetic techniques in combination with classical approaches as a means of gaining further insight into the role of CRF in these disparate brain regions. Specifically, the panel will highlight the use transgenics, conditional gene knockout, viral methodologies, pharmacogenetics and optogenetics. Dr. Victoria Risbrough (Univ. of California, San Diego) will discuss the role of

forebrain CRF signaling during development in modulating startle reactivity and stress response traits in adulthood. Dr. Thomas Kash (Univ. of North Carolina, Chapel Hill) will present data demonstrating that 5HT acts on a subset of CRF neurons in the bed nucleus of the stria terminalis to regulate inhibitory microcircuits and gate multiple behaviors. Dr. Larry Zweifel (Univ. of Washington) will discuss the role of CRF and CRF producing neurons in the central nucleus of the amygdala for modulating acute fear responses and cued fear acquisition. Dr. Julia Lemos (NIAAA/NIH) will present data on the cellular actions of CRF in the nucleus accumbens and its role in motivated behavior.

PANEL • MONDAY, 7:30–9:30 AM • CHEYENNE

19. Reward mechanisms across disease processes

Chair: Jon-Kar Zubieta
Presenters: Jon-Kar Zubieta, Sara Weisenbach, Jill Becker, Harriet de Wit

Reward response circuitry and mechanisms form an integral part of the organism's interaction with the environment, organizing behavior and the pursuit, or withdrawal, from potential goals. Alterations in their function have been implicated in the pathophysiology of mood and substance use disorders. This panel will present new data on the influences that impact on reward mechanisms across pathologies. Dr. Zubieta will present data showing exaggerated responses of the nucleus accumbens to anticipated loss in adults diagnosed with Major Depression (MD) compared to healthy controls (HC) that were related to lower dopaminergic function in this area and further linked to treatment responses to placebo and antidepressants. Dr. Weisenbach will expand these data to older MD adults using a task of sustained attention and attentional switching while undergoing fMRI. MD patients, compared to HC demonstrated more diffuse, potentially compensatory activation that were associated with incentive-motivational, apathy scores. Dr. Becker will discuss sex differences in substance use in animal models and the role of ovarian hormones in modulating escalation of drug taking. In a self-administration paradigm more females than males prefer cocaine, with antagonism of α1A-noragrenergic receptors reducing cocaine self-administration only in females, with implications for the treatment of drug abuse. In humans, Dr. de Wit will show that self-rated reward sensitivity predicts susceptibility to stimulant positive drug effects. Trait extraversion was associated with the experience of euphoria and well being after a single dose of d-amphetamine, suggesting that individual variations in reward processing contribute to vulnerability to positive drug effects, increasing liability for future drug use.

20. Opto- and chemogenetic insights into natural and pathological motivation and reward

Chair: Michael Stefanik

Presenters: Kay Tye, Stephen Mahler, Michael Stefanik, Kyle Smith

What compels us to have another Cheeto, do cocaine, or even ski? While some answers might be relatively apparent (Cheetos are delicious), even behaviors that are potentially harmful (like skiing down an icy mountainside or doing drugs) are driven by powerful underlying motivations and rewards.

Understanding these behaviors requires a better comprehension of the brain circuitry that receives, interprets, and responds to salient experiences. Historically, however, heterogeneity within brain regions implicated in reward processing—and therefore in the connectivity between these regions—has made has made this an extremely difficult task. Optogenetics and Designer Receptors Exclusively Activated by Designer Drugs (DREADDS) have provided tremendous insights into how individual cell populations within precisely defined circuits function to produce meaningful behavioral outcomes. This panel will present data obtained using these technologies that advance our knowledge of the neurobiology involved in motivational processes, both for natural and drug rewards.

Kay Tye (MIT) will first present data on how in vivo electrophysiology and optogenetic-mediated photoidentification of ventral tegmental area (VTA) -to-lateral hypothalamus (LH) projections have been used to help establish a casual relationship between the VTA and LH in compulsive sucrose seeking. Second, Stephen Mahler (UC Irvine) will discuss the use of DREADDs and TH:Cre transgenic rats to tease out the role of VTA dopamine neurons in learning, motivation, and reward. Michael Stefanik (Rosalind Franklin University) will explain how optogenetic silencing of nucleus accumbens (NAc) cells or afferents differentially impacts cocaine-seeking behavior and dendritic spine morphology. Kyle Smith (Dartmouth) will conclude the session by presenting new work that utilizes chemogenetic silencing to discern information about how the NAc and ventral pallidum interactions add motivational value to reward-predictive cues.

PANEL • MONDAY, 7:30–9:30 AM • LAKE

21. Steep slopes: Understanding new sites and substrates for sleep and sedation

Chair: Andrew Jenkins
Presenters: Andy Jenkins, John Huguenard, Dave Uygen, Ken Solt

Normal patterns of sleep are essential for optimal health. Harmful sleep disturbances are often secondary to lifestyle choices or disease, but they can also occur sui generis as complex neurologic events that lead to insomnia or excessive sleepiness. In order to reverse these symptoms, humans have constantly sought to chemically modulate the brain's sleep circuitry. For example, today alone, over 2 billion cups of coffee will be consumed around the world and 40 million people will use illegal stimulants. At the other end of the wakeful spectrum, recreational sedatives will by used illicitly by another 300 million people.

Despite the fact we all experience sleepiness and most of us actively modulate our sleep/wake balance chemically on a daily basis, our understanding of how our brain regulates sleep remains incomplete. This panel will discuss our latest data and ideas on the endogenous and exogenous regulation of wakefulness. Andy Jenkins (Emory) will discuss endogenous GABAergic modulators that are associated with pathological sleepiness in humans. John Huguenard (Stanford) will discuss recent findings related to endozepines, endogenously occurring compounds that mimic the actions of benzodiazepines. Dave Uygun (Imperial) will describe zolpidem's (Ambien™) actions in the frontal cortex and in hypothalamic histaminergic neurons. Finally, Ken Solt (Harvard) will describe recent successes in the chemical and electrical "reanimantion" of anesthetized rats.

At the end of the session, as we look forward to future bouts of sedation, either in the bar or as we contemplate the surgeries we need to fix damaged knee ligaments, it is worth remembering that we are in good company. Over the next year, the alcoholic beverage market will exceed $1 trillion and 10 million surgical patients will be sedated by general anesthetics via the pathways and mechanisms discussed in this panel.

22. Non-coding RNA in brain development and disorders

Chair: Murray Cairns
Presenters: Murray Cairns, Christopher Dayas, Xinyu Zhao, Timothy Bredy

The molecular determinants of behaviour are encoded by a large proportion of the genome. Regulation of this complex matrix is important in many aspects of neural development, homeostasis, neuroplasticity and cognition. Highly structured neural tissues need every mechanism at their disposal, in this respect, including the transcription of significant amounts of non-coding regulatory and structural RNA. These molecules display complex expression patterns and are themselves vulnerable to neurodevelopmental dysregulation and dysfunction. This symposium will showcase recent investigation of non-coding RNA expression and function in neural development and neuropsychiatric/neurodevelopmental disorders. Panel discussion will be opened by Murray Cairns (Schizophrenia Research Institute) with an overview of this topic and discussion of research on neurodevelopmental miRNA expression and their significance in neuropsychiatric conditions. Chris Dayas (University of Newcastle, Callaghan) will discuss recent work showing addiction vulnerability is associated with a generalized pattern of downregulated synaptic plasticity genes. Interestingly, miRNA predicted to target these genes, such as Arc, show corresponding changes in striatal subregions. Xinyu Zhao (University of Wisconsin, Madison) will talk about her investigation of the role of noncoding RNA in regulation mammalian neural stem cell differentiation and development and their implication in neurodevelopmental disorders. Timothy Bredy (University of California, Irvine) will conclude the session with discussion of his work investigating experience dependent expression of long non-coding RNAs (lncRNAs) in the medial prefrontal cortex of mice. In particular, the activity-dependent and schizophrenia-related lncRNA, Gomafu, was robustly down-regulated and appears to play a key role in anxiety-like behavior, potentially through interactions with the polycomb repressor complex and the schizophrenia-related Crybb1 gene.

23. Cyclic Nucleotide Phosphodiesterases: Roles in Diverse Neurodegenerative, Psychiatric and Mood Disorders

Chair: Gretchen Snyder

Presenters: Michy Kelly, Jos Prickaerts, Ying Xu, Nick Brandon, Anthony West

Enzymes belonging to the cyclic nucleotide phosphodiesterase (PDE) superfamily are abundantly expressed in brain regions governing cognition, motor activity, and mood. This panel will highlight the roles of specific PDE family members in diverse CNS diseases at both the preclinical and clinical level. Michy Kelly (U South Carolina) will discuss the role of PDE11A in social cognition models and the potential role for this PDE as a target for addressing negative symptoms in schizophrenia. Jos Prickaerts (Maastricht University) will focus on the cognitive effects of inhibitors for PDE4 and PDE5 in models of Alzheimer's disease. Ying Xu (U. Buffalo) will discuss how chronic stress stimulates depression-/ anxiety-like behaviors and structural remodeling of neurons through up-regulation of NADPH oxidase and PDE2 activity. She will review the central role for PDE2A in certain forms of oxidative stress and the potential of PDE2A inhibitors as novel treatments for mood disorders. The final two talks will explore the role of PDE isoforms in movement disorders. Tony West (Rosalind Franklin University) will review the therapeutic effects of PDE10A and PDE9A manipulation in rodent models of Huntington's disease focusing on the electrophysiological effects of enzyme inhibition on disease signatures. Nick Brandon (Astra-Zeneca) will describe progress in understanding the recent discovery of a non-synonymous mutation in human PDE10A2 in a non-progressive chorea in a two-generation pedigree. He will discuss the use of a preclinical transgenic knock-in mouse model to study the movement disorders associated with this mutation and the emerging clinical characterization of this mutation in patients. Together, these presentations will explore isoform-specific involvement of the PDE superfamily of enzymes in multiple diseases affecting cognition, mood, and motor function.

MINI-PANEL • MONDAY, 4:30–5:30 PM •

DUNRAVEN/OBSIDIAN

24. Parkinson's disease genes, pathways, and therapeutics

Chair: Warren Hirst

Presenters: David Park, Matt LaVoie, Warren Hirst, Peter LeWitt,

Parkinson's disease (PD) affects 1% of the population over the age of 65 and current therapies target only the symptoms. Recent progress in both the identification of mutations that cause disease, and in the mapping of common variants that alter risk for PD, suggests that many forms of PD contain a genetic component. Mutations in leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) genes have been linked to PD, together comprising the most common known causes of this neurodegenerative disorder. This panel will discuss these genes, the molecular pathways that are providing new insights into their function together with human biology that may link these targets to sporadic disease and conclude with a review of the recent advances in therapeutics. David Park (University of Ottawa) will describe how fly models are being used to identify genetic interactors of LRRK2 providing insights into this complex protein's mechanistic functions. Matt LaVoie (Harvard Medical School) will discuss the role LRRK2 plays in the homeostatic control of aggregation-prone proteins and emerging data that demonstrates that this protein may not only play a role within neurons but also contributes important biological functions within non-neurons cells. Warren Hirst (Pfizer Neuroscience Research Unit) will present data measuring the levels and activity of LRRK2 and GBA in sporadic and mutation carrier PD patient brains. These results have the potential to provide a critical link, which is currently missing, between LRRK2, GBA and sporadic PD. Peter LeWitt (Henry Ford Hospital) will discuss the challenges and recent advances in improving therapeutics for PD including strategies for enhancing the consistency of levodopa effect, gene therapy and non-dopaminergic drugs. The patients unmet needs and therapeutics of the future will also be presented.

MINI-PANEL • MONDAY, 5:30–6:30 PM • DUNRAVEN/OBSIDIAN

25. The ups and downs of gene therapy for CNS disorders; will ongoing clinical attempts in Parkinson's live up to its expectations?

Chair: Krystof Bankiewicz
Presenters: Jude Samulski, Peter LeWitt, Krystof Bankiewicz, Howard Federoff

The number of patients worldwide who have received some kind of gene therapy is now in the thousands. A subset of that number have received intracranial injections of adeno-associated viruses (AAV) encoding various therapeutic genes directed at ameliorating Parkinson's Disease (PD). In this panel we will examine the current status of Phase 1 and Phase 2 trials of gene therapy for PD and preview improvement in construction and production of viral vectors and delivery technology that promise to make adeno-associated virus-based gene therapy for PD safer and more accessible to interventional neurologist around the world.

Jude Samulski (University of North Carolina) will discuss principles of gene therapy from point of view of molecular biologist that pioneered in vivo gene transfer technology. Peter LeWitt (Henry Ford Hospital) will present data on the AAV-GAD clinical trial in PD, including some of the pre-clinical data that led to the trial. Howard Federoff will provide rational and update on use of growth factors in PD. Krystof Bankiewicz (University of California San Francisco) will discuss ongoing clinical gene delivery trials that utilize MR-controlled delivery of AAV for dopamine replacement in PD and pediatric neurotransmitter deficiency.

PANEL • MONDAY, 4:30–6:30 PM • CANYON

26. Controversies in Ictogenesis and Epileptogenesis

Chair: Claude Wasterlain
Presenters: Angus Wilfong, Ed Dudek, Claude Wasterlain, Anne Anderson

This session will continue our tradition of starting with a clinical case, and of using animal models to discuss some of the most controversial aspects of seizures in the immature brain. We will discuss the significance of the spectacular response to cannabis extracts seen in a few cases of intractable epilepsy, the effect of these intractable seizures on neuronal survival and brain development, the age-specificity of those responses, and the role of inflammation in seizure-associated brain damage. Is the plasticity of the immature brain an asset or a liability for the long-term consequences of

seizures? Is the spectacular response of a few cases to cannabis extracts specific to a gene defect (e.g. SCN1A in Dravet)? Does inflammation make things better or worse, and can we develop effective treatments targeting that mechanism? The speakers of this panel have been at the forefront of progress –and controversy- in those areas.

Angus Wilfong (Baylor) will present a case of a child with intractable status epilepticus and a spectacular response to cannabis extracts, and will discuss whether these therapeutic responses are mediated through cannabinoid receptors, or not. Ed Dudek (University of Utah) will discuss seizure susceptibility versus susceptibility to brain damage and to epileptogenesis in the immature brain. Claude Wasterlain (UCLA) will present a new animal model which causes extensive neuronal loss in very immature rats, and will discuss the role of critical periods of brain development in the long-term consequences of seizures. Anne Anderson (Baylor) will discuss the role of inflammation in seizure-associated neuronal injury, and its therapeutic implications.

This session is designed to be highly interactive, with brief presentations followed by extensive discussion. Audience participants will be allowed three minutes and a single slide to present their own point of view during the discussion period.

PANEL • MONDAY, 4:30–6:30 PM • CHEYENNE

27. Impairments Caused by Cocaine: Cells, Circuits, and Cognition

Chair: Caitlin Orsini
Presenters: Caitlin Orsini, Michael Saddoris, Federica Lucantonio, Leslie Whitaker, Kyle Frantz

Drug addiction is associated with a range of cognitive and motivational alterations, which have the potential to promote continued drug use and relapse. A powerful treatment strategy for addiction could therefore be to attenuate such drug-induced alterations, so as to mitigate further drug-seeking and potential relapse. A step toward this goal is understanding the neural mechanisms of drug-induced alterations in cognition and motivation. This symposium will review our current understanding of how the brain mediates some of the maladaptive behaviors that result from exposure to a prototypical drug of abuse (cocaine) and will provide a forum for discussion between expert panelists and attending scientists. Dr. Orsini will highlight contributions of

the basolateral amygdala and orbitofrontal cortex to risky decision-making in drug-naïve rats, and discuss how alterations in these brain regions may mediate maladaptive risk-taking after cocaine exposure. Dr. Saddoris will describe how chronic exposure to cocaine profoundly affects the neural signaling necessary for aspects of appetitive behavior, and how these deficits are tied to abnormal neural processing during learning. Dr. Lucantonio will explore the effects of previous cocaine exposure on the ability to mentally simulate potential outcomes, with a focus on altered neurotransmission in the orbitofrontal cortex. Finally, Dr. Whitaker will complement these previous presentations by discussing how distributed neuronal populations play a causal role in relapse to cocaine-seeking behavior. Together, these unique perspectives on the common theme of maladaptive behavior resulting from drug use will foster discussion about the state of the field and its future trajectory.

PANEL • MONDAY, 4:30–6:30 PM • GALLATIN

28. Recent Findings in the Regulation of Depressed Mood by Glutamate Receptors

Chair: Gustavo Turecki

Presenters: Gerard Sanacora, Salah El Mestikawy, Fritz Henn, Gustavo Turecki

Major depressive disorder (MDD) is highly prevalent in the general population and is associated with grave consequences, including excessive mortality, disability and secondary morbidity. Treatment of MDD includes a variety of biopsychosocial approaches, but in medical practice antidepressant drugs are the most common therapy. The vast majority of antidepressants act through regulation of monoaminergic neurotransmission. More recently, however, there has been growing evidence pointing to glutamatergic dysfunction in MDD, and similarly, to the efficacy of glutamatergic drugs in treatment of depression. This symposium will discussed recent studies focusing on glutamate and depression. Dr. Sanacora will present rodent studies examining the sequence of events stimulated by NMDAR antagonist drugs that appear to be related to antidepressant action. Dr. El Mestikawy will present interesting data on vesicular glutamate transporter differences in the depressed brain. Dr. Henn will follow presenting data on new glutamatergic targets for antidepressants, particularly focusing on the glutamate uptake transporter. Finally, Dr. Turecki will present translational data on regulation of metabotropic glutamate receptors by non-coding RNA in the depressed brain.

29. Intracellular signaling mechanisms affecting alcohol actions and drinking behavior

Chair: Hanting Zhang

Presenters: Han-Ting Zhang, Dorit Ron, Subhash Pandey, Leslie Morrow

The cyclic AMP (cAMP)-protein kinase A (PKA) signal pathway plays an important role in the mediation of alcohol actions and alcohol drinking. Phosphodiesterases (PDEs) such as PDE4 regulate alcohol-drinking behavior via cAMP-PKA signaling. However, the mechanisms still remain elucidated. This will be discussed in this panel. In addition, alcoholism-related microRNAs such as miR206 and the target brain-derived neurotrophic factor (BDNF) will be highlighted. More specifically, Han-Ting Zhang (WVU) will discuss the effects of PDE4 inhibitors on ethanol drinking and ethanol withdrawal-induced anxiety-like behavior in rodents. He will also present demonstration for the contribution of cAMP-PKA-CREB signaling. Dorit Ron (UCSF) will present data suggesting that a breakdown in the corticostriatal BDNF signaling pathway is a driving force of the shift from recreational alcohol use to uncontrolled compulsive drinking. She will also emphasize the novel role of microRNAs in the process. Her presentation will help understand the molecular mechanisms underlying the transition from social drinking of alcohol to excessive uncontrolled consumption. Subhash Pandey, a junior scientist from the NIAAA, will provide solid demonstrations for the role of miR-206 in alcoholism. Her data will strongly support that induction of miR-206, which decreases BDNF in the medial prefrontal cortex (mPFC), is a contributing mechanism behind escalated alcohol self-administration following dependence. Leslie Morrow (UNC) will discuss ethanol-induced adaptations in GABA-A receptors that are moderated by activation of PKA. She will present evidence in PKA RIIbeta knockout mice and cerebral cortical cultured neurons that suggest a role for PKA in ethanol regulation of GABA-A receptor subtypes. PKA activation can prevent or reverse GABA-A receptor adaptations that are associated with ethanol dependence phenotypes.

BRAIN TALK TOWN MEETING • 7:00–8:30 PM • TALUS

Attendance is open to all

Treating Brain Disorders Using Electricity

Andres Lozano *MD, PhD, University Professor and Canada Research Chair, University of Toronto*

Deep brain stimulation is a neurosurgical procedure involving the implantation of a medical device that sends electrical impulses through implanted electrodes to specific parts of the brain. This procedure has been approved as a treatment for Parkinson's disease, dystonia (a neurological movement disorder), essential tremor, and obsessive-compulsive disorder. In addition, deep brain stimulation is showing remarkable success in clinical trials for many other disorders including treatment-resistant depression, chronic pain, Alzheimer's and Huntington's disease, and some forms of epilepsy. Disorders that were once incurable now can be treated.

PANEL • MONDAY, 7:00–8:30 PM • AMPHITHEATRE

30. Timing, Training, Treats: How is dopamine related to reward expectation?

Chair: Kate Wassum
Presenters: Kate Wassum, Erik Oleson, Matthew Wanat, Catharine Winstanley

While dopamine function is clearly implicated in reward seeking, the precise information coded by such signaling remains unknown. Long-standing evidence suggests that striatal dopamine may encode a reward-prediction error signal, but emerging evidence suggests that dopamine relates not simply to passive learning, but also to motivation. In either case reward expectation plays role. Reward expectation can be influenced by a variety of factors including the timing of reinforcement, reinforcement rate and reward-predictive signals. This panel will present research examining the role of dopamine and dopamine receptor activation in learning, motivation and reward expectation. Kate Wassum (University of California Los Angeles) will discuss the role of phasic mesolimbic dopamine release in action sequence learning and motivation, focusing on how dopamine's relationship to reward seeking changes as a function of training. Erik Oleson (University of Colorado Denver) will present evidence that phasic dopamine release in the ventral striatum functions as a neural timer encoding the initiation of motor sequences that are conducive to reward. Matthew Wanat (University of Texas San Antonio) will discuss how dopamine encodes relative reward rates even in the absence of direct comparisons. Finally, Catharine Winstanley (University of British Columbia)

will discuss data using a rat slot machine task to measure near-miss effects in rodents. In particular, she will share recent data indicating that dopamine has a critical role to play in mediating reward expectancy in this paradigm, and that this effect is mediated via D4 receptors within the anterior cingulate cortex.

PANEL • MONDAY, 7:00–8:30 PM • LAMAR/GIBBON

31. Serotonin and the desire to ski

Chair: Kathryn Commons
Presenters: Kathryn Commons, Jeremiah Cohen, Olivier Berton

Serotonin has a pervasive effect on behavior and emotion, influencing not only our actions but how happy we are in our activities. How serotonin does this still remains largely a mystery: is it a diffuse and tonic system or is there functional, spatial and temporal specificity? How exactly does the serotonin system go wrong to generate states characterized by anhedonia (depression) or the opposite, addiction to pleasurable ends? Our understanding of the function of the serotonin system has been largely derived from pharmacological manipulations that give less insight into how the endogenous serotonin system works. Kathryn Commons (Children's Hospital/Harvard Medical School) will provide an overview of the organization of the ascending serotonin system. Based on new genetic tools, as well as classic functional neuroanatomy, a vision is emerging of two major limbs of the ascending serotonin system, whose organization does not match well with the traditional divide between the dorsal and median raphe nuclei. To surmount the challenge of recording the activity of serotonergic neurons in animals performing behavioral tasks, Jeremiah Cohen (Johns Hopkins University) is using optogenetics to identify serotonergic neurons. His work gives new insight into the relationship between serotonergic neuron activity and reward states on different timescales. Olivier Berton (University of Pennsylvania) will report on the use of optogenetics and viral-based connectomics to examine cortical control of serotonin neurons. These studies give insight into how conscious thought could influence our emotional state. Moreover, they lay the groundwork for deep-brain-stimulation-based therapeutics for disorders of emotion.

PANEL • MONDAY, 7:00–8:30 PM •

DUNRAVEN/OBSIDIAN

32. Neurons that fire together expire together: Large-scale, network modeling via co-activation and co-atrophy patterns

Chair: Peter Fox

Presenters: Peter Fox, Nicolas Crossley, Amit Etkin

Hebb's law states that co-firing is the fundamental principal underlying neuronal network formation. In accord with this law, co-activation patterns have proven an exceptionally powerful construct for discovering and modeling neural networks using a wide variety of recording methods. Meta-analytic co-activation modeling—mining the human functional neuroimaging literature to create network models—is a new, highly accessible, rapidly growing strategy for network discovery. An exciting (potential) corollary of Hebb's law is that neurological and psychiatric disorders may exhibit their network organization via their co-atrophy patterns. This suggests that the structural neuroimaging literature (most notably voxel-based morphometry or VBM) can be used to discover both disease-related neuronal networks via their orderly decline (i.e., co-atrophy patterns). In this panel, Peter Fox (University of Texas) will give an overview of co-activation and co-atrophy modeling methods and present a new meta-analytic model of major depressive disorder. Nicolas Crossley (King's College London, UK; P. Catholic University, Chile) will present graphic theoretical co-activation modeling evidence that functional brain abnormalities in schizophrenia and structural changes in brain disorders broadly defined selectively effect connectome hubs. Amit Etkin (Stanford University) will present co-atrophy models a range of mental illnesses, demonstrating atrophy of a common neural network across disorders, and its relation to both cognition in healthy individuals and cognitive dysfunction in mental illness. Implications for neuropsychiatric nosology will be discussed.

PANEL • MONDAY, 7:00–8:30 PM • CHEYENNE

33. The Dark Side of Opioids: Novel Approaches to Attack Tolerance and Hyperalgesia

Chair: Howard Gutstein
Presenters: Tuan Trang, Howard Gutstein, Anna Taylor

Opioids are the pharmacological cornerstone of modern pain therapy. However, their use is plagued with major side effects that limit their utility in controlling pain, such as loss of pain relieving effects (analgesic tolerance), paradoxical pain (hyperalgesia), and drug dependence. The relationship between these side effects is a major contentious issue in the field. In this workshop we will highlight recent breakthroughs that debunk the prevailing dogma that opioid tolerance and hyperalgesia are inevitable consequences of opioid use that reflect a single underlying cellular and molecular mechanism. We will present two novel mechanisms that dissociate the core components of opioid tolerance (Gutstein) and hyperalgesia (Trang). In addition, we will present new evidence that will spark debate about the importance of toll-like receptor-4 in mediating these negative effects of opioids (Taylor). This workshop will engage participants in discussions that challenge traditional views of opioid analgesia.

PANEL • MONDAY, 7:00–8:30 PM • LAKE

34. Illuminating dendrite and spine plasticity

Chair: Oswald Steward
Presenters: Theresa Jones, Oswald Steward, Gary Bassell

This session was organized as a tribute to William Greenough, and highlights areas of research that Bill pioneered. The focus is on how experience alters synapses as evidenced by experience-dependent modifications in dendrites, spines, and synapses and how these processes are altered in developmental disorders, especially Fragile X syndrome. The session will be introduced by Kathie Olson, highlighting Bill (and that hat) at WCBR. Theresa Jones will describe dendritic spine plasticity underlying motor skill learning and motor recovery after stroke, as examined in rodent models. This includes live animal imaging studies of dendritic spine plasticity during skill learning and new directions in the use of live animal imaging to understand the coordination of dendritic and vascular plasticity during motor rehabilitative training after stroke. Os Steward will describe dynamic aspects of mRNA trafficking in dendrites and synapse-specific localization using live cell imaging and activity-dependent regulation of mRNA translation at synapses during activity-induced synaptic modifications. Gary Bassell will discuss the seminal early role that Bill Greenough played in exploring the neurobiology of Fragile X syndrome and how this disorder affects synaptic plasticity. This body of work includes several

major stories, including the discovery and characterization of the dendritic spine phenotype in human patients and the mouse model, as well as providing insight into the mechanism and function of FMRP localization within dendrites and spines. In recognition of Bill's commitment to training the next generation, the session will end with brief presentations by students or postdocs relevant to the topic and that use of "illuminating" and "dynamic" technologies that Bill would enjoy.

TUESDAY, JANUARY 27, 2015

PANEL • TUESDAY, 7:30–9:30 AM • AMPHITHEATRE

35. What on earth is the orbitofrontal cortex doing up there?

Chair: Geoffrey Schoenbaum
Presenters: Christina Gremel, Peter Rudebeck, Geoffrey Schoenbaum, Erie Boorman

The orbitofrontal cortex (OFC) has gone from a prefrontal backwater to one of the more popular cortical areas. At present, Pubmed is averaging over 50 papers per month including the term 'orbitofrontal'. Increasingly, it is implicated in nearly every behavior and neuropsychiatric disorder. With this high level of interest however has come increasing confusion over what the OFC does and how it does it. Response inhibition, cognitive flexibility, Pavlovian outcome expectancies, credit assignment, model-based behavior, a cognitive state space, and even regret - what does it all mean? Our panel will expose some of these new results and how they might change our view of the OFC. First up, Christina Gremel will present evidence from reinforcer devaluation studies suggesting that a core function of the orbitofrontal cortex is signaling the current value of predicted outcomes, in both instrumental as well as Pavlovian settings. Her data call into question the idea that the OFC is not concerned with self-initiated actions controlled by value. Peter Rudebeck will build on this, showing comparable data in primates while also presenting controversial results disputing this region's long-standing involvement in response inhibition, emotion regulation and reversal learning. Then, in the last two talks, Geoffrey Schoenbaum will present single unit recording data from rats engaged in an unblocking task, which suggest that OFC neurons are best tuned to features of predicted rewards rather than value, and Erie Boorman will present data from fMRI studies in humans showing that the OFC is engaged when rewards are contingent and in fact represents those rewards dependent on antecedent events. Together, these data are contrary to the idea that OFC signals a common currency value. At the end of the panel, we will reserve time for discussion of how these datasets relate and what explanations of OFC function they perhaps allow us to rule out and which deserve more study.

36. GPCRs and the regulation of synaptic transmission

Chair: Christopher Ford

Presenters: Reagan Pennock, Nicholas Oesch, Christopher Ford, Mark Dell'Acqua

Multiple neurotransmitters throughout the nervous system signal through G-protein coupled receptors to shape the activity of neural circuits. Located at both pre-and post-synaptic sites, GPCRs modulate the release of transmitters, control the excitability of post-synaptic cells and initiate second messenger pathways that regulate synaptic transmission. The differential coupling to G-proteins and effectors at various regions allows fine-tuning that efficiently shapes signaling and communication between different neurons. In this panel speakers will discuss recent work examining the different roles of GPCRs in controlling synaptic physiology. First, Reagan Pennock (Colorado State) will discuss differential coupling and desensitization of opioid and GABAB receptors at pre- and post-synaptic sites that regulate GABAergic circuitry in hypothalamic circuits. Nicholas Oesch (NINDS/NIH) will present data examining how mGluR6 receptor translates phasic glutamate release from photoreceptors into depolarization in rod bipolar cells by using archaerhodposin-based voltage imaging approaches. Christopher Ford (Case Western) will talk about how efficient coupling between dopamine D2-receptors and GIRK channels can provide an electrophysiological readout of the synaptic time course of dopamine transmission at synapses in the dorsal striatum. Lastly, Mark Dell'Acqua (UC Denver) will present data on the regulation of postsynaptic cAMP and calcium signaling by AKAP scaffold protein anchoring of PKA and calcineurin. He will discuss how this AKAP79/150 signaling complex is linked to the beta2-adrenergic receptor, AMPA receptors, and L-type voltage-gated Ca2+ channels at excitatory synapses.

PANEL • TUESDAY, 7:30–9:30 AM •

DUNRAVEN/OBSIDIAN

37. Allosteric Modulation of Cannabinoid Receptor Signaling: The Promise of Nonpsychoactive Cannabinoid Therapeutics

Chair: Andrea Hohmann

Presenters: Ruth Ross, Alex Straiker, Elizabeth Cairns, Andrea Hohmann

Direct activation of cannabinoid CB1 receptors produces both desirable therapeutic properties and unwanted (psychoactive) side effects that limit clinical use. The recent discovery of an allosteric binding site on the cannabinoid CB1 receptor– a site distinct from the classical (orthosteric) binding site– has emboldened drug discovery efforts to develop positive allosteric modulators (PAMs) of CB1 signaling. Because PAMs change the affinity of the endogenous orthosteric ligand without binding to the orthosteric binding site, they are likely to elicit minimal cannabimimetic side effects compared to direct CB1 agonists. We have gathered an international panel of scientists at the forefront of research on cannabinoid allosteric modulators to probe the state of current research and explore the therapeutic potential of CB1 PAMs. The panel will characterize small molecule PAMs at multiple levels of analysis (binding, signaling, electrophysiology, preclinical models). Ruth Ross (University of Toronto) will introduce the pharmacology of CB allosteric modulators using in vitro binding and signaling assays and highlight opportunities for development of new therapeutics. Alex Straiker (Indiana University) will explore allosteric modulation of endocannabinoid signaling at synaptic CB1 receptors using patch clamp electrophysiology and an autaptic neuronal culture model. Elizabeth Cairns (Dalhousie University) will discuss neuroprotective effects of CB1 PAMs in ocular disease models, and highlight therapeutic possibilities for treatment of chronic ocular diseases, including glaucoma. Andrea Hohmann (Indiana University) will close by presenting preclinical data suggesting that CB1 PAMs suppress neuropathic pain without producing tolerance, withdrawal, or unwanted CB1-mediated side effects. Thus, cannabinoid allosteric modulators offer the potential to produce a more circumscribed and beneficial spectrum of biological effects compared with direct activation of CB1 receptors.

PANEL • TUESDAY, 7:30–9:30 AM • CANYON

38. How to manage cognitive decline in the aging population?

Chair: Arjan Blokland
Presenters: Arjan Blokland, Jos Prickaerts, Jeroen Schmitt, Kristine Hoffman,

There is a growing number of older people and most of these older people are confronted with a decline in cognitive functions. Aging research has been interested in the factors that underlie the decrease in brain function. Based on this research various approaches have been suggested to prevent or treat the decline in cognitive functions in old age. One approach suggests that nutritional ingredients can preserve and improve brain function. Various studies show that nutrition can have a beneficial effect on cognitive function. Jeroen Schmitt (Nestle Research, Switzerland) has been involved in this research area and has been active in this area for many years. He will provide an overview of the status in this field and present the potential benefits of nutrition. Kristine Hoffmann (Danish Dementia Research Centre, Denmark) will present data that show that a healthy life style is an important factor that contributes to a healthy brain and hence preserved cognitive function in old age. Jos Prickaerts (Maastricht University) has been involved in the development of cognition enhancing drugs. He will present data on the development of new drugs that may treat cognitive impairments. Finally, Arjan Blokland (Maastricht University) will present data of studies using brain stimulation to improve cognitive functions. The aim of this session is to discuss the four possibilities to improve or preserve cognitive functions in old age.

PANEL • TUESDAY, 7:30–9:30 AM • CHEYENNE

39. The double black diamonds of stress and drug abuse: Crossing trails in the mesocorticolimbic system

Chair: Ryan LaLumiere
Presenters: Jayme McReynolds, Matthew Hill, Jason Radley, Olivier George

It has long been suggested that the effects of stress impinge on the mesocorticolimbic-based reward system and that such effects interact with those systems underlying drug abuse and addiction. Indeed, both clinical and pre-clinical evidence suggests that stress alters multiple facets of drug addiction, including reward and relapse, that are regulated by regions such as the prefrontal cortex (PFC), amygdala, nucleus accumbens, and ventral tegmental area (VTA). However, the nature of these effects and the mechanisms by which stress and drug addiction interact remain unclear. The panel will discuss recent findings on these issues, addressing stress interactions both with

systems known to regulate reward and with the processes of addiction. First, Ryan LaLumiere (University of Iowa) will provide introductory comments. Jayme McReynolds (Marquette University) will discuss work indicating that stress potentiates relapse produced by other stimuli and that this effect is mediated through alterations in the nucleus accumbens and interactions with the endocannabinoid system in the prelimbic cortex. Matt Hill (University of Calgary) will discuss how endocannabinoids buffer the effects of stress in the brain, focusing on recent findings indicating that endocannabinoid signaling in the PFC and the amygdala produce their anti-stress effects through distinct mechanisms. Jason Radley (University of Iowa) will present data showing that repeated self-administration of cocaine in rats leads to impairments in prefrontal structural plasticity, working memory deficits, and increased adrenocortical activity. Olivier George (Scripps Research Institute, CA) will provide evidence suggesting the existence of a novel population of corticotropin-releasing factor neurons in the VTA that appear to play a critical role in multiple aspects of nicotine addiction.

PANEL • TUESDAY, 7:30–9:30 AM • GALLATIN

40. Genomic and neurobiological studies of RNA binding proteins in complex traits relevant to psychiatric disorders

Chair: Camron Bryant
Presenters: Camron Bryant, Vivek Kumar, Christopher Cowan, Joseph Dougherty

Many psychiatric disorders, including the addictions and autism spectrum disorders, possess a strong genetic component; however, genome-wide studies have yet to explain most of the heritability. Regulation of gene transcription and translation functionally bridges genetic variation with disease. RNA binding proteins act in the nucleus and cytoplasm to affect RNA metabolism and stability, splicing, transport, localization, and translation. Recent genome-wide analysis of behaviors and specific cell types converge on the identification of RNA binding proteins that exert pleiotropic effects on addiction and autism traits. This panel discusses the identification of these RNA binding proteins and their closely associated molecular partners. Camron D. Bryant (Boston University School of Medicine) will describe a forward genetic, transcriptome, and genome editing analysis that identifies Hnrnph1 (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene for behavioral sensitivity to methamphetamine—a gene implicated in mu opioid receptor splicing and heroin addiction. Vivek Kumar (The Jackson Laboratory) will discuss the identification of Cyfip2 (cytoplasmic FMRP interacting protein) as a quantitative trait gene that influences cocaine behaviors and plasticity in the nucleus accumbens and new results in Cyfip1 and Cyfip2 conditional knockout

mice. Complementary to this discussion, Christopher W. Cowan (Harvard Medical School, McLean Hospital) will describe recent findings regarding fragile X mental retardation protein (FMRP) and the regulation of cocaine-induced synaptic and behavioral plasticity. Finally, Joseph D. Dougherty (Washington University School of Medicine) will conclude with convergent genetic analysis in humans and cell type-specific analysis of the transcriptome in mice that identifies Celf6 as a gene involved in autistic-like behaviors and new studies regarding the neural circuitry and molecular mechanisms of mammalian communicative behavior.

PANEL • TUESDAY, 7:30–9:30 AM • LAKE

41. Neurotensin in the hypothalamus and ventral midbrain: Signaling mechanisms and motivated behavior

Chair: Mike Beckstead

Presenters: Daniel S. Zahm, Gina Leinninger, Pierre-Paul Rompre, Mike Beckstead

Neurotensin (NT) is a modulatory peptide that exhibits a broad central distribution and numerous functional roles. Although it was first described in the 1970s, recent findings from multiple laboratories are providing new insights into the mechanisms through which NT can act through hypothalamic and ventral midbrain circuits to alter locomotor, feeding and drug abuse behaviors. This panel will present findings related to NT signaling that were obtained using a variety of approaches. Zahm (St. Louis Univ.) will introduce the circuitry relevant to the session and will then address whether NT- and GABA-mediated input to dopamine neurons in the ventral tegmental area (VTA) originate in neurons where NT and GABA are co-localized or are separate neuronal subsets. He will discuss this and other issues related to the accumbens, lateral preoptic area-ventral pallidum, RMTg and VTA, utilizing tract-tracing and immunohistochemistry at light and electron microscopic resolution. Leinninger (Michigan State Univ.) will present data concerning the NT-expressing neurons in the lateral hypothalamic area that regulate body weight by coordinating metabolism and motivation. Her work combines genetic mouse models and site-directed technologies to define the neuronal circuits, signaling and behaviors regulated by these neurons, and how disruption of this system can lead to obesity. Rompre (Univ. of Montreal) will describe the sensitizing effect of NT receptor activation on amphetamine-induced locomotion, conditioned place preference, and ERK activation. These effects occur in the midbrain and are dependent on NMDA receptor activation, NTS2 receptors and the MAP

kinase pathway. Finally, Beckstead (UTHSC, San Antonio) will show that NT induces long-term depression of D2 dopamine autoreceptor-mediated synaptic currents in mouse midbrain slices. These effects are mediated by NTS2 receptors and calcineurin, and may suggest a role for endogenous NT as a retrograde messenger in the midbrain.

MINI-PANEL • TUESDAY, 4:30–5:30 PM • AMPHITHEATRE

42. What's your gut reaction?

Chair: Minda Lynch
Presenters: Laura O'dell, Pietro Cottone, Ralph DiLeone, Devon Graham

Feeding related peptides in the gut gain access to the brain via the enteric nervous system and systemic circulation. Recent evidence suggests that peptides regulating feeding and appetite are also positioned to control central processes that modulate reward and motivated behavior. Thus, overlapping substrates sub-serving drug reward and feeding may be under control of similar and/or convergent biochemical processes. This panel will explore mechanisms by which feeding regulatory systems gain access to neuronal signaling in mesocorticolimbic reward regions of the brain, altering drug abuse vulnerability. Panel participants will discuss the role of central neurotransmitter systems and reward-related brain circuitry in the development of food addiction and overeating behavior. The panel includes researchers working at various levels of analysis to elucidate factors that promote compulsive behaviors. First, Dr. Laura O'Dell (University of Texas El Paso) will provide introductory comments and a discussion of brain systems believed to modulate motivated behavior. She will present work in the area of insulin regulation of enhanced nicotine intake in rodent models of diabetes. Second, Dr. Pietro Cottone (Boston University) will present findings on the biological bases of eating disorders, the role of stress in addiction, and overlapping phenotypes for excess intake in both models. Dr. Ralph DiLeone (Yale University) will present data illustrating cortical regulation of feeding and addictive behavior via central dopaminergic mechanisms. Dr. Devon Graham (Vanderbilt University) will then discuss brain-gut interactions and the role of glucagon-like peptides in modulating rewarding effects of cocaine. Finally, the Chair, Dr. Minda Lynch (NIDA), will summarize key points of the panel discussion and provide an overview of the implications of identifying neurobiological risk factors that lead to eating disorders and drug abuse.

MINI-PANEL • TUESDAY, 5:30–6:30 PM •

AMPHITHEATRE

43. Exploring individual variations in behavior to understand addiction

Chair: Benjamin Saunders

Presenters: Donna Calu, Vedran Lovic, Catharine Winstanley, Jeremy Clark

Recent studies have demonstrated considerable individual variation in rodent learning strategies, responsivity to reward cues, and decision-making. Understanding the factors that contribute to this variation will be important for developing targeted interventions for addiction and other impulse control disorders. The speakers in this panel will present new research focusing on individual differences in such reward-related processes, and insights gleaned about the underlying neural circuitry. Benjamin Saunders (University of California-San Francisco) will first provide opening comments. Donna Calu (NIDA) will present data exploring how individual differences in conditioned responding during auto-shaping (sign- and goal-tracking) predict differences in learning about changing reward value in devaluation and unblocking. She will also discuss neural recording data in basolateral amygdala and nucleus accumbens of sign- and goal-tracking rats to determine the potentially dissociable neural correlates underlying these individual differences. Vedran Lovic (MIT) will discuss data demonstrating that sign-tracking rats, relative to goal-tracking rats, show sensitized dopamine transmission in the nucleus accumbens, and greater cue-propagated reinstatement, in response to the short-acting opioid, remifentanil. Catharine Winstanley (University of British Columbia) will present new findings showing that rats who make disadvantageous choices of "high-risk, high-reward" options on a rat gambling task show worsened performance after acquisition of cocaine self administration, but decision-making in rats that choose optimally on the task is unaffected by drug-taking. Finally, Jeremy Clark (University of Washington) will present data examining the hypothesis that chronic, early-life alcohol use biases learning strategies in adulthood, in parallel with alterations in dopamine transmission.

44. Novel Molecular Pathways in Psychotic Illnesses

Chair: Jeremy Koppel
Presenters: Robert Sweet, Jeremy Koppel, Katherine Burdick, Anil Malhotra

Schizophrenia, Alzheimer's disease, and bipolar disorder represent phenotypically distinct behavioral disorders that share an element of disease expression in those who suffer from delusions and hallucinations as well as cognitive dysfunction. The current panel will present new data from human, animal, and in vitro studies that suggest novel pathways that may point the way towards a new era of disease-modifying therapeutics. Dr. Robert Sweet will present findings in post-mortem tissue derived from the auditory cortex of individuals suffering from schizophrenia that suggest impaired signaling of glutamate protein networks to the cytoskeleton, including alterations in microtubule-associated protein 2 (MAP2), with supportive follow-up studies in animal and in-vitro models. Dr. Anil Malhotra will outline the results of a recent MRI study of fist episode schizophrenia implicating drug-induced changes in cortico-striatal functional connectivity with severity of psychosis. These results suggest that increased functional connectivity of the striatum with prefrontal and limbic regions may be a biomarker for improvement in symptoms associated with antipsychotic treatment. Dr. Jeremy Koppel will present data from a post-mortem study of individuals with Alzheimer's disease with and without psychosis that suggest a gender-specific tau-driven vulnerability in psychotic Alzheimer's disease. Additionally, results from a follow-up study in a tau mouse model implicating the same pathogenic phospho-tau species in driving a psychosis-like behavioral phenotype in tau mice will be presented. Dr. Katherine Burdick will highlight the results of an investigation of a multiplex assay of plasma cytokines in individuals with bipolar disorder with and without psychosis, with a focus on interactions in immune pathways with disrupted cognition and the potential significance of these findings for cognition-based therapies.

PANEL • TUESDAY, 4:30–6:30 PM •

DUNRAVEN/OBSIDIAN

45. Interdisciplinary Approaches to the Study of Social Stress Effects on Brain and Behavior in Non-Human Primates

Chair: Gretchen Neigh

Presenters: Zachary Johnson, Mar Sanchez, Vasiliki Michopoulos, Gretchen Neigh

Social subordination stress in female macaques has profound effects on somatic disease and psychological function. The behavioral, physiological and neurobiological effects of this stressor will be examined from multiple perspectives in this symposium. Dr. Zachary Johnson will give an overview of the female macaque model of social subordination stress. His discussion will include review of the behavioral and physiological phenotypes that differentiate dominant from subordinate monkeys and research findings this model has facilitated to date. Dr. Mar Sanchez will discuss the effects of subordination on the development of neural circuitry involved in emotional behavior and the regulation of stress responses. Dr. Sanchez will present recent findings using structural MRI, DTI and resting state functional MRI techniques and will integrate the discussion of the effects of social experience on brain maturation with those caused by developmental increases in estradiol during adolescence. Dr. Vasiliki Michopoulos will detail the effects of social status differences on feeding behavior, metabolic profile, and dopaminergic neurochemistry (PET neuroimaging) and detail the dependence of these effects on dietary environment. Additionally, she will describe data indicating that activity of the stress axis is critical for the emotional feeding in subordinate females, as well as the hypofunctional reward system characteristic of subordinate females. Finally, Dr. Gretchen Neigh will demonstrate functional consequences of subordination on glucocorticoid receptor responses and examine the influence of stress-induced changes in immune function on disease outcome in simian immunodeficiency virus. Together, these presentations will emphasize that socially housed rhesus monkeys represent a cogent animal model in which to systematically study the physiological and behavioral consequences of chronic psychosocial stress exposure in humans.

PANEL • TUESDAY, 4:30–6:30 PM • CANYON

46. Plasticity of identified inputs to dopaminergic neurons

Chair: Carlos Paladini
Presenters: Stephan Lammel, John Williams, DeNard Simmons, Carlos Paladini

Dopaminergic neurons in the substantia nigra pars compacta (SNC) and ventral tegmental area (VTA) generate one of the most essential neuronal signals in the brain. Their firing pattern encodes reward prediction error, which is essential for reinforcement learning. The cells normally fire constantly at a low rate, and speed up, firing a phasic burst when reward exceeds prediction (e.g. an unexpected reward) or pause when an expected reward does not occur. To do this, dopaminergic neurons must integrate sensory, motor, and cognitive information not only between excitatory and inhibitory afferents, but also among excitatory and inhibitory afferents originating from different nuclei. Distinct inputs releasing the same neurotransmitter may have different effects on dopaminergic neuron activity, plasticity, and responses to drugs of abuse. This panel will cover a diversity of effects identified afferents can have even onto a single dopaminergic neuron. Stephan Lammel (University of California, Berkeley) will focus on the functional organization of afferent and efferent connections in the mesohabenular system. John Williams (Oregon Health and Science University) will speak about dopamine-dependent synaptic transmission in the substantia nigra and its modulation by l-DOPA. DeNard Simmons (University of Texas San Antonio) will focus on how identified inhibitory inputs to VTA dopaminergic neurons express different forms of GABAergic plasticity. Carlos Paladini (University of Texas San Antonio) will present data on how identified excitatory inputs to SNC dopaminergic neurons respond with changes to cocaine exposure.

PANEL • TUESDAY, 4:30–6:30 PM • CHEYENNE

47. Neurobiology of Cognitive Aging

Chair: Jennifer Bizon
Presenters: Peter Rapp, Sheri Mizumori, Jennifer Bizon, Mark Baxter

Aging is associated with a number of epigenetic, hormonal, and signaling alterations, which can together contribute to dysfunction in brain systems that support cognition. Two cognitive domains that are particularly vulnerable to decline with advanced age are memory supported by the hippocampus/medial temporal lobe system and working memory supported by the prefrontal cortex. Across individuals, there is significant variability in the presence and severity of decline associated with these distinct cognitive domains and these individual differences can be leveraged to identify those aspects of brain aging that are

uniquely associated with both decline and preservation of cognitive abilities. Taking advantage of individual differences among aged rodent and nonhuman primate populations, this panel will highlight new data regarding specific neural mechanisms that mediate different aspects of age-related cognitive decline. Dr. Peter Rapp (NIA) will describe recent findings in which epigenetic modifiers have been used to determine how acetylation dynamics influence spatial learning ability in aged rodents. Dr. Sheri Mizumori (University of Washington) will then discuss how midbrain circuits influence spatial perception and response selection and how age-related changes in these circuits contribute to spatial learning deficits in aged rodents. Dr. Jennifer Bizon (University of Florida) will present data to support that altered excitatory/inhibitory signaling dynamics in prefrontal cortical circuits of rodents contribute to age-related deficits in working memory. Dr. Mark Baxter (Mt. Sinai) will then present work from nonhuman primate which extends prior associations between hormone therapy, density of thin dendritic spines in prefrontal cortex, and working memory function and which supports an association between presynaptic mitochondrial morphology and working memory.

PANEL • TUESDAY, 4:30–6:30 PM • GALLATIN

48. Why do ion channels interact with RNA binding proteins?

Chair: Leonard Kaczmarek

Presenters: Gary Bassell, Leonard Kaczmarek, Vitaly Klyachko, Laurent Ferron

The pore-forming alpha subunits of ion channels interact with a variety of ancillary subunits that regulate aspects of channel functions such as their voltage-dependence, kinetics, membrane trafficking and subcellular localization. A striking recent addition to the list of ancillary subunits is the mRNA-binding protein FMRP (Fragile X Mental Retardation Protein). FMRP is required for activity-dependent translation of some the mRNAs to which it is bound. Loss of FMRP in humans results in Fragile X Syndrome, the leading cause of inherited intellectual impairment, and is associated with increased sensitivity to sensory stimuli and epileptic seizures. Among the mRNAs that bind FMRP are those for the voltage-dependent potassium channel Kv4.2, the sodium-activated Slack potassium channel, the large conductance calcium-activated BK potassium channel and the voltage-dependent calcium channel CaV2.2. Gary Bassell will describe cellular and molecular mechanisms by which FMRP and microRNAs regulate the levels of expression of neuronal proteins, including the Kv4.2 channel, which is required for the rapidly inactivating A-current in the dendrites of hippocampal neurons. Len Kaczmarek will describe how activation of Slack channels is coupled to activity-dependent protein translation

in neurons, and how mutations in the C-terminus of Slack, which interacts directly with FMRP, produce severe intellectual impairment in humans. Vitaly Klyachko will describe experiments demonstrating that FMRP binds directly to both alpha and beta subunits of BK channels and that that the FMRP/BK channel interaction directly regulates action potential width and evoked neurotransmitter release in hippocampal neurons. Finally Laurent Ferron will describe the direct interaction of FMRP with CaV2.2 in dorsal root ganglion neurons, where the binding of FMRP to the channel regulates synaptic exocytosis as well as the targeting of the channel to proteosomes.

MINI-COURSE 1 • TUESDAY, 4:30–6:30 PM • LAKE

49. What's new in neurodegeneration research? A tale of four diseases

Chair: Peter LeWitt

Presenters: Peter LeWitt, Adam Boxer, Irene Litvan, Cristina Sampaio

Ongoing efforts to arrest and prevent neurodegenerative disorders require many strands of information from the clinical realm to engage with the capabilities of laboratory research. Each of the 4 clinician-researchers will describe the challenges faced by patients afflicted 4 of the mid-life neurodegenerative disorders: corticobasal degeneration (CBD), Huntington disease (HD), Parkinson disease (PD), and progressive supranuclear palsy (PSP). They will summarize current understanding of the disease mechanisms and opportunities for enhanced diagnosis and therapeutic interventions. Adam Boxer (UCSF) will discuss tau protein dysfunction as a core feature of several neurodegenerative diseases. Using PSP as an archetypical tauopathy; he will touch on new therapies in clinical testing and biomarkers targeting this protein. Irene Litvan (UCSD) will discuss another tauopathy, CBD, which presents with a challenging array of clinical presentations and involves degeneration pathways with similarities to other disorders (including PSP). Peter LeWitt (Henry Ford Hospital) will provide an overview of the most common synucleinopathy, PD, for which several neuroprotective approaches in clinical trials have been based on promising insights from analysis of the PD brain, epidemiology, laboratory models of Parkinsonism, and (unfortunately!) loose analogies. Finally, Cristina Sampaio (CHDI Foundation) will provide an update on new advances in understanding HD, including therapeutics approaches and biomarker research in HD. This autosomal-dominant disorder (in which production of a mutated protein, huntingtin, results in widespread neuronal damage) offers the possibility of gene modification therapeutics. The speakers will highlight the wide scope of current research in these disorders and opportunities for collaboration.

PANEL • WEDNESDAY, 7:30–9:30 AM • AMPHITHEATRE

50. Molecular and Imaging Approaches to Understanding Obsessive-Compulsive Disorder (OCD)

Chair: Jim Knowles

Presenters: James Knowles, Chris Pittenger, Stephanie Dulawa, Andrew Jaffe

Obsessive-Compulsive Disorder (OCD) is a complex, illness of the brain, which is likely to be polygenic, and causes enormous human suffering. The disorder is characterized by the presence of obsessions (thoughts) and/or compulsions (behaviors) that are distressing, time consuming and/or significantly impairing. OCD has a lifetime prevalence of 1-3% (Nestadt et al., 2010; Ruscio et al., 2010) and is a leading global cause of non-fatal illness burden by the World Health Organization (WHO) in 2006 (Ayuso-Mateos 2006). As in other complex genetic disorders, it is thought that the development of OCD is probably influenced by a multitude of genetic and environmental factors. Chris Pittenger describe the features of clinical OCD, brain imaging data from his group and others, and a model of cortico-striatothalamo-cortical (CSTC) circuitry abnormalities in the disorder. Jim Knowles will then present the data from the first two genome-wide association studies (GWASs) of OCD, including association to BTBD3, and data from whole genome sequencing of members of multiply affected families. Stephanie Dulawa will present two mouse models of OCD-like behavior. She will describe the development and validation of a serotonin 1B agonist-induced model, and a BTBD3 knockout mouse model, which are both characterized by compulsive behaviors and reductions in exploratory behavior that are prevented by chronic treatment with serotonin reuptake inhibitors (SRIs). Finally, Andrew Jaffe will discuss the functional characterization of clinical risk SNPs for obsessive syndromes, including OCD and the eating disorders, evaluated in human postmortem brain tissue, and describe the genes that are differentially expressed between patients with obsessive psychiatric syndromes and non-psychiatric controls.

PANEL • WEDNESDAY, 7:30–9:30 AM • LAMAR/GIBBON

51. Emerging Pharmacotherapeutics for Cocaine Use Disorder

Chair: Kathryn Cunningham
Presenters: Phil Skolnick, Noelle Anastasio, Carrie Jones, Kathryn Reissner

Cocaine use disorder remains a significant health problem in the United States. Safe and effective pharmacotherapeutic approaches are urgently needed to maximize treatment success. Dr. Skolnick will discuss challenges and issues in developing these therapies. Three presentations will describe new chemical entities which target cocaine use disorder through the serotonin 5-HT2C receptor, the glutamate mGlu5 receptor and glutamate transporter. Dr. Anastasio will demonstrate that dampened 5-HT2CR signaling capacity may contribute to phenotypic vulnerability to cocaine use disorder and that small molecule positive allosteric modulator (PAM) of 5-HT2CR tone may be useful to suppress relapse. She will discuss progress in the development of these molecules. Dr. Jones will highlight the discovery of partial mGlu5 receptor negative allosteric modulators (NAMs) that block the rewarding effects of cocaine within a dose range that does not induced the dosing-limiting, adverse side effects associated with full mGlu5 NAMs. Dr. Reissner will discuss astrocytes as pharmacotherapeutic targets for cocaine addiction, with emphasis on how cocaine-dependent suppression of astroglial glutamate uptake in the nucleus accumbens can modulate cocaine seeking. Thus, this panel will highlight concepts and directions in cocaine abuse disorder and relapse medications.

PANEL • WEDNESDAY, 7:30–9:30 AM • DUNRAVEN/OBSIDIAN

52. The learning brain: Cognitive neuroscience for the educational system

Chair: Kyle Frantz
Presenters: Laurie Cutting, Tanya Evans, Valerie Darcey, Susan Magsamen, Kyle Frantz

Educational neuroscience is an emerging scientific field exploring interactions between mind, brain and educational practices. The field seeks to make positive changes in educational practices by (1) capitalizing on a rich knowledge base in the disciplines of developmental, cognitive, and educational psychology, (2) integrating this work with emerging areas of research in cognitive neuroscience, and (3) using functional imaging, electrophysiology, psychophysics, and cognitive genomics tools to conduct both basic and applied research. Studies

that fall under the umbrella of educational neuroscience are diverse in that they explore a variety of complex human behaviors such as reading, numeracy, attention, and memory, in part to help design interventions to ameliorate disorders such as dyslexia, dyscalculia, ADHD, and autism. The ultimate goal of this synthesis is to provide scientists and educators with information to enhance the educational experiences of children and adults both in and outside of traditional classroom settings. After a brief introduction by Kyle Frantz, Laurie Cutting will explore the cognitive development of language and reading, focusing on the neural correlates of word-level (decoding) versus discourse processing (comprehension). Tanya Evans will consider the neural bases of numerical processing, highlighting the overlap between language and mathematical faculties at the behavior and brain level. Valerie Darcey will discuss the influence of short- and long-term nutritional factors on cognitive function and academic performance, emphasizing the impact of breakfast and dietary fats. Susan Magsamen will conclude with present perspectives of the field, paying special attention to the evolving role of curiosity in shaping how we learn and grow. In keeping with the ultimate goal of educational neuroscience, each presenter will highlight areas to target for paradigm shifts in educational practices.

PANEL • WEDNESDAY, 7:30–9:30 AM • CANYON

53. I'm only sleeping: Regulation of dopamine receptor responsiveness in dopamine neurons

Chair: Kim Neve
Presenters: Mark Brodie, Brooks Robinson, Kim Neve, Jennifer Whistler

The dopamine D2 receptor is abundantly expressed in dopamine neurons of the ventral midbrain. Activation of D2 autoreceptors inhibits dopamine neuron firing and dopamine synthesis and release. D2 autoreceptor responsiveness and, therefore, dopamine release, is highly sensitive to brief or long-term exposure to dopamine, and to acute or chronic treatment with abused drugs such as cocaine. Mark Brodie will describe D2 receptor desensitization in dopamine neurons of the ventral tegmental area in response to long-term treatment with modest concentrations of extracellular dopamine, producing a loss of dopamine inhibitory activity (dopamine inhibition reversal). This desensitization is a calcium-dependent process that also involves dynamin, GPCR kinase 2, and anaplastic lymphoma kinase (ALK). Brooks Robinson will present data on the effect of cocaine on rapid calcium-dependent desensitization of a G protein-regulated potassium conductance (GIRK) activated by the D2 receptor splice variants D2L and D2S in dopamine neurons of the substantia nigra. Kim Neve will discuss interactions between the D2 receptor and S100B, one of several calcium-binding proteins that bind to the D2 receptor and could mediate

calcium-dependent desensitization or resensitization. Jennifer Whistler has identified GPCR-associated sorting protein-1 (GASP1) that is responsible for the targeting of the D2 receptor for degradation after endocytosis. She will present her recent work indicating that GASP1-mediated down regulation of the D2 receptor is critical for cocaine-induced plasticity in dopamine neurons of the ventral tegmental area.

PANEL • WEDNESDAY, 7:30–9:30 AM • CHEYENNE

54. Shocking old/new world: Moving towards the more selective stimulation of the human brain

Chair: Miklos Argyelan
Presenters: Wilder Doucette, Marom Bikson, Christopher Abbott, Miklos Argyelan

Neurostimulation techniques are widely used in routine clinical practice; however our understanding of their mechanism of action is very limited.

The goal of this panel is to provide an overview of current research to understand the mechanism of DBS (deep brain stimulation), tDCS (trascranial direct current stimulation) and ECT (electroconvulsive therapy) and their potential application in human brain disorders.

These techniques represent a tradeoff between safety and selectivity. Selectivity is important so to avoid unnecessary side effects and improve potential effects. Since the invasiveness of a technique is rarely modifiable, this panel will focus on how new approaches could improve the effect/size effect ratio, by making the technique either anatomically or functionally more selective.

Wilder Doucette, from the Geisel School of Medicine at Dartmouth, will discuss how DBS might influence reward circuitry, depending on the subregion specific stimulation of the nucleus accumbens. His recent studies of binge eating rats could eventually lead to a better understanding and to potential clinical applications in eating disorders and addiction disorders. Marom Bikson, one of the leading pioneers in the newly emerging tDCS era from the City College of New York, will talk about the fundamental questions on how to individualize treatment. His research focuses on understanding the basic mechanisms of "functional targeting" and its potential applicability in various psychiatric conditions. Christopher Abbott, from The University of New Mexico, will discuss his neuroimaging research in unilateral ECT in elderly depressed patients with the main focus of predicting response. Miklos Argyelan, from The Zucker Hillside Hospital, one of the largest ECT center in the U.S., will present data on the relationship between electrical current models and neuroimaging findings. This new data could lead to targeted ECT that would maximize the effect and minimize memory side effects.

PANEL • WEDNESDAY, 7:30–9:30 AM • GALLATIN

55. Regulation of excitatory synaptic transmission

Chair: James Howe
Presenters: Jeff Diamond, James Howe, Katherine Roche, Roger Nicoll

This session will focus on how excitatory synaptic transmission is shaped by the properties, number, and localization of glutamate receptors. Jeff Diamond (NIH) will discuss the role of NMDA receptors in direction selective ganglion cells in the retina. By multiplicatively amplifying postsynaptic signals, NMDARs preserve direction selectivity over a wide stimulus range, a functional computation that relies both on the voltage-dependence of the NMDAR conductance and the properties of the retinal circuitry. Jim Howe (Yale, session Chair) will present recent single molecule data showing that association of auxiliary TARP subunits with AMPA receptors promotes distinct gating modes that are not seen with pore-forming subunits alone and that have a large impact on the size and shape of ensemble currents evoked by rapid pulses of glutamate. Katherine Roche (NIH) will describe recent findings with neuroligins, postsynaptic proteins that interact with presynaptic neurexins to promote synapse formation and maintenance. Her laboratory recently showed that neuroligin-dependent potentiation of excitatory synapses is dramatically regulated by phosphorylation and that phosphorylation of the intracellular C-termini of various neuroligin isoforms by CaMKII and PKC has dramatic effects on synaptic transmission and differs for different neuroligin isoforms. Roger Nicoll (UCSF) will present recent work demonstrating that deletion of MAGUKs, a family of scaffolding proteins expressed at all synapses, results in a profound loss of both AMPA and NMDA receptors. As expected the frequency of miniature EPSCs (mEPSCs) is markedly reduced, but remarkably the remaining mEPSCs are of normal size. He will describe a winner-take-all mechanism whereby most of synapses completely lose their glutamate receptors, while the rest reacquire a normal compliment of receptors.

PANEL • WEDNESDAY, 7:30–9:30 AM • LAKE

56. Role of flexible intrinsic firing properties in spinal neurons organizing locomotion

Chair: Ronald Harris-Warrick
Presenters: Ronald Harris-Warrick, Laurent Vinay, Frédéric Brocard, Kimberly Dougherty

Neural networks called Central Pattern Generators (CPGs) organize the timing, phasing and intensity of muscle activity for flexible rhythmic behaviors such as locomotion and respiration. Understanding the synaptic organization of the network is not sufficient to explain how the behavior is organized: research

in invertebrate CPGs has demonstrated the critical roles that the intrinsic firing properties of network neurons play in shaping the behavior. This work is now being extended to the vertebrates with new work on interneurons and motoneurons in the rodent spinal networks for locomotion. Our panel will explore these properties, and their flexible modulation in normal behavior, during development and after spinal cord injury. First, Ron Harris-Warrick (Cornell University) will discuss the postnatal development of intrinsic properties in identified spinal network interneurons, and their modulation by serotonin. Laurent Vinay (University of Aix-Marseille) will discuss the role of the chloride transporter KCC2 in lumbar spinal cord function during development and after spinal cord injury. Frédéric Brocard (University of Aix-Marseille) will discuss the role that changing extracellular ionic concentrations and temperature play in expression of bistability and bursting properties in neurons of the locomotor network. Finally, Kimberly Dougherty (Drexel University) will discuss the identification, cellular rhythmicity, and connectivity of constituent interneurons of the locomotor rhythm generator. Results presented in all talks will describe recent experiments using state-of-the-art electrophysiological, genetic and optogenetic techniques in order to reveal how the intrinsic properties of spinal neurons affect the locomotor network, and to determine the functional implications of these properties and their flexibility in the behaving animal.

MINI-COURSE 2 • WEDNESDAY, 4:30–6:30 PM • AMPHITHEATRE

57. Illuminating the Brain

Chairs: Lakshmi Devi, Susan Ferguson
Presenters: Matt Cater, Susan Ferguson, Krystof Bankiewicz

Over the past decade, several techniques have been developed that allow specific areas of the brain to be directly manipulated. Some of these techniques are useful for animal models investigating brain function, while others have been adapted to the treatment of human brain disorders. This mini-course will focus on three new techniques, which will be explained at a level aimed at non-experts in the field. Matt Cater will describe the technique of optogenetics, which uses light to selectively activate or inactivate neuronal activity in specific neurons of animals. The use of optogenetic tools to investigate neural circuits in living animals will be discussed. The presentation will include both the fundamental concepts of optogenetics as well as an overview of the necessary reagents, materials, and resources required to use this powerful technique. Matt will conclude with the application of optogenetics to solve problems in behavioral neuroscience. Susan Ferguson will describe a pharmacological technique to specifically activate certain neurons in animals; Designer

Receptors Exclusively Activated by Designer Drugs (DREADDs). Like optogenetics, the DREADD technique requires an animal model that expresses a unique protein in certain cells, but whereas optogenetics uses light to influence those neurons, the DREADD technique uses chemicals that influence only the modified cells. Susan will describe viral-mediated gene transfer techniques that permit DREADDs to be targeted to different cell types. She will discuss the use of DREADDs to selectively activate neurons and investigate the neural circuits that regulate behaviors associated with addiction. Krystof Bankiewicz will discuss translating animal studies into the clinic, with a focus on the direct injection of therapeutic agents into specific regions of the brain. Direct delivery of drugs and agents into the CNS avoids penetration issues due to the blood brain barrier, and also provides high concentrations of the drug at the target without affecting either surrounding brain tissue or organs outside of the brain. To prevent unwanted leakage outside the target of interest, magnetic resonance imaging is used to track the distribution of infused drug. Clinical uses of this technique will be presented. Collectively, these three presentations will describe cutting-edge research techniques aimed at manipulating specific cells in small brain regions. Ample time for questions and discussion will be provided following each of the three lectures.

PANEL • WEDNESDAY, 4:30–6:30 PM • LAMAR/GIBBON

58. Treatment Targets for Stress and Substance Use Disorders

Chair: Jacqueline McGinty
Presenters: Chantelle Ferland, Foster Olive, Nicholas Gilpin, Nicholas Goeders

Stress can cause complex neuroadaptations that lead to seeking and/or taking of addictive substances. However, there are no effective treatments that target common substrates underlying these disorders in dually-diagnosed patients. This panel will discuss novel therapeutic approaches to treat interactions between stress and drug taking/seeking based on concomitant changes in the brain that are common to both conditions. Chantelle Ferland (Medical University of SC) will discuss how prior traumatic stress exposure exacerbates methamphetamine-seeking which is correlated with epigenetic disruption of Bdnf expression in the prefrontal cortex of rats. She will also show data indicating that systemic administration of oxytocin attenuates meth-seeking, suggesting that oxytocin is a novel therapeutic target for the treatment of comorbid substance use and post-traumatic stress disorder. Foster Olive (Arizona State U) will present research findings implicating the epigenetic regulator MeCP2 in response to early life stress as well as vulnerability to methamphetamine self-administration. Post-translational modification of

MeCP2 in mouse models of cocaine addiction and binge eating will also be discussed. Nick Gilpin (LSU Health Sciences Ctr, New Orleans) will discuss data collected using rodent models of traumatic stress and alcohol self-administration, in which predator odor exposure increases alcohol self-administration in rats. He will also show data that implicate brain CRF-CRF1 receptor signaling in mediating traumatic stress-induced increases in alcohol drinking and nociception. Nicholas Goeders (LSU Health Sciences Center, Shreveport) will discuss the development of the combination of the corticosterone synthesis inhibitor, metyrapone, and the benzodiazepine, oxazepam, for the treatment of cocaine addiction, from the bench to the clinic. He will also describe how the effects of this drug combination are mediated centrally, including actions via neuroactive steroids.

PANEL • WEDNESDAY, 4:30–6:30 PM •

DUNRAVEN/OBSIDIAN

59. Why do we eat too much? Corticostriatal circuits and feeding behaviour

Chair: Stephanie Borgland

Presenters: Robyn Brown, Christina Gremel, Stephanie Borgland, Alain Dagher

Obesity can be viewed as a disorder of decision-making. While homeostatic energy balance signals and proximal food cues influence appetite, there is evidence that eating is also affected by psychosocial stress, variety and availability of low cost calorically-dense foods, and habitual factors, all of which may impact food intake at the planning stages. This places eating within the realm of decision-making, and implicates the frontal lobes and corticostriatal circuits. Robyn Brown (Florey Institute, Aus) will present data demonstrating that rats prone to diet-induced obesity display enhanced palatable food-seeking behavior and cortico-accumbal synaptic dysfunction akin to that observed in animal models of drug addiction. Specifically, these rats had a loss of long-term depression and an increased AMPA/NMDA receptor ratio in the nucleus accumbens core. Christina Gremel (NIH/NIAAA) will show using an instrumental outcome revaluation task, that endocannabinoid CB1 receptors in orbitostriatal circuits are involved in habitual action control over food reward. She proposes that one way habitual feeding-related behavior may predominate over more flexible decision-making is via endocannabinoid receptor-mediated inhibition of orbitostriatal circuits. Stephanie Borgland (Hotchkiss Brain Institute) will demonstrate that rats with extended access to a cafeteria diet exhibit compulsive-like feeding behavior and neuroadaptations in the lateral OFC neurons. Lateral OFC pyramidal neurons from rats with extended access to a cafeteria diet have increased excitability due to reduced

inhibitory input. Finally, Alain Dagher (Montreal Neurological Institute) will review the anatomical and functional imaging literature on decision-making, food valuation, and appetite control as they relate to weight gain in humans. He will provide evidence that the major determinants of weight gain in humans implicate the frontal lobes.

PANEL • WEDNESDAY, 4:30–6:30 PM • CANYON

60. An integrative approach probing putative mechanism(s) contributing to injury-induced cognitive impairment

Chair: Akiva Cohen

Presenters: Edward Hall, Herb Geller, Catharine Winstanley, Akiva Cohen

More than 1% of Americans suffer a traumatic brain injury each year with a significant number of these cases coming from downhill skiing and snowboarding. Even mild traumatic brain injury (mTBI) can cause long-lasting neurological effects. Despite its prevalence, no therapy currently exists to treat the underlying cause of cognitive impairment suffered by mTBI patients. Therapeutics based on a singular approach or mechanism have proven ineffective. An approach that integrates multidisciplinary streams of research holds significantly more promise. The central goal of this panel is to use an integrative approach to investigate different aspects that may contribute to cognitive impairment caused by brain injury. Specifically this panel will focus on diverse elements i.e., mitochondrial dysfunction, changes in the extracellular matrix, inflammatory mediators and excitatory-inhibitory (E-I) synaptic imbalances. First, Akiva S. Cohen will provide introductory comments. Then Ed Hall will discuss the alterations in cellular metabolism and mitochondrial dysfunction focusing on activation of the Nrf2-antioxidant response element (ARE) pathway with the natural product carnosic acid as a neuroprotective approach that appears to be effective as a post-TBI therapy with at least an 8 hour therapeutic efficacy window. Herb Geller will then discuss the potential role of changes in extracellular matrix following TBI in modulating axonal growth and plasticity. Next Catharine Winstanley will then present novel data demonstrating that frontal TBI causes long-lasting impairments in higher-order cognitive functions reminiscent of the core psychiatric symptoms reported in TBI patients, including deficits in impulse control, attention and motivation that are accompanied by persistent elevations in select pro-inflammatory cytokines. Finally, Akiva Cohen will discuss regional hippocampal synaptic imbalances that underlie and contribute to injury-induced cognitive impairment.

PANEL • WEDNESDAY, 4:30–6:30 PM • CHEYENNE

61. The dark side of dopamine: Negative reinforcement and aversion

Chair: Kimberly LeBlanc
Presenters: Kay Tye, Erik Oleson, Kimberly LeBlanc, Mary Kay Lobo

There is a wealth of research implicating dopamine in appetitive motivation and positive reinforcement. While it is clear that a portion of dopamine's actions is committed to motivational value, there has been mounting evidence for the role of dopamine and dopaminergic circuitry in motivational salience generally, including aversive motivation. The development of optogenetic and chemogenetic techniques has enabled us to probe the function of cell-type specific projections within the dopaminergic circuitry to reveal that dopamine circuitry is more diverse than previously thought, producing aversive behaviors such as avoidance and depressive-like symptoms. Using these techniques, this panel will investigate dopamine neurons and their targets in the striatum and prefrontal cortex in mediating aversive behaviors. Kay Tye will present data from experiments combining fast-scan cyclic voltammetry and optogenetics to investigate how dopamine within the medial prefrontal cortex elicits aversive behavior. Erik Oleson will present results demonstrating the effects of optogenetic stimulation and DREADD activation of dopamine neurons during negative reinforcement. Kimberly LeBlanc will show that optogenetic stimulation of dopamine D2-receptor expressing medium spiny neurons (D2-MSNs) in the dorsal striatum induces anxiety-like behaviors. Finally, Mary Kay Lobo will examine the mechanism by which activation of D2-MSNs produces negative affective behaviors and activation of dopamine D1-receptor expressing MSNs reverses these behaviors in social defeat stress.

PANEL • WEDNESDAY, 4:30–6:30 PM • GALLATIN

62. Are you SERTain it's DAT?

Chair: Amy Newman
Presenters: Anders Kristensen, Habibeh Khoshbouei, Sara Jones, Ulrik Gether

Disturbances in dopaminergic and serotonergic signaling are of central importance in several common brain diseases and neuropsychiatric disorders. Dysfunctional dopaminergic signaling is associated with e.g. parkinsonism, attention deficit hyperactivity disorder (ADHD), autism, schizophrenia, and addiction; whereas diseases like migraine, anxiety and depression are believed to involve alterations in serotonergic signaling. The dopamine and serotonin transporters (DAT and SERT, respectively), belonging to the class of neurotransmitter:sodium symporters (NSSs), are key players in maintaining monoamine homeostasis and both serve as critical targets for medications

used to treat neuropsychiatric disorders. Moreover, the inhibition of dopamine reuptake via DAT is the primary mechanism underlying the psychostimulant and euphoric properties of cocaine and methamphetamine while the empathogenic drug, MDMA (3,4-methylendioxy-N-methylamfetamin), inhibits SERT activity. Amy Newman will begin the session by providing a brief introduction to the topic, followed by Anders Kristensen who will describe real-time measurements of SERT protein dynamics in the absence and presence of antidepressant drugs using voltage-clamp fluorometry and FRET (fluorescence energy resonance energy transfer) measurements. Habibeh Khoshbouei will discuss how methamphetamine activation of intracellular targets can influence DAT activity and Sara Jones will describe recent results suggesting that the diurnal control of extracellular dopamine levels is controlled by DAT. Ulrik Gether will wrap up the session by describing how the use of novel photostable fluorescent cocaine and citalopram analogues, as well as superresolution microscopy techniques, (PALM/STORM) allow unprecedented insight into the subcellular distribution and trafficking dynamics of both SERT and DAT.

PANEL • WEDNESDAY, 4:30–6:30 PM • LAKE

63. Molecular Signaling Pathways that Regulate Excitatory Synapses

Chair: David Bredt

Presenters: Elva Diaz, Geoffrey Swanson, A Villu Maricq, David Bredt

This panel will describe recent advance in our mechanistic understanding of the molecular machinery that controls synaptic plasticity and contributes to behavior.

Diaz will discuss the role of palmitoylation in the post-translational regulation of synaptic function. Palmitoylation attaches specific fatty acids to target membrane proteins and can modify protein transport and function. Palmitoylation of the AMPA receptor accessory protein SynDIG1 is activity-dependent and regulates the stability, localization and function of AMPA receptors, and thus, synaptic strength.

Swanson will provide new mechanistic insights into the molecular and structural basis for Neto modulation of kainate receptor function. These auxiliary proteins associate with kainate receptors and are expressed in the central and peripheral nervous systems. New evidence implicates Neto proteins in glutamate-mediated pain neurotransmission by primary sensory neurons.

Maricq will discuss molecular regulation of the delivery and removal of synaptic AMPARs. Kinesin-mediated transport provides a rapid-response mechanism for modifying the number of AMPARs at synapses. The Ca2+-dependent kinase CaMKII regulates this transport. In CaMKII mutants, AMPAR transport

and glutamate-gated currents are disrupted. These results suggest that nervous system plasticity is regulated in part by activity-dependent modulation of receptor transport.

Bredt will describe exciting new developments in the identification and characterization of proteins that contribute to AMPAR function. Proteomic approaches have identified a large number of proteins that tightly associate—directly or indirectly—with synaptic AMPARs. New biochemical and functional studies show that some of these proteins profoundly regulate AMPA receptor channels in recombinant cells and neurons, and may possibly contribute to synaptic plasticity.

THURSDAY, JANUARY 29, 2015

PANEL • THURSDAY, 7:30–9:30 AM • AMPHITHEATRE

64. Green circles or black diamonds? Cue discrimination and generalization in fear and reward

Chair: Joshua Gordon

Presenters: John Howland, Joshua Gordon, Larry Zweifel, Lilliane Mujica-Parodi

Associative learning, in which one learns to predict specific outcomes based on specific cues, plays a fundamental role in survival. Yet the degree of specificity, too, is crucial. Up on the mountain, learning to discern the difference between slopes might save your life. Afterwards, understanding that one long-necked bottle is about as useful as the next is almost as important. In the real world, of course, failures of discrimination or generalization may lead to pathology, including anxiety and substance abuse disorders. Understanding the mechanisms that govern these processes is therefore a key goal for neuroscience. The first three speakers will describe data from rodent models, using a combination of cellular and circuit-based approaches to clarify the neural mechanisms underlying cue discrimination and generalization. First, John Howland will discuss the role of a small population of neurons in the lateral amygdala that are critical for associating environmental cues with cocaine rewards in mice. Next, Joshua Gordon will present data demonstrating that projections from the medial prefrontal cortex modulate amgydala activity during successful discrimination in a learned fear paradigm in the mouse; inhibiting these projections also disrupts generalization. Larry Zweifel will follow with a discussion of the role of dopamine neurons in the regulation of cue discrimination coding and plasticity in the lateral amygdala using a mouse model of generalized fear. The final panelist will directly relate these findings to patients. Lilianne Mujica-Parodi will present findings from human

functional imaging studies, demonstrating abnormalities in dopaminergic and corticolimbic systems during overgeneralization of fear in patients with generalized anxiety disorder. Together, the presentations will provide a framework for understanding the mechanisms of cue discrimination and generalization, and the role played in human disease by disruptions of these mechanisms.

PANEL • THURSDAY, 7:30–9:30 AM • LAMAR/GIBBON

65. From GWAS to brains to models: Inflammation in Schizophrenia

Chair: Patricio O'Donnell

Presenters: Lisa Boulanger, Patricio O'Donnell, Cynthia Weickert, Elliot Hong

Schizophrenia is highly heritable, and the strongest genetic links consistently fall within a gene region known for its roles in the immune response (the MHC region). Postmortem studies suggest that immune markers are elevated in the brain, and blood samples from patients show consistent changes in cytokine levels. However, the biological causes of the links between schizophrenia and altered immune signaling remain elusive. This panel will discuss changes in immune signaling in patients with schizophrenia, and consider how these changes affect the roles that immune signaling plays in normal brain development and plasticity. Lisa Boulanger will show recent evidence that MHCI is an endogenous regulator of NMDAR-mediated synaptic transmission and plasticity, and discuss this new role for MHCI in the context of current models of schizophrenia. Patricio O'Donnell will provide evidence of increased cytokine gene expression in the prefrontal cortex, hippocampus, and striatum in several different developmental models of schizophrenia research. Since elevation of IL6 affects excitation-inhibition balance and parvalbumin levels in some models, elevated cytokines might affect the function of circuits which are disrupted in schizophrenia. Cyndi Weickert will present data highlighting elevated inflammatory markers in brains from patients with schizophrenia relative to matched controls. Elliot Hong will present data exploring the link between stress and immune dysregulation in schizophrenia patients, using the salivary response to psychological stress. IL6 levels increased with stress, but their attenuation by cortisol (observed in controls) was not present in the patients, suggesting an inability to downregulate inflammatory responses in patients. Overall, the panel will highlight possible mechanisms by which both genetic and environmentally-triggered changes in immune signaling may play a role in the pathophysiology of schizophrenia.

PANEL • THURSDAY, 7:30–9:30 AM •

DUNRAVEN/OBSIDIAN

66. Understanding human brain development and disease through transcriptomics

Chair: Ed Lein

Presenters: Ed Lein, Michael Oldham, Dan Geschwind, Andrew Jaffe

Transcriptional profiling is a powerful methodology to identify the molecular underpinnings of nervous system development, function and disease. Recently this methodology has been applied at scale to map transcript usage at fine anatomical and temporal resolution in the developing human (BrainSpan and BrainCloud) and non-human primate (NIH Blueprint NHP Atlas) brain to create powerful freely accessible data resources. At the same time, methodologies have advanced rapidly from DNA microarrays to RNA sequencing, thereby increasing dynamic range, coverage and resolution, and are being widely applied to the study of human disease. The panel will discuss the application of these techniques to study normal brain development and to identify transcriptional signatures of disease that provide mechanistic insight into their molecular and cellular bases. Ed Lein (Allen Institute for Brain Science) will describe the generation of large-scale human and non-human primate developmental transcriptome resources and how they can be used to understand how the transcriptome codes for human neocortical development. Michael Oldham (UCSF) will present work comparing transcriptional signatures of radial glia during human and mouse cortical development, and describe a signaling pathway that is active in human but not mouse radial glia and promotes neural stem cell self-renewal. Dan Geschwind (UCLA) will describe the use of RNAseq analysis to profile postmortem brain from patients with autism spectrum disorder (ASD), identifying shared pathways that are dysregulated in ASD including specific changes in development, synaptic function and microglia as well as changes that are shared with other disorders such as schizophrenia and bipolar disorder. Andrew Jaffe (Lieber Insitute for Brain Development) will present work detailing the role of genetic variation on RNAseq-based gene expression in the dorsolateral prefrontal cortex and its potential role in schizophrenia and development.

PANEL • THURSDAY, 7:30–9:30 AM • CANYON

67. Variety is the spice of the life: Adding flavor to neural function

Chair: Paul Katz
Presenters: Paul Katz, Ralf Sommer, Akira Sakurai, Timothy O'Leary

Differences between individuals can be encoded by differences in their nervous systems with obvious differences in behavior. But sometimes differences in the nervous system can be hidden with no overt differences in behavior unless there are challenges to the nervous system, such as an injury. How much can the properties of neurons and synapses vary while still allowing the neural circuits to function? Recent exciting work in several invertebrate systems is uncovering new types of variation, their functional implications, and how that variation is regulated. Paul Katz (Georgia State University) will give a short presentation on the topic, tying it to the evolution of neural circuits. Ralf Sommer (Max Planck, Tübingen) will discuss phenotypic variations in the nematode Pristionchus pacificus. This roundworm has the same complement of precisely 302 neurons as its more famous cousin, Caenorhabditis elegans, but its behavior differs. Furthermore, individual P. pacificus differ from each other in the organization of their mouthparts and sensitivity to pheromones, both of which are induced by their environment. In another example of individual variation, Akira Sakurai (Georgia State University) will describe how individual sea slugs (Tritonia diomedea), which show no overt differences in behavior, differ in their susceptibility to severing a central brain commissure and in their ability to recover from this injury. These differences are shown to be caused by individual variation in particular synapses. Finally Timothy O'Leary (Brandeis University) will provide a theoretical framework for how neurons can regulate their conductances from activity-dependent feedback in a way that generates consistent behavior from variable underlying parameters. One interesting application is that neurons can find variable solutions that make them robust to global perturbations, exemplified by changes in environmental temperature.

PANEL • THURSDAY, 7:30–9:30 AM • CHEYENNE

68. Neurobiology, bad decisions and drug seeking

Chair: Fulton Crews
Presenters: Paul Phillips, Heather Trantham-Davidson, Fulton Crews, Jacqueline McGinty

Drugs of abuse share multiple circuits that contribute to drug dependence. Paul Phillips (University of Washington) will present studies of phasic dopamine activity to drug cues during or before cocaine self-administration sessions that find that decreases in dopamine release produce increased drug

consumption whereas concomitant increases in dopamine release increase drug seeking. Heather Davidson (Medical College of South Carolina) will describe the effects of chronic and adolescent binge-like exposure to ethanol on dopaminergic modulation of prefrontal function, behavioral flexibility and decision making. Our findings suggest that ethanol exposure at any age results in similar cognitive impairments but the mechanisms which mediate this change involve very distinct and specific changes in dopamine modulation of prefrontal projections to the dorsal striatum, nucleus accumbens and amygdala depending on the age of exposure. Fulton Crews (University of North Carolina) will discuss chronic ethanol induced persistent increases in neuroimmune gene expression in prefrontal cortex altering neurocircuitry and behavioral flexibility in animals and relate them to changes in post-mortem human brain. Jacqueline McGinty ((Medical College of South Carolina) will present studies on dynamic patterns of gene regulation that alter prefrontal circuitry. Findings suggest that strengthening of prefrontal inhibitory control over drug-seeking is most effective when the intervention occurs during early withdrawal from cocaine-taking. Specifically, unpublished studies will be presented that TrkB activation in the dorsomedial PFC of rats during early withdrawal prevents cocaine-induced disturbances in NMDA receptor activity via a Src family kinase-mediated processes that are critical to inhibiting cocaine seeking. Together these studies will integrate multiple neuronal circuits related to drug dependence.

PANEL • THURSDAY, 7:30–9:30 AM • GALLATIN

69. Recent developments in NMDA receptor research: From structure-function to physiology

Chair: Kasper Hansen

Presenters: Ehud Isacoff, Kasper Hansen, Stephen Traynelis, Michael Kavanaugh

NMDA receptors mediate a slow, Ca2+-permeable component of excitatory synaptic transmission and are involved in a number of brain functions, including development, learning and memory. NMDA receptors are also implicated in several neurological disorders and are therefore of considerable therapeutic interest. This panel will discuss recent studies that reveal new insights to the structure-function and physiological roles of NMDA receptors using a combination of conventional and innovative experimental approaches. Dr. Isacoff will discuss the development of light-activated NMDA receptors that can be controlled using tethered, photo-isomerizable ligands. These novel light-activated receptors can be powerful tools to study the physiological roles of NMDA receptors and can uncover previously unrecognized features of receptor structure and function. Dr. Hansen will review recently uncovered roles of GluN3A-containing NMDA receptors in normal brain function and disease, and provide new data for their subunit stoichiometry, function, and

pharmacology. Dr. Traynelis will discuss subunit-selective positive allosteric modulators that are selective for GluN2C-containing NMDA receptors. Mutagenesis data suggest that these compounds bind in a previously unrecognized cavity at the interface between the GluN2C amino-terminal and ligand binding domains, and have the unusual property of sensing GluN2 subunit stoichiometry. Finally, Dr. Kavanaugh will discuss recent data concerning the activity of synaptic NMDA receptors in the hippocampus and the cooperative roles played by channel kinetics, synaptic frequency, and glutamate transporters in controlling NMDA receptor signaling. These four presentations will provide a comprehensive discussion that covers novel aspects of receptor activation, subunit stoichiometry, subunit-selective allosteric modulation, and synaptic signaling, thereby providing up-to-date and new perspectives on NMDA receptors from structure-function to physiology.

PANEL • THURSDAY, 7:30–9:30 AM • LAKE

70. The science of intractable epilepsy: When small molecules fail

Chair: Thomas Swanson
Presenters: Detlav Boison, Bruce Ransom, Josh Lawrence, Dave Poulsen

One out of 26 people will get epilepsy. One third of these patients do not respond to current drug therapies, typically small molecules targeted to receptors or ion channels. The reasons for medical intractability are many, and incompletely understood. This session discusses novel approaches to understanding the science of medically intractable epilepsy. Epigenetics is the study of factors that activate or deactivate the genome. Such epigenetic influences radically affect which genes are expressed, and thus how brain chemicals interact with neurons and glia. Animal models of epilepsy are incompletely understood, and more often than not, do not model the human disease. Lastly, radical new types of therapies aimed at diverse targets should be considered. Swanson (Montana Comprehensive Epilepsy Program) will introduce each speaker and stimulate controversy and discussion. Boison (Legacy Research Institute) will discuss epigenetics, showing how changes in DNA methylation patterns are key determinants of epilepsy progression and how adenosine augmenting treatments can reverse DNA hyper-methylation and break the cycle of increasing seizure severity. Ransom (University of Washington) will discuss possible roles of glia in modulating energy substrates and other aspects of brain function that would be expected to impact seizure initiation, propagation and cessation. Lawrence (University of Montana) will discuss new insights into how cholinergic receptors on parvalbumin positive

hippocampal interneurons may participate in pilocarpine-induced seizures, a popular animal model of epilepsy, whose mechanism of seizure genesis is incompletely understood. Poulsen (University of Montana) will discuss how treatment with methamphetamine within 8 hours after severe traumatic brain injury, significantly reduces susceptibility to PTZ-induced seizures and the incidence of spontaneous tonic-clonic seizures.

PANEL • THURSDAY, 4:30–6:30 PM • AMPHITHEATRE

71. New insights into the role of immune cells in brain function and pathology

Chair: Miles Herkenham

Presenters: Carol Colton, Kim Green, Jonathan Godbout, Miles Herkenham

The panel will address roles that microglia and other immune cells play in regulating brain structure and function. Colton will argue that in contrast to the common view that M1/proinflammatory events are the dominant immune phenotype in an Alzheimer's disease (AD) model, M2/immunosuppression is a factor in disease progression. In disease progression, microglia express genes reminiscent of monocyte-derived suppressor cells leading to reduced amino acid levels and nutrient deprivation. The changes are also found in humans with AD. Green will that microglia in the healthy adult brain are dependent upon colony-stimulating factor 1 receptor (CSF1R) signaling for their survival. Administration of selective CSF1R inhibitors eliminates all microglia for the duration of treatment. This treatment was applied to a 3xTg-AD model to determine the roles of microglia in formation and maintenance of Abeta and tau pathologies and in cognitive impairments. Elimination of microglia resulted in marked improvements in learning but had no impact on Abeta, plaque, or tau pathologies indicating that microglia drive cognitive impairments but are not able to protect against AD pathologies. Godbout has data from models of stress, aging, and spinal cord injury (SCI) in which activated microglia augment the recruitment of bone marrow-derived monocytes/macrophages to the CNS. In SCI, there is selective recruitment of repair-promoting macrophages. This process is impaired in older mice and is associated with reduced functional recovery. In psychological stress, the active recruitment of "inflammatory" macrophages to the brain amplifies neuroinflammatory signaling and mediates the development of anxiety-like behavior. Herkenham will show that stress alters peripheral lymphocytes that can induce an antidepressant state when adoptively transferred into a naive host, demonstrating the ability of the stress-conditioned adaptive immune system to regulate hippocampal neurogenesis and mood states.

PANEL • THURSDAY, 4:30–6:30 PM • LAMAR/GIBBON

72. Early cortical circuits–from function to dysfunction

Chair: Patrick Kanold
Presenters: Patrick Kanold, Anna Hoerder-Suabedissen, Patrick McQuillen, Matthew Colonnese

Neuronal activity drives early brain development. Initial activity is dominated by spontaneously generated patterns that are subsequently replaced by sensory evoked responses. Recent work has identified specific circuits and processes that are crucial for these early developmental processes in the cerebral cortex. Since dysfunctions of early circuits might underlie neurodevelopmental disorders, the four presentations will review these new findings in the context of both normal and pathologic development. Anna Hoerder-Suabedissen (University of Oxford) will describe new insights on how the diversity of cells in the cerebral cortex is generated in evolution and development, and how specific genes linked to major neurodevelopmental disorders are enriched in the developing cortex. Patrick Kanold (University of Maryland) will describe how some of the earliest generated cortical neurons form specialized circuits that enable cortical maturation. Matthew Colonnese (George Washington) will describe how spontaneous activity is generated in the brain while Patrick McQuillen (UCSF) will describe how neonatal brain injuries can alter early spontaneous activity and development leading to subsequent changes in evoked activity and plasticity.

PANEL • THURSDAY, 4:30–6:30 PM • DUNRAVEN/OBSIDIAN

73. Androgens, androgen receptors and motoneurons: Relevance to injury and disease

Chair: Kathryn Jones
Presenters: Kathryn Jones, Dale Sengelaub, Ashley Monks, Diane Merry

There is strong evidence in the literature supporting the ability of androgens to influence motoneuron structure and function via the androgen receptor. Neurotrophic actions of androgens, acting directly on the motoneuron or indirectly via target musculature, have led to the concept that these agents have therapeutic potential in peripheral nerve injury and repair. Kathryn Jones will lead off this panel with a review of androgens as neurotherapeutics in different nerve injury models. She will provide a molecular mechanism to explain the accelerative effects systemic treatment with androgens has on regenerating motor axons, and will also discuss combinatorial approaches to peripheral nerve regeneration that include electrical stimulation and steroid treatment. This talk will focus on cranial nerve damage primarily. Dale Sengelaub will

discuss his discoveries of androgenic neuroprotection in spinal motoneurons, with particular emphasis on intraspinal circuitry and dendritic arborization. Comparison of data provided from cranial vs. spinal motoneurons will be provided as well. Ashley Monks will describe several mouse models related to Kennedy's disease (spinal bulbar muscular atrophy), a motoneuron disease in which a mutation in the androgen receptor (AR) gene is inherited in an X-linked recessive manner. He will discuss how wild type AR overexpression in motoneurons and/or muscle produces a Kennedy's phenotype, and the therapeutic implications. Diane Merry will discuss molecular aspects of androgen-dependent protein toxicity in Kennedy's disease.

PANEL • THURSDAY, 4:30–6:30 PM • CANYON

74. Rethinking how mu opioid receptors in the ventral tegmental area produce reinforcement: Count the ways

Chair: Elyssa Margolis

Presenters: Derek van der Kooy, Leslie Sombers, Kevin Wickman, Elyssa Margolis

Increased dopamine release from the ventral tegmental area (VTA) neurons is thought to be critical to the motivational effects of all drugs of abuse. Opiates that activate the mu opioid (MOP) receptor produce reinforcement, and activation of this receptor in the VTA is both sufficient to produce reward and required for the rewarding effects of systemically administered opiates. The key synaptic action of MOP receptors in the VTA is believed to be disinhibition of dopamine neurons: MOP receptor activation inhibits VTA GABAergic interneurons or GABA terminals synapsing onto dopamine neurons, thereby increasing dopamine neuron firing. However, experimental observations are accumulating that are inconsistent with this model. In this session we will discuss recent work probing VTA MOP receptor function at the neuronal, circuit, and behavioral levels, all of which indicate the disinhibition model must be updated. Dr. Derek van der Kooy (University of Toronto) will begin by describing the different circuits through the VTA that produce MOP reward in opiate naïve and dependent animals, and the role BDNF plays in this change. Dr. Leslie Sombers (NC State) will then demonstrate that even though microinjections of MOP receptor agonists and antagonists into the VTA have opposing behavioral effects (reward and aversion, respectively), they both increase dopamine release in the ventral striatum. Dr. Kevin Wickman (University of Minnesota) will then provide evidence that activation of G protein coupled inwardly rectifying K+ channels, the presumed effector of MOP receptor activation, is not required for MOP induced motor stimulation/reward. Finally, Dr. Elyssa Margolis (UCSF) will discuss a novel mechanism by which MOP receptors can directly excite VTA neurons, and the projection targets of the neurons that show this response. Together, these discoveries provide alternative mechanisms that may be used to improve our understanding of how opiates produce reinforcement.

PANEL • THURSDAY, 4:30–6:30 PM • CHEYENNE

75. Vasopressin/Oxytocin and the development of mammalian social behavior

Chair: Elliott Albers

Presenters: Elliott Albers, Elizabeth Hammock, Matthew Paul, Alexa Veenema

The arginine-vasopressin (AVP)/ oxytocin (OT) family of neuropeptides is involved in the regulation of social behavior in diverse species. Over the last 30 years these neuropeptides and their receptors have been shown to influence social phenomena such as affiliation, social communication, aggression and social recognition. Because of the critical importance of these neuropeptides in controlling social behavior, social cognition and emotion, they have also become a focus for the investigation of the basic mechanisms underlying psychiatric disorders. The vast majority of these studies have been conducted in adults. Recent studies in neonates and juveniles, however, have indicated that AVP and OT play critical roles in the development of social behaviors, and elucidating these roles may contribute to our understanding of the emergence of developmental disorders such as autism. This panel will discuss the roles of AVP and OT in the development of mammalian social behavior, highlighting the recent contributions of three early career stage investigators. First, Elliott Albers (Georgia State University) will provide brief introductory remarks and introduce the three early career stage investigators. Elizabeth Hammock (Florida State University) will discuss AVP and OT in early emerging social orienting behavior. Matthew Paul (University at Buffalo) will present data on the role of AVP in the development of social play and ultrasonic communication. Finally, Alexa Veenema (Boston College) will discuss sex-specific regulation of social play behavior by AVP and OT.

PANEL • THURSDAY, 4:30–6:30 PM • GALLATIN

76. Composition and Regulation of AMPA Receptors

Chair: Johannes Hell

Presenters: Johannes W. Hell, Hey-Kyoung Lee, Bernd Fakler, Richard L. Huganir

Glutamatergic transmission is central to brain function. Glutamate receptor composition and posttranslational modification such as phosphorylation control functional availability of those receptors. Long-lasting changes underlie many brain functions and especially information storage in various forms. At the same time, dysregulation of glutamate receptor function is at the basis of many mental and neurological disorders. This panel will discuss glutamate receptor composition and regulation in different brain regions. Johannes Hell will describe how Ca/Calmodulin caps the very N-terminus of PSD-95 to mediate a reduction in its palmitoylation and thereby its postsynaptic

displacement upon Calcium influx via NMDARs. Bernd Fakler will talk about 'functional proteomics' and their significance for analyzing the protein composition and function of native glutamate receptors in various brain regions. Hey-Kyoung Lee will discuss the molecular mechanisms that regulate synaptic AMPAR function in the sensory cortices to adapt to changes in the sensory environment. She will describe functional consequences of those mechanisms on circuit function. Richard Huganir will speak about visualizing AMPAR synaptic plasticity in vivo by multi-photo imaging to examine the dynamic trafficking of pHluorin tagged AMPARs in the somatosensory and motor cortex. He will show that AMPAR trafficking is NMDAR dependent and is regulated by sensory stimulation and motor learning.

PANEL • THURSDAY, 4:30–6:30 PM • LAKE

77. Novel therapies for brain disease in those patients that are going downhill fast

Chair: Thomas Swanson

Presenters: Detlav Boison, Jacci Bainbridge, Pavel Klein, Thomas Swanson

Medically intractable epilepsy is a significant problem: about 1/3 of the current epilepsy patients fail traditional small molecule therapy. A recent Institute of Medicine report clearly identifies one problem as underuse of available therapies by physicians untrained in epilepsy management. However, there is no doubt that the explosion of new drugs over the last 20 years has done little for the refractory epilepsy patient. It is becoming increasingly clear that individual patient variables may contribute to this intractability. Epigenetic variability in gene expression may explain why one patient responds to a drug, while another does not. Boison (Legacy Research Institute) will discuss examples of potential epigenetic therapies in epilepsy. Absorption, hepatic metabolism, and transport into the brain are other key factors that appear to be regulated differently among patients. Bainbridge (University of Colorado) will discuss hepatic enzyme efflux transporters, gut transporters, ATP binding cassettes, and anion transporters which may inhibit absorption or otherwise prevent drugs from getting to the site of action. When patients do not respond to current drug therapy, alternative therapies are needed. Klein (Mid-Atlantic Epilepsy and Sleep Center) will address the ketogenic diet in epilepsy including mechanisms of action and its potential in other brain disease therapies. Lastly, there has been a large upswing in public opinion regarding the use of marijuana in epilepsy and other neurological disease. Swanson (Montana Comprehensive Epilepsy Program) will discuss the potentials and perils of cannabinoid therapy in the epilepsies, reviewing relevant clinical trials and pre-clinical data.

Poster Abstracts

SUNDAY, JANUARY 25, 2015

P1. Effects of exercise on brain intrinsic network connectivity in overweight/obese adults

Kristina McFadden, Korey Wylie, Marc-Andre Cornier, Edward L. Melanson, Jamie L. Bechtell, Jason R. Tregellas*

Understanding how exercise affects neuronal response in overweight/obese individuals may provide insight into mechanisms of weight loss. The current study investigated the effects of a 6-month exercise intervention (supervised treadmill walking) on activity in the default mode network (DMN), a functionally connected intrinsic brain network that includes posterior cingulate cortex, cuneus/precuneus, medial prefrontal cortex, medial temporal lobe, and inferior parietal cortices. We and others have previously found activity in the network to be increased in obese and reduced-obese compared to lean individuals. Twelve overweight/obese adults completed the study (5 women, 7 men; mean body mass index (BMI) 33.3±4.3 mg/kg2; mean age 38.2±9.5 years). Using independent components analysis, we observed decreased within-network DMN activity (precuneus) following exercise, compared to baseline (t=4.50, p=0.003, FWE-corrected). A whole-brain between-network connectivity analysis was then performed, with a focus on regions in the DMN. Compared to all other gray matter voxels in the brain, we observed high levels of between-network connectivity in the DMN at baseline, particularly in the posterior cingulate cortex (PCC). Granger causality analysis was used to determine directionality of information flow between the PCC and other networks. This analysis demonstrated a reduction in connectivity from the PCC to other networks following exercise, compared to baseline (t=7.06, p=0.001, uncorrected). Given previous reports of DMN overactivity in overweight/obese individuals, the present findings may indicate an exercise-related normalization of DMN network function. Altered exercise-related connectivity between DMN and other networks suggests that exercise may also induce changes in the communication between large-scale brain networks.

P2. Visual influences on intermuscular coherence during the control of postural sway

Adriana Degani, Charles Leonard, Alessander Danna-dos-Santos*

Postural balance relies on a highly developed neural network and complex sensory-motor integration. Deprivation of visual input seems to have an impact on the ability to produce optimal levels of muscular coordination to move and/or stabilize a given joint to control balance and avoid fall. Recent studies have been proposed that correlated neural inputs may be the mechanism to organize multi-muscle synergies. The present study was designed to investigate the role of vision on neuromuscular control of posture. The distribution of correlated neural inputs was measured using intermuscular coherence estimates method (IMCoherence). Nine volunteers (mean age 26 ± 2.7 years old) performed 2 experimental tasks: quiet upright stance for 30 seconds with and without visual information (opened eyes and closed eyes, respectively). The muscular activity of 6 postural muscles (tibialis anterior, rectus femoris, rectus abdominis, soleus, biceps femoris, and lumbar erector spinae) was recorded by surface electrodes and the IMCoherence estimates were computed for 12 muscle pairs formed by these muscles. IMCoherence for the experimental task with visual input was only found to be significant for pairs formed solely by either posterior or anterior muscles. The significant coherence found was within a distinct frequency interval bounded between 1 and 10Hz. However, the IMCoherence presented a significant decrease in absence of visual input within this same frequency interval. No significant coherence was found for mixed muscle pairs formed by one anterior muscle and one posterior muscle. These results not only support previous findings that the central neural system uses correlated neural inputs to organize synergistic muscle groups, but also show that this neural mechanism is affected by removal of visual inputs. Understanding the role of vision on postural control is important to advance studies related to balance disorders.

P3. Mild traumatic brain injury increases fear behaviors that are accompanied by increased cortical GABA levels

Alana Conti, Brandy Schneider, Farhad Ghoddoussi, Jennifer Charlton, Robert Kohler, Shane Perrine*

Those with mild traumatic brain injury (mTBI) can develop changes in affect including anxiety, depression or symptoms resembling posttraumatic stress disorder (PTSD). Mechanisms underlying the development of such symptoms remain unclear; however studies suggest decreased prefrontal cortex (PFC) activation alters responses in downstream regions associated with fear learning, such as amygdala and hippocampus. Here, we used a mouse model to examine

the effects of mild TBI on fear behaviors and related neurochemical alterations in the PFC. Male C57BL/6 mice (10-12 wks) were anesthetized and impacted over the sagittal suture of the intact skull or exposed to surgery alone (sham controls). To assess levels of excitatory and inhibitory neurochemicals, PFC was harvested for proton magnetic resonance spectroscopy analysis ex vivo at 11.7 T at 8 d post-injury. A second group of mice was used to assess fear responses (freezing) to contextual fear conditioning (FC) at 14 d post-TBI. FC consisted of 5 phases: habituation, acquisition, extinction, reinstatement, and extinction recall of conditioned fear. Injured mice showed significantly increased freezing during acquisition and extinction that was accompanied by significantly increased GABA levels in the PFC compared to controls. No differences in baseline freezing, freezing during reinstatement, or extinction recall after reinstatement were observed between injured and control mice. The increased acquisition and slower extinction of conditioned fear observed in mTBI mice resemble features of FC reported in PTSD and mTBI patients. Increased GABA in the PFC may reflect increased inhibitory activity and support the hypothesis that mTBI-induced PFC hypoactivity limits top-down control over subcortical areas involved in FC; thereby increasing susceptibility to affective disorders. This model of mTBI-induced changes in PFC may give valuable insight into mechanisms involved in the development of affective symptoms after mTBI.

P4. A Novel Mouse Model of Genetic Risk for Excessive Alcohol Drinking

John Crabbe, Nick Grahame*

Abusive alcohol drinking is characterized by ingesting large amounts chronically as well as tending to drink in binges, defined by the NIAAA as a pattern leading to blood ethanol concentrations (BECs) > 0.8 mg/ml (i.e., exceeding the legal limit for driving) during a period of approximately 2 hr. The cHAP mouse was selectively bred for high levels of chronic intake when water and alcohol were continuously available—these mice drink as much as 25-30 g/kg/day. High Drinking in the Dark mice were selected for attaining high BECs after a short period of binge-like drinking during limited access to alcohol during their circadian dark period, and reach average BECs > 1.5 mg/ml. We recently initiated a new line—HAP-HDID mice—by intercrossing these two selected lines and continuing to breed selectively for both high DID BEC and high chronic alcohol preference. We report progress in this dual-trait selection.

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P5. Gene expression clusters in the central nervous system characterize the estrous cycle in the rat

Sonsoles de Lacalle, Robert Schmidt, Lonnie Welch, Paul Micevych*

The impact of hormones in susceptibility to mental disorders is far from understood. But it is well documented that fluctuations and eventual decline in ovarian hormone production (as during peri- and menopause), are associated with sleep problems, mood swings, anxiety, difficulty concentrating, disorientation and memory lapses. This suggests that irregularities in cyclicity affect both reproductive and non-reproductive areas of the brain. To understand the extent of these effects, we dissected basal forebrain (BF), frontal cortex (FC) and hippocampus (H) from young female rats at 10 am (n=4) and 6 pm (n=4) on proestrus day, and at 10 am on diestrus day (n=4), processed the samples for microarray analysis and applied several algorithms to identify differentially expressed genes across time points and brain regions. Comparison of the 3 time points revealed 198 probes and 106 genes differentially expressed ($p < 0.05$). Considered separately, there were 58 probes and 31 genes differentially expressed in the BF, 177 probes and 110 genes in the FC, and 39 probes and 21 genes in the H. The BETR algorithm also identified 465 probes and 273 genes differentially expressed, with probability greater than 0.99, across the three time points, E6, E10 and D10, in all brain regions. Each of the 3 brain regions individually exhibited larger number of differentially expressed probes and genes compared to the probes and genes expressed across all brain regions: 693 probes and 422 genes in the FC; 798 probes and 529 genes in the BF; and 1642 probes and 1054 genes in the H. Using fuzzy clustering we identified nine biologically significant gene expression patterns. The results highlight the profound effect that changes in hormone levels can exert on a variety of biological functions through widespread changes in gene expression. The study suggests that hormonal rhythmicity may be crucial not only in regulating internal metabolic processes, but also in coordinating with the environment.

P6. GABAergic bouton vesicular GABA transporter and GAD67 relative protein levels in the prefrontal cortex of subjects with schizophrenia

Kenneth Fish, Brad Rocco, David Lewis*

Convergent mRNA and protein findings indicate that cortical GABA circuitry is altered in schizophrenia. Studies conducted over the past decade have consistently found reduced levels of GAD67 mRNA in the prefrontal cortex (PFC) of subjects with schizophrenia. Analyses at the cellular level

have revealed that the density of GABA neurons with detectable levels of GAD67 mRNA is reduced by ~25-35% across layers 2-5. More recently, the mRNA encoding the vesicular GABA transporter (vGAT), which is required to package GABA for release, was reported to be modestly reduced in the PFC of subjects with schizophrenia. Knowing how these transcript deficits affect GABAergic bouton vGAT and GAD67 protein levels is important for understanding the ability of the schizophrenia brain to synthesize ready-releasable pools of vesicular GABA. Therefore, PFC tissue sections from 20 schizophrenia and matched comparison subjects were immunolabeled for vGAT, which is concentrated in GABAergic boutons, and GAD67, and imaged using quantitative fluorescence microscopy techniques. Across all layers and within individual layers, the density of vGAT+ boutons and the relative amount of vGAT protein per bouton were unchanged in schizophrenia. In contrast, across all layers vGAT+/GAD67+ bouton density was significantly 24% lower in schizophrenia, and GAD67 bouton levels within the remaining vGAT+/GAD67+ boutons were significantly 23% lower. In addition, a laminar analysis found similar results in layers 2-6. In concert, our findings suggest that GABAergic bouton density is unchanged in schizophrenia; however, the ability of a subset of GABAergic boutons to synthesize GABA is markedly reduced in the disease.

P7. Modulation of the IL-1ß effect on Hippocampal LTP by MK-801

Tammy Ivanco, Katrina Zmavc*

Cytokines, the signaling molecules of the immune system, activated by experience regulate remodeling of neuronal circuitry under normal conditions, but under strong immune activation the balance is upset and there are detrimental effects on brain plasticity. Much of the research on brain plasticity and cytokine interaction focuses on the Interleukin 1 (IL-1) family. The administration of pro-inflammatory cytokine Interleukin-1 beta (IL-1β) disrupts long-term potentiation (LTP), a physiological model of learning and memory, in the hippocampus and impairs performance on hippocampal dependent memory tasks. IL-1ß protein, however, is necessary for LTP maintenance in the hippocampus. Endogenous IL-1ß enhances calcium influx through NMDA receptors in the hippocampus, but how additional IL-1ß influences LTP and learning is not known. One possibility is that excessive IL-1β inhibits synaptic plasticity by increasing the amount of Ca2+ entering the cell through NMDA receptors, perhaps altering calcium-dependent phosphatases. We hypothesized rats given MK-801, an NMDA antagonist, in the presence of increased IL-1β would show LTP, but either drug alone would

cause the expected lack of potentiation. The presence of LTP was determined by comparing pre- and post-train stimulation baselines and input/output (I/O) curves. Both response slopes and EPSP amplitudes increased after trains when MK-801 and IL-1β were provided, supporting our hypothesis. The data provide further confirmation to the theory that there is an interactive effect between the nervous system and the immune system. This data suggests possible mechanisms to investigate for rescuing learning impairments for those with chronic immune system activation.

P8. ALK regulates binge ethanol consumption, ethanol reward and dopamine receptor sensitivity in the ventral tegmental area

Amy Lasek, John Dutton, Hu Chen, Chang You, Mark Brodie*

ALK is a receptor tyrosine kinase expressed in the nervous system that we previously found to regulate behavioral responses to ethanol in mice. To further characterize the ability of ALK to control ethanol consumption, we treated mice systemically with the ALK inhibitor, TAE684, and tested them for binge-like drinking using the drinking in the dark (DID) protocol. Mice treated with TAE684 drank less ethanol than controls, indicating that ALK activity in adult mice promotes binge-like drinking. Mice treated with TAE684 also exhibited attenuated ethanol reward, as measured by conditioned place preference. Since the ventral tegmental area (VTA) is a key brain region involved in the rewarding and reinforcing effects of ethanol, we examined whether Alk expression in the VTA might be important for ethanol consumption. A lentiviral-delivered short hairpin RNA (shRNA) targeting Alk or a non-targeting control shRNA was delivered into the VTA. Mice expressing Alk shRNA in the VTA drank less ethanol in the DID test compared to mice expressing a control shRNA. We characterized the expression of ALK in the VTA using immunohistochemistry and found that ALK is expressed on dopamine neurons, suggesting that ALK might regulate the firing properties of these neurons. Extracellular recordings of putative dopaminergic (pDA) neurons in VTA slices treated with TAE684 showed that there was no difference in the ability of dopamine to inhibit firing of pDA neurons. However, TAE684 prevented the desensitization of dopamine D2 receptors induced by prolonged exposure to moderate concentrations of dopamine. Together, these data indicate that ALK activity in the VTA regulates binge-like ethanol consumption, ethanol reward, and the desensitization of dopamine D2 receptors. Moreover, the desensitization of dopamine D2 receptors in the VTA may be involved in the regulation of binge ethanol consumption.

P9. Cellular mechanisms of serotonin regulation of orbitofrontal cortex function following cocaine self-administration

Carl Lupica, Alexander Hoffman, Agustin Zapata, Andrew Wright*

The orbitofrontal cortex (OFC) is involved in decision-making and the formulation of expectations based on the value of environmental reinforcers. This makes the OFC critical for adaptive learning and behavioral flexibility. Drug addiction is characterized by poor judgment and behavioral inflexibility (Lucantonio et al., Nat. Neurosci., 15:358, 2012), and we recently demonstrated that cocaine self-administration (SA) is associated with behavioral inflexibility and impaired neurotransmission in the OFC (Lucantonio et al., Nat. Neurosci., 17: 1092, 2014). As the OFC is innervated by serotonergic (5-HT) neurons from the dorsal raphe nucleus, and manipulation of OFC 5-HT function impairs OFC-dependent behaviors (Roberts, Biol. Psychiatry, 69: 1185, 2011), we examined the mechanisms of 5-HT regulation of OFC neurons following cocaine SA in rats using whole-cell electrophysiology in vitro. We found that 5-HT (20 μM) generated outward inhibitory currents in 35% of OFC pyramidal neurons, and this was associated with an increase in conductance. The effect of 5-HT was mimicked by the 5HT1a agonist 8-OH-DPAT, and blocked by the 5HT1a antagonist WAY100635.. The frequency of spontaneous glutamatergic synaptic currents (sEPSCs) was also increased by 5-HT (20 μM) in OFC neurons from control rats, though the receptor responsible for this action of 5-HT has not yet been identified. In contrast to the effects of 5-HT in control rats, experiments conducted in OFC brain slices obtained from animals following cocaine SA (0.75 mg/kg/infusion; 2 hr/day, 12d) revealed the absence of 5-HT actions on pre- or postsynaptic electrophysiological measures. These observations define cellular mechanisms of 5-HT effects in OFC neurons, and demonstrate the loss of 5-HT control of OFC neuron function following cocaine SA. Thus, 5-HT may be one of the critical regulators of OFC activity, whose disruption may lead to cognitive dysfunction in addiction.

P10. Deficits in tactile learning in a mouse model of Fragile X Syndrome

Aaron McGee, Megan Arnett, David Herman*

The fragile X mental retardation 1 mutant mouse (Fmr1 KO) recapitulates several of the neurologic deficits associated with Fragile X syndrome (FXS). As tactile hypersensitivity is a hallmark of FXS, we examined the sensory representation of individual whiskers in somatosensory barrel cortex of Fmr1 KO and wild-type (WT) mice and compared their performance in a whisker-dependent learning paradigm, the gap cross assay. Fmr1 KO mice exhibited

elevated responses to stimulation of individual whiskers as measured by optical imaging of intrinsic signals. In the gap cross task, initial performance of Fmr1 KO mice was indistinguishable from WT controls. However, while WT mice improved significantly with experience at all gap distances, Fmr1 KO mice displayed significant and specific deficits in improvement at longer distances which rely solely on tactile information from whiskers. Thus, Fmr1 KO mice possess altered cortical responses to sensory input that correlates with a deficit in tactile learning.

P11. Expression of CHRNA7 and CHRFAM7A and binding properties of the α7 nicotinic acetylcholine receptor show large inter-individual differences in human cortex

Jens Mikkelsen, Majbrit Jensen, Mads Dyrvig, Søren Christiansen, Lars Pinborg, Morten S Thomsen, Jacek Lichota*

Novel drugs targeting the α7 nicotinic acetylcholine receptor (nAChR) are in development for the treatment of Alzheimer's disease and schizophrenia. Even though clinical trials have shown promising effects there are observed large interindividual variabilities. Variabilities reported in the promoter region of the α7 nAChR gene, CHRNA7, and in the partial duplicated CHRNA7 gene (CHRFAM7A) are linked to schizophrenia.

Because CHRFAM7A is only present in human, expression of CHRNA7 and CHRFAM7A as well as DNA methylation of the CHRNA7 promoter was examined in human temporal cortical tissue obtained from neurosurgery. The mRNA level of CHRNA7 was found to be four times higher than CHRFAM7A. An inverse correlation between promoter DNA methylation and CHRNA7 mRNA levels ($r=-0.854$, $p=0.0034$) were observed, suggesting that not only promoter variations, but also the level of methylation is critical for expression of the gene. Binding properties of the α7 nAChR selective [125I]-α-bungarotoxin (α-Bgt) were also studied in the human cortical tissue. Concentration-inhibition curve with Encenicline was best fitted to a two-site model in some human individuals giving IC50 values of 3.9 nM and 2.2 μM, whereas only the lower-affinity component was identified in other individuals (IC50 ~5.8 μM). These data emphasises large variations in methylation status, gene expression, and binding properties of the α7 nAChR in native human brain tissue and further underlie the basis for large individual differences in responses to α7 nAChR modulators.

P12. Decoding neural circuit components in compulsive sucrose-seeking

Edward H. Nieh, Gillian A. Matthews, Stephen A. Allsop, Kara N. Presbrey, Craig P. Wildes, Rachael Neve, Kay M. Tye*

The lateral hypothalamus (LH) was one of the first brain regions to be implicated in reward processing, yet little is known about how neurons in this region compute different aspects of reward-related behaviors. A tremendous amount of heterogeneity exists across LH neurons in terms of function, and connectivity. One region reciprocally connected with the LH is the ventral tegmental area (VTA), which has been characterized in the context of reward. We show that the LH sends predominantly excitatory input to VTA dopamine (DA) neurons and a mixture of excitatory and inhibitory input onto VTA GABA neurons. To achieve a new level of insight towards how the LH-VTA circuit mediates reward processing, we employed in vivo electrophysiological recordings in freely-moving mice combined with optogenetic-mediated photoidentification of VTA-projecting LH neurons. We observed a substantial number of LH neurons that either project to the VTA or receive feedback from the VTA, and we show that VTA-projecting LH neurons primarily encode reward retrieval, while LH neurons receiving VTA feedback encode both the reward-predictive cue and the sucrose reward itself. Given the robust encoding of reward retrieval by VTA-projecting LH neurons regardless of whether or not the reward was omitted, we probed the role of the LH-VTA projection in mediating compulsive sucrose-seeking. We establish a causal relationship between LH-VTA activation and compulsive sucrose-seeking, due to increased drive for feeding rather than a reduction in analgesia.

P13. The pharmacological studies of mGlu5-GABA B receptor interplay in animal models of psychosis

Andrzej Pilc, Joanna Wieronska, Natalia Kleczek*

Diverse preclinical studies exploiting the modulation of the GABAergic and/or glutamatergic system in brain via metabotropic receptors suggest their potential therapeutic utility. N,N'-Dicyclopentyl-2-(methylthio)-5-nitro-4,6-pyrimidinediamine (GS39783) and 3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB), a positive allosteric modulators of the GABAB and mGlu5 receptors, respectively were previously shown to reverse behavioral phenotypes in animal models thought to mimic the selected (predominantly positive) symptoms of schizophrenia.

We focused mainly on the aspects of their efficacy in the models of negative and cognitive symptoms of schizophrenia. We used modified swim test, social interactions (models of negative symptoms) and novel object recognition

(model of cognitive disturbances). The activity of the compounds was also tested in haloperidol-induced catalepsy test. We also focused on the mutual interaction between GABAB/mGlu5 ligands.

Both mGlu5 and GABAB receptor modulators effectively reversed MK-801-induced deficits in animal models of negative and cognitive disturbances. Moreover, the concomitant administration of sub-effective doses of CDPPB and GS39783, induced a clear antipsychotic-like effect in all the procedures used, except DOI-induced head twitches. Activation of both types of receptor may be a promising mechanism for the development of novel antipsychotic drugs, efficacious towards positive, negative and cognitive symptoms.

P14. Brain Banking for Modern Research on Mental Illness

Jonathan Sirovatka, Brent Harris, Robin Kramer, José Apud, Stefano Marenco, Barbara Lipska*

Postmortem human brains are necessary to make progress in research on human brain structure and function, and on the pathogenesis of neuropsychiatric disorders. Other model systems, such as animals, blood and stem cells provide important information but do not always allow for extrapolations to the complexity of the human brain. Imaging of the living human brain, although powerful and informative, lacks the resolution of single cells and molecules. Access to human brains through brain banking is particularly important at a time of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative launched to develop new tools and technologies to aid in the understanding of neural circuit function. However, the major source of brain tissue donations, the clinical autopsy, is on a dramatic decline in the US. New strategies, including prospective brain donations, donations through medical examiner's offices, and banking in networks are required. We will present brain tissue collection practices of the Human Brain Collection Core at the NIMH, which focuses on schizophrenia and other mental illnesses, such as mood disorders and substance abuse, and consists of ~1,000 brains. We will describe the procedures of collecting brain tissue through donations from medical examiner's offices in the Washington, DC metropolitan area and Virginia, and share standardized protocols and quality control methods that assure high sample quality. We will show how we gather and track extensive phenotypic and genetic data obtained postmortem on the subjects with mental disorders and non-psychiatric controls, as well as the data related to tissue samples and derivatives (e.g., RNA and DNA specimens), and how we integrate this information using comprehensive databases. We will describe the mechanisms by which these rich specimen and data resources are being made available to investigators in order to stimulate their research on the human brain.

P15. A voltammetric characterization of serotonin and histamine during Parkinson's disease and therapies

Aya Abdalla, Parastoo Hashemi*

Parkinson's disease (PD) is a neurodegenerative disease that affects 1 million people in the United States alone. Despite wide research into the relief of the motor symptoms of PD, its non-motor symptoms like depression are largely unstudied. This is mainly due to the poor understanding of the effects of PD on neuromodulators other than dopamine. Histamine and serotonin are two important neuromodulators in PD, linked to many of its non-motor symptoms. To more clearly understand these non-motor symptoms and to eventually be able to minimize or relieve their effects on patents, it is first important to study the modulation of serotonin and histamine in PD in different brain regions. In this work, we do this with fast scan cyclic voltammetry (FSCV) by measuring serotonin and histamine using a single carbon fiber microelectrode (CFM). These measurements, combined with pharmacological manipulations enable us to perform a mathematical analysis on the extent, direction and magnitude of serotonin/histamine modulation and how their levels change due to PD. We plan on taking our studies further and studying serotonin/histamine modulation of each other in PD mouse models.

P16. Exposure to dietary high-fat modifies reward processing in the brain

Travis Brown, Rebecca Darling, Paige Dingess*

Both obesity and drug addiction can be defined by an exaggerated saliency for a specific reward (food or drug) at the expense of other rewards. Numerous studies have shown comparable neurobiological overlaps between the two disorders. However, whether food is "addictive" is highly debated. Utilizing behavioral and histological techniques we compared and contrasted adaptations in the reward circuitry after exposure to dietary high fat (HF) with those traditionally reported for cocaine. A hallmark of cocaine is its ability to induce locomotor sensitization, by which repeated exposure to cocaine causes a progressive increase in cocaine-induced locomotor activity. Concomitant with cocaine-induced locomotor sensitization is an increase in dendritic spine density within the nucleus accumbens (NAcc) and prefrontal cortex (PFC), key brain regions in reward processing. We hypothesized that if HF influences the reward system similarly to drugs of abuse we would see increased locomotor activity to cocaine in animals fed a HF diet (60%). Our results showed that 3 weeks of either calorically matched or ad libitum access to HF did not result in cross-sensitization with cocaine, but in fact significantly reduced the locomotor stimulating effects of cocaine. In addition, rats maintained on the HF diet

showed a significant reduction in dendritic spine density within the PFC and no changes were observed within the NAcc. To address whether there is a general hypo-responsiveness of the reward circuitry rats were placed on a HF diet for 3 weeks, fasted for a 24-hr period and subsequently tested in an overnight sucrose self-administration task. Our results showed that rats fed HF for 3 weeks had a significant attenuation in active lever responding for sucrose. Taken together this data suggests that intake of dietary HF, which leads to an obese state, does not simply recapitulate neural adaptations traditionally seen with drugs of abuse and causes a reduction in reward seeking behaviors.

P17. Juvenile onset of stereotypy with loss of BDNF signaling in D1R expressing striatal neurons

Michel Engeln, Ramesh Chandra, Ashley La, T. Chase Francis, Mary Kay Lobo*

Imbalance between D1- vs. D2-receptor containing medium spiny neuron (MSN) basal ganglia output-pathways is implicated in stereotyped disorders including Tourette Syndrome (TS). Surprisingly, there is little information on the molecular role of MSN subtypes in TS or other stereotypy disorders. We have a mouse model carrying a deletion of TrkB (the BDNF receptor) in D1-MSNs (D1-Cre-flTrkB mice), in which a subset of mice display involuntary stereotypic behaviors beginning around 3 weeks of age. Consistent with an impaired GABAergic system in TS, these mice display a decrease in striatal GABA-A subunits accompanied by reduced inhibition in striatal D1-MSNs. We first characterized repetitive behaviors in D1-Cre-flTrkB mice with stereotypy (S), or with no stereotypy (NS), and D1-Cre control mice. Complete turns, head tics, rearing, and grooming are assessed weekly from ages 3 to 8 weeks. Since the transcription factor, early growth response 3 (Egr3) is regulated by BDNF and Egr3 transcriptionally regulates a subset of GABA-A subunits, we are examining striatal Egr3 mRNA in all groups. We found that D1-Cre-flTrkB-S mice display more complete turns at all ages compared to D1-Cre-flTrkB-NS and control mice. D1-Cre-flTrkB-S mice exclusively display head tics, which decline from juvenile to adult ages. Our preliminary data demonstrates decreased Egr3 mRNA in the striatum of D1-Cre-flTrkB mice. We are investigating if this change is specific to D1-Cre-flTrkB-S mice and are using chromatin immunoprecipitation to examine Egr3 transcriptional regulation of GABA-A subunits in these mice. Our findings demonstrate that D1-MSNs through dysfunctional BDNF signaling play a role in juvenile onset of stereotypy behaviors. The enhanced stereotypy behaviors potentially occur through reduced inhibition in D1-MSNs via altered Egr3 regulation of GABA-A subunits. Our ongoing studies can provide novel insight into the cell subtypes and molecular mechanisms underlying stereotypy disorders.

P18. CaMKII binding to GluN2B is differentially affected by macromolecular crowding reagents

Dayton Goodell, Tatiana Eliseeva, Steven Coultrap, K. Ulrich Bayer*

Binding of the Ca2+/calmodulin(CaM)-dependent protein kinase II (CaMKII) to the NMDA-type glutamate receptor (NMDAR) subunit GluN2B controls long-term potentiation (LTP), a form of synaptic plasticity thought to underlie learning and memory. Regulation of this interaction is well-studied biochemically, but not under conditions that mimic the macromolecular crowding found within cells. Notably, previous molecular crowding experiments with lysozyme indicated an effect on the CaMKII holoenzyme conformation. Here, we found that the effect of molecular crowding on Ca2+/CaM- induced CaMKII binding to immobilized GluN2B in vitro depended on the specific crowding reagent. While binding was reduced by lysozyme, it was enhanced by BSA. The differential effect of lysozyme (14 kDa) and BSA (66 kDa) was not due to size difference, as both dextran-10 and dextran-70 enhanced binding. By contrast, crowding with immunoglobulin G (IgG) reduced binding. Notably, lysozyme and IgG but not BSA directly bound to Ca2+/ CaM in an overlay assay, suggesting a competition of lysozyme and IgG with the Ca2+/ CaM-stimulus that induces CaMKII/ GluN2B binding. However, lysozyme negatively regulated binding even when it was instead induced by CaMKII T286 phosphorylation. Alternative modes of competition would be with CaMKII or GluN2B, and the negative effects of lysozyme and IgG indeed also correlated with specific or non-specific binding to the immobilized GluN2B. Thus, the effect of any specific crowding reagent can differ, depending on its additional direct effects on CaMKII/GluN2B binding. However, the results of this study also indicate that, in principle, macromolecular crowding enhances CaMKII binding to GluN2B. Importantly, the positive regulation by nucleotide and macromolecular crowding reagents did not alleviate the requirement for CaMKII stimulation to induce GluN2B binding.

P19. Activation of hypothalamic oxytocin neurons blunts obstructive sleep apnea-mediated cardiovascular dysfunction

Heather Jameson, David Mendelowitz*

Daytime tachycardia and hypertension are associated with Obstructive Sleep Apnea (OSA),a very common, yet poorly understood disease that increases the incidence of stroke, myocardial infarction and other adverse cardiovascular events. Oxytocin (OXT), a conserved neuropeptide released from neurons in the paraventricular nucleus of the hypothalamus (PVN), has been shown to reduce responses to social stressors, such as isolation and anxiety. This

study tests the hypothesis that activation of oxytocin neurons in the PVN can reduce the adverse cardiovascular consequences that occur with long term episodic periods of hypoxia and hypercapnia that are hallmarks of OSA. To test this hypothesis the PVN in male rats was microinjected with two viral vectors: one expressing Cre recombinase under an OXT promoter, and the second expressing a floxed excitatory hM3Dq DREADDs to selectively and chronically activate OXT neurons in the PVN. Male rats serving as controls were injected with a sham virus. Animals from both groups were implanted with a wireless telemetry device to monitor arterial blood pressure and EKG activity. Animals received daily injections of clozapine-N-oxide (CNO) to activate PVN OXT neurons. Selective activation of PVN OXT neurons in telemetry equipped animals expressing DREADDs decreased resting BP and HR, but CNO injection had no effect on HR and BP in sham virus control animals. Furthermore, chronic PVN OXT neuron activation in animals expressing DREADDs prevented the elevations in blood pressure and heart rate that occurs in untreated animals exposed to 21 days of chronic intermittent hypoxia/hypercapnia.

P20. Dopaminergic neuromodulation of the subthalamic nucleus

Asha Lahiri, Hong-Yuan Chu, James Surmeier, Mark Bevan*

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

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

In PD, the motor cortex (M1) and STN exhibit abnormal, synchronous beta band activity. In order to test the impact of dopaminergic neuromodulation on cortical patterning of STN activity, M1-STN axon terminals were optogenetically stimulated at 20 Hz for 1 second in the presence and absence of dopamine. Dopamine profoundly reduced cortical excitation of STN neurons (control = 7.1 spikes; dopamine = 1.9 spikes; $n = 6$; $p < 0.05$). Together, these findings demonstrate that dopamine is a potent neuromodulator of autonomous activity, synaptic transmission and synaptic integration in the STN. Furthermore, loss of dopaminergic modulation in the STN may contribute to abnormal cortical patterning of STN activity in PD.

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P21. Comparison of neural ensembles engaged by novelty and cocaine

Christopher Olsen*, Natalie Nawarawong, Matthew Muelbl, Hu Zhu, Yi Wei Lim, Bryan Roth

Elevated novelty seeking is a personality trait associated with an increased vulnerability for substance abuse. Previous studies have shown that both novelty and drugs of abuse have actions within the mesocorticolimbic dopamine system, although it is unknown whether the same neural ensembles are engaged by these two stimuli. In this project, we measured overlap of neurons engaged by novelty and cocaine administration within regions of the mesocorticolimbic dopamine circuit. We also assessed functional overlap by chemogenetic tagging and silencing of neurons engaged by the novelty and cocaine. Using the TetTag mouse model, we differentially identified neurons engaged by novelty and/or cocaine within the prefrontal cortex and nucleus accumbens. Results from this study indicate a significant overlap in neurons engaged by novelty and cocaine that is most prominent in the nucleus accumbens. To assess functional overlap, we used a complementary "TetDREADD" approach to express Gi-coupled DREADDs in neurons engaged by novelty or cocaine. With this approach, we examined behavioral effects of silencing neurons engaged by cocaine on novelty seeking and vice-versa. Consistent with the TetTag results, data from TetDREADD mice also indicate overlap in neurons engaged during cocaine and novelty.

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P22. Behavioral deficits and serotonin reductions in rats after chronic L-dopa

Branden Stansley, Bryan Yamamoto*

L-dopa is administered to Parkinson's disease (PD) patients to increase brain dopamine and recover motor function. Serotonin (5-HT) neurons, which are capable of taking up L-dopa and decarboxylating it to dopamine, are credited for the therapeutic effectiveness but also some of the debilitating side effects of L-dopa. Indeed, over time the drug loses efficacy and side effects such as dyskinesia and mood disorders occur. Furthermore, high amounts of L-dopa administered to rats results in dysregulation of the 5-HT system. Chronic L-dopa treatment in rats has been shown to result in 5-HT neuron decreases in a subregion of the dorsal raphe nucleus (DRN), an effect that is mediated by oxidative mechanisms. Given these findings, it was hypothesized that chronic L-dopa treatment decreases 5-HT tissue concentrations throughout the rat brain and lead to behavioral impairments.

Rats were treated chronically with L-dopa (6 mg/kg; twice daily) for 10 days to investigate the effects on 5-HT content in the DRN, amygdala, striatum, hippocampus and prefrontal cortex. Studies to investigate cognitive and affective behaviors included the forced swim test, conditioned fear test, elevated plus maze and Barnes maze. Results indicated that after 10 days of L-dopa treatment, 5-HT tissue content was significantly decreased in the dorsal DRN subregion ($q=4.8$, $p<0.05$) and prefrontal cortex ($q=3.42$, $p<0.05$). These effects were blocked by co-treatment with ascorbic acid. Further, rats treated with chronic L-dopa exhibited potentiated freezing behavior in the conditioned fear test ($q=4.44$, $p<0.05$), an effect that was also blocked by ascorbic co-treatment. Finally, L-dopa treated rats trained on the Barnes maze had significantly increased latency time in finding the goal box during the recall trial compared to vehicle treated rats ($q=-2.23$, $p<0.05$). Experiments examining ascorbic acid effects on L-dopa induced deficits in Barnes maze are in progress.

P23. Cognitive Impairment in a Rat Model of TBI: The Role of Individual Differences

Cole Vonder Haar, Frederick Lam, Wendy Adams, Catharine Winstanley*

Traumatic brain injury (TBI) is a major health issue across the world with millions of TBIs occurring annually. However, brain injury is very heterogeneous both in type (concussive, focal; frontal, parietal) and severity (mild to severe). The majority of injuries are mild and many people exhibit spontaneous recovery with no intervention. This is not the case for all patients—some exhibit worsening cognitive symptoms even due to minor insults. These individual variations have not been addressed widely in animal

models of TBI. Typically this variation is taken as a nuisance and either excluded or folded into larger numbers of animals in order to detect effects. In this study we analyzed a group of animals across a spectrum of injury (sham, mild, moderate, severe) on a complex cognitive behavioral task. The five-choice serial reaction time task has been used to characterize contributions of a number of neurotransmitter systems and brain regions on attention and motor impulsivity. Here we show that rats demonstrate impairments in a severity-dependent fashion across multiple measures. However, rats given mild or moderate injuries showed considerable variation in their recovery, often performing at near-sham or near-severe levels. To investigate why these differences occur, we evaluated several markers of neuroinflammation using a cytokine multiplex ELISA. The immune response is one of the most chronic physiological consequences of TBI and has also recently been implicated as playing a complex role in cognitive processes. We observed several cytokines with elevated levels, which correlated with behavioral function and lesion cavity formation. The observed spread of effects on a clinically-relevant behavioral task replicates the spectrum of deficits observed in human TBI. We plan to use this model of individual differences to further assess other factors that may contribute to recovery or decline of function in order to better target treatments to vulnerable populations.

P24. Single neuron coding of fairness in the human anterior midcingulate cortex

David Devilbiss, Rick Jenison*

The anterior midcingulate cortex (aMCC) has been shown to encode negative perception provoked by unfairness, and the anticipation of intense aversive stimuli. However, the neural coding of fairness and punishment-related decision-making in the aMCC remains poorly understood. The Ultimatum Game is a widely used bargaining paradigm for economic decision-making, and has been used to reveal the influence of unfairness on choice. Typically, a proposer is endowed with a sum of money and offers a portion to a second player (the responder). If the responder accepts the offer, both participants keep the suggested amounts otherwise each player earns nothing. The offer is rejected half of the time when proposals fall below 20% of the endowment. The current study examined aMCC neuron spiking activity recorded from patients undergoing diagnosis and, later, surgical treatment for pharmacologically intractable epilepsy. Placement of recording electrode microcontacts within the aMCC was confirmed with high resolution MRI. Subjects acted as responders in a series of 80 trials of the Ultimatum Game over two blocks. Endowments ranged from $2 to $25 and proposals ranged from 0 to 50% of the endowment. For example, in each trial the participant first saw the picture and name of someone making an Ultimatum offer. Next, participants were presented with an

offer and allowed unlimited time to consider the offer and respond ("Accept" or "Reject") with a button press. We investigated whether single and multi-unit activity covaried with the responder's acceptance or rejection of the proposer's offers. We modeled the neural spiking activity using non-parametric Peri-Event Time Histograms and a generalized linear model (Poisson-GLM) that models the moment-by-moment correlation with the decision to accept or reject the proposer's offer. Our results demonstrate that aMCC neurons can code multiple aspects of the Ultimatum Game including the perceived fairness in the proposed division of money.

P25. Conditional Reprogramming and Immortalization of Rat Primary Astrocytes

Brent Harris, Lanier Heyburn, Saed Sadeghi, Galam Khan, Jamie Hollowman, Robert Walker*

Astrocytes are one type of glial cells with wide varieties of functions and morphologies. They have significant roles in nutritional and biochemical support, synapse physiology and synaptogenesis, and formation of blood brain barrier. Astrocyte dysfunction may also play a role in many CNS pathologies. Our goal in this study is to conditionally reprogram primary rat cortical astrocytes in vitro to immortalize them while maintaining some of their normal physiologic characteristics. We reprogrammed E18-19 embryonic rat astrocytes by using a co-culture system of irradiated rat fibroblasts (or conditioned medium from the same) with addition of Rho-associated protein kinase (ROCK) inhibitor Y-27632, a method prior shown to immortalize conditionally many epithelial cell types. We, and others, have found that rat primary astrocytes cannot be passaged more than 6 or 7 times, at which point start to undergo physiologically senescent. In our co-culture/Rho Kinase inhibitor conditions the cultures are found to continually proliferate with passages up to 25 times tested to date. Additionally, the astrocytes in the co-culture can be frozen down, thawed, and maintain active proliferation. Astrocytes morphology in co-culture rapidly changes to a fibrous, spindled, and reticular type appearance. When returned to standard astrocyte culture conditions they show more flattened typical primary astrocyte morphology, express typical astrocyte proteins such as GFAP, S100, and glutamine synthase, and have more limited passage capability. Further development of primary rat and human astrocyte "cell lines" will be important in glial biology research and possibly human disease therapy.

P26. Functional Analysis of the Schizophrenia- and Autism-associated Gene, Transcription Factor 4 (TCF4) During Cortical Development

Brady Maher, Matthew Rannals, Stephanie Cerceo-Page, Andrew Jaffe, Morganne Campbell, Ryan Gallo, Thomas Hyde, Joel Kleinman, Daniel Weinberger*

Transcription Factor 4 (TCF4) is a pleiotropic gene for which genetic variants are associated with Schizophrenia and haploinsufficiency results in Pitt-Hopkins Syndrome (PTHS), a rare autism spectrum disorder (ASD). We have created an in vivo cellular model of PTHS by knocking down TCF4 expression in prefrontal cortical neurons immediately prior to neurogenesis. Downregulation of TCF4 results in a significant reduction in action potential output that is associated with an increase in the amplitude of the afterhyperpolarization. By combining in utero electroporation (IUE) and translating ribosome affinity purification (TRAP) we identified two ion channel genes, KCNQ1 and SCN10 whose translation was significantly up regulated by TCF4 knockdown. This candidate mechanism was validated by phenotype rescue using KCNQ1 antagonists and phenocopy by overexpression of recombinant SCN10a. Taken together, our study identifies TCF4 as a regulator of intrinsic excitability and we suggest this molecular mechanism may be responsible for cognitive deficits associated with PTHS and potentially SZ.

P27. The search for LRRK2 kinase inhibitors: A selective and brain available compound to probe the function and safety of LRRK2 as a target for PD

Jaclyn Henderson, Matthew Hayward, Bethany Kormos, Paul Galatsis, Ravi Kurumbail, Elie Needle, Stephen Noell, Harry Samaroo, Warren Hirst*

LRRK2 (Leucine-rich repeat kinase 2) was identified through GWAS studies as a promising target for Parkinson's disease, and as such has received a great deal of attention from both academia and industry. However, LRRK2 is not just a kinase, it is a large and multi-domain protein, which has made elucidating its normal function and connecting its disregulation to the pathology of Parkinson's disease a challenging task.

In order to assist in probing the function of LRRK2's kinase domain, a number of inhibitors have been published, covering a range of chemical classes. However, many of these inhibitors are not ideal either due to their lack of selectivity over other kinases, or due to poor ADMET properties making them unsuitable for in vivo experiments. Through our ongoing drug discovery program, we have identified a number of promising lead series for the identification of selective LRRK2 kinase inhibitors with suitable properties

for both application as chemical tools and for progression towards the clinic. Here we describe the development of one of our lead series, comparing key compounds to published LRRK2 inhibitors. We will also show how our highly potent, selective and brain penetrant LRRK2 compounds are helping to probe the function of LRRK2 both in vitro and in vivo, and derisk the target as we progress towards the clinic.

P28. The Big Sky Brain Project: Bringing experiential neuroscience to Montanans

Amanda Duley, Jessie Herbert, Hannah Motl, Holly Truitt and Michael Kavanaugh*

The Big Sky Brain Project is a five-year STEM project funded by the NIH with the goal of fostering experiential neuroscience education for K-12 students. Collaboratively created by faculty from the University of Montana Neuroscience Center and the University's science museum, spectrUM. The project includes interactive exhibits, a working neuroscience lab, internships for middle, high and college students, field trip programming for K-12 students, guest lectures for college classes and a mobile traveling brain exhibit to serve local as well as isolated, underserved, rural and tribal schools. The project co-PIs are Michael Kavanaugh, Ph.D., Director of the Neuroscience Center and Holly Truitt, Director of spectrUM. Our BrainLab manager, Dr. Amanda Duley, serves as liaison between project members and our greater community of learners.

P29. Cognitive Control Network Function in Alcohol Use Disorder Before and During Treatment with Lorazepam

Claire Wilcox, Andrew Mayer, Josef Ling, Michael Bogenschutz, Charlene Dekonenko, Rose Bigelow*

In individuals with alcohol use disorder (AUD), impairments in cognitive control contribute to difficulty maintaining abstinence. Benzodiazepines are being explored (in combination with disulfiram) for relapse prevention in individuals with co-occurring anxiety and AUD (clinicaltrials.gov identifier: NCT00721526). We compared brain function in AUD to healthy controls (HC), examined the effects of treatment with a combination of a benzodiazepine and disulfiram in AUD. 7 AUD from an open-label trial of disulfiram plus lorazepam and 9 HC performed a Stroop task during fMRI (in AUD both pre and 5-7 days post initiation of medication). Evoked BOLD signal during the task and resting state functional connectivity were compared (HC vs. AUD; Scan 1 in AUD vs. Scan 2 in AUD). For seed-based resting state connectivity analyses, seeds were placed in the cognitive control network

(caudate, DLPFC, dorsal ACC). AUD demonstrated slower reaction time during the task compared to HC. Although there were no significant Group (AUD vs. HC) X Condition (Incongruent vs. Congruent) or Time (Scan 1 vs. Scan 2) X Condition interactions, AUD participants demonstrated greater activation than HC (overall Group effect) in a variety of brain regions known to be involved in cognitive control including insula, parietal lobe, DLPFC, supplementary motor area (SMA), dorsal ACC, basal ganglia and thalamus. AUD demonstrated decreased connectivity in a variety of regions involved in cognitive control but increased connectivity between caudate and cingulate. None of the changes from Scan 1 to Scan 2 occurred in areas where there were differences between HC and AUD for either evoked or resting state analyses. In summary, AUD demonstrated a variety of functional brain changes in the cognitive control network. Treatment with a combination of disulfiram and lorazepam neither resulted in a significant normalization of these brain changes, nor did it appear to worsen related brain function.

P30. Individual Differences in Eye Movements During Speech Perception

Michael Beauchamp, Nathan Doyle*

Understanding speech is one our most important cognitive abilities and makes use of both the auditory and visual modalities. A demonstration of this multisensory integration is an illusion known as the McGurk effect. When presented with some combinations of auditory and visual syllables, subjects perceive neither the auditory nor the visual syllable but a third, completely different syllable. However, some subjects do not experience this illusion and only report the auditory syllable, suggesting that they do not make use of visual speech information.

19 healthy adults viewed two-second videos of a person saying a syllable (30 repetitions of 4 congruent syllables and 2 McGurk syllables) and reported their percept. Subjects' eye movements using an infrared eye tracker. The amount of time subjects spent fixating the eyes and mouth of the talker were measured.

There was large variability in the amount of time individuals spent fixating the mouth and eyes of the speaker. Some subjects looked mostly at the eyes, while others looked mostly at the mouth. Across subjects, mouth fixation time ranged from 0-72%. There was also large variability in subjects' perception of the McGurk effect, ranging from 0-100%. The amount of time spent looking at the mouth correlated with susceptibility to the McGurk effect.

We found that individuals utilize different eye movement patterns to understand audiovisual speech. The McGurk effect requires the observer to use visual cues; individuals who spend more time fixating the mouth of the

talker were more likely perceive the McGurk effect, implying that they are more influenced by the visual component of speech. If looking at the mouth increases the influence of visual speech, training eye movements in the patients with language impairments could improve speech comprehension.

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P31. Ghrelin inhibits GABAergic neurotransmission to cardiac vagal neurons in the nucleus ambiguus

Ned Cauley, Valerie Amann, Jhansi Dyavanapalli, David Mendelowitz*

Ghrelin is a neuropeptide secreted predominantly by oxyntic cells within the gastric mucosa that promotes food intake through the stimulation of gastric acid secretion and gastric motility. However, Ghrelin may also have effects on the cardiovascular system, as brainstem application of Ghrelin has been shown to decrease arterial pressure and heart rate, as well as augment the baroreflex. The parasympathetic component of heart rate is dominated by the activity of pre-motor parasympathetic cardiac vagal neurons (CVNs) located in the nucleus ambiguus (NA) and dorsal motor nucleus of the vagus (DMV) in the brainstem. The aim of this study was to examine the effects of Ghrelin on inhibitory and excitatory neurotransmission in CVNs. Retrogradely labeled CVN neurons were identified on brainstem slices of two to six day-old Sprague-Dawley rats. Whole-cell patch clamp recording was used to record synaptic events and membrane properties of CVN neurons. Bath application of Ghrelin (100 nM) significantly decreased the frequency and amplitude of GABAergic inhibitory postsynaptic currents (IPSCs), but did not affect the frequency or amplitude of Glycinergic IPSCs and Glutamatergic excitatory postsynaptic currents (EPSCs). These results indicate Ghrelin dis-inhibits CVNs via diminished inhibitory GABAergic neurotransmission, thereby increasing parasympathetic activity to the heart and decreasing heart rate.

P32. "Autonomous" CaMKII mediates NMDAR-dependent LTP, LTD and cell death

Steven Coultrap, Ronald Freund, Kelsey Barcomb, Isabelle Buard, Guiying Deng, Tim Benke, Mark Dell'Acqua, Paco Herson, K. Ulrich Bayer*

Generation of CaMKII "autonomy" (Ca2+-independence) by T286 auto-phosphorylation is regarded as a form of "molecular memory", and is indeed critically important in long-term potentiation of synaptic strength (LTP) and in learning and memory. However, "autonomous" CaMKII is not fully active,

but instead significantly further stimulated by Ca2+/CaM. We show here that "autonomous" CaMKII is important for both NMDAR-dependent LTP and LTD, as well as for cell death. While the role for T286 auto-phosphorylation in potentiation of synaptic strength has been well established, we show that further Ca2+/CaM stimulation of "autonomous" CaMKII is required to enhance synaptic strength. Furthermore, we show that "autonomous" CaMKII also mediates NMDAR-dependent LTD, and that substrates of CaMKII may differ in the two forms of plasticity. In addition to its role in plasticity, we found that 'autonomous" CaMKII activity is also an important mediator of cell death following cardiac arrest and reperfusion. Cell death was significantly reduced in a mouse expressing "autonomy"-deficient CaMKIIα and was also reduced by a peptide that inhibits all CaMKII activity. Thus, "autonomous" CaMKII is critical for mediating three distinct modes of glutamate signaling: prolonged weak stimuli that depress synaptic strength, brief strong stimuli that potentiate synaptic strength, and prolonged strong stimuli that lead to cell death.

P33. LPS-induced changes in SOCS-3 are reversed by the cannabinoid agonist CP-55,940 in nodose ganglia

Gaylen Edwards, Juliane Johnston, Kimberly Freeman*

In earlier work we demonstrated that cannabinoids can decrease activation of nodose ganglion neurons by lipopolysaccharide (LPS). In these studies we have examined the potential role of TLR-4 receptors in LPS activation of nodose ganglion neurons by measuring the levels of downstream signaling molecules NF-kappaB (phosphorylated and non-phosphorylated), and SOCS-3 using Western blots. In addition, we have assessed the effect of the cannabinoid agonist CP 55,940 on the changes in these signaling molecules induced by LPS. Nodose ganglia were extirpated and desheathed. The ganglia were then treated with: 1. Media; 2. LPS; 3. CP 55,940; 4. CP 55,940 followed by LPS; 5. AM 251; or 6. AM 251 and CP 55,940 followed by LPS. LPS treatment caused a decrease in expression of pNF-kappaB and NF-kappaB in nodose ganglia in addition to an increase in SOCS-3 expression. Pretreatment with CP 55,940 did not have an effect on pNF-kappaB or NF-kappaB expression in the nodose ganglia in response to LPS, but it did significantly reduce SOCS-3 expression induced by LPS. This reduction was reversed by the cannabinoid receptor antagonist AM 251. These observations suggest that cannabinoids may interact with LPS activation of nodose ganglion neurons through an indirect effect that may involve production of cytokines.

P34. Imaging presynaptic proteins that may contribute to defects in synaptic transmission in a Drosophila model of amyotrophic lateral sclerosis

Hong Fei, Irwin Levitan*

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease characterized by neuromuscular dysfunction. One gene associated with ALS encodes the DNA/RNA binding protein Fused in Sarcoma (FUS). There now exists a Drosophila model of FUS-related ALS in which human FUS with ALS-causing mutations is expressed in fly motor neurons. These flies exhibit larval locomotor defects and early death. We demonstrated previously that synaptic transmission at the neuromuscular junction in FUS larvae is severely compromised, as a result of decreased release of neurotransmitter, and that this functional defect is accompanied by aberrant structure of presynaptic active zones (Shahidullah et al, J. Neurosci. (2013) 33:19590-19598). To determine what presynaptic proteins might contribute to the synaptic dysfunction, we have visualized a variety of synaptic vesicle and other presynaptic proteins involved in synaptic transmission, using confocal microscopic analysis of larval neuromuscular junctions. Flies were engineered to express either wild type or mutant (R521C) human FUS in motor neurons, and larvae were stained with antibodies against synaptic proteins. While several presynaptic proteins including synapsin and cysteine string protein appear to be expressed at normal levels and are localized correctly in mutant FUS larvae, there is a change in expression and aberrant organization of presynaptic synaptotagmin at mutant as compared with wild type neuromuscular junctions. Because of the central role of synaptotagmin as a calcium sensor necessary for neurotransmitter release, this finding may account for the severe disruption of synaptic transmission in FUS mutant flies.

P35. Insensitivity to outcome devaluation in sign-tracking rats

Kimberly Fiscella, Yu-wei Chen, Alex Kawa, Donna Calu*

During a simple autoshaping procedure, where the extension of a lever precedes the delivery of reward, rats show individual differences in conditioned responding; some rats approach/contact the lever (sign-tracking (ST)), while other rats approach/contact the food cup (goal-tracking (GT)). We sought to determine whether ST rats show deficits in goal-directed behavior by examining their sensitivity to outcome devaluation prior to the ST/GT assessment. We trained rats to associate a light conditioned stimulus (CS) with a food outcome, and assigned them to paired or unpaired groups. Paired rats

received home-cage access to food pellets, followed immediately by injections of LiCl (0.3M, 5 ml/kg i.p.), which causes gastric malaise. Unpaired rats received home-cage exposure to pellets and LiCl injections, separated by 24 h. Conditioned responding to the light CS was measured in a single probe session, in which paired rats spent less time in the foodcup compared to unpaired rats. Subsequently, we characterized rats' behavior as ST or GT using liquid sucrose reward. The level of conditioned responding during outcome devaluation correlated with the rats' preference for sign or goal tracking responses. Paired rats that were more sensitive to outcome devaluation had a greater preference for goal-tracking responses, whereas paired rats that were less sensitive to outcome devaluation had a greater preference for sign-tracking responses. This result is consistent with our previous finding that ST conditioned responses are insensitive to outcome devaluation. This suggests that ST rats have pre-existing deficits in learning or using information about devalued outcomes to guide goal-directed behavior.

P36. Activation of neuronal cotransporters as possible molecular mechanism of spreading depolarization-induced dendritic beading

Sergei Kirov, Annette Steffensen, Jeremy Sword, Deborah Croom, Nanna MacAulay*

Spreading depolarizations (SDs) are waves of sustained neuronal and glial depolarization that propagate massive disruptions of ion gradients through the brain. SD is associated with migraine aura and recently recognized as a novel mechanism of injury in stroke and brain trauma patients. SD leads to neuronal swelling as assessed in real time with 2-photon laser scanning microscopy (2PLSM). Pyramidal neurons do not express aquaporins and thus display low inherent water permeability. Yet, SD rapidly induces focal swelling (beading) along the dendritic shaft by unidentified molecular mechanisms. To address this issue, we induced SD in hippocampal slices by focal KCl-microinjection and visualized the ensuing dendritic beading by 2PLSM.

We confirmed that dendritic beading failed to arise during large (100 mOsm) hyposmotic challenges, underscoring that neuronal swelling does not occur as a simple osmotic event. SD-induced dendritic beading was not prevented by pharmacological interference with the cytoskeleton, supporting the notion that dendritic beading may entirely result from excessive water influx. Dendritic beading was strictly dependent on the presence of Cl- and accordingly, combined blockade of Cl—coupled transporters, in addition to lactate transporters, led to a significant reduction in dendritic beading without interfering with SD. Furthermore, our in vivo data showed a strong inhibition of dendritic beading upon pharmacological blockage of these cotransporters.

We propose that SD-induced dendritic beading takes place as a consequence of the altered driving forces and thus activity for these cotransporters, which by transport of water during their translocation mechanism may generate dendritic beading independently of osmotic forces.

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P37. Activation of metabotropic glutamate 7 receptors decreases nicotine taking and nicotine-seeking in rats

Athina Markou, Astrid Stoker, Xia Li*

The reinforcing and motivational aspects of nicotine and cue-induced reinstatement of nicotine seeking are associated with increased glutamate transmission in mesocorticolimbic brain circuits. Decreasing glutamate transmission by targeting metabotropic glutamate receptors (mGluRs), such as activation of presynaptic mGluR2/3 or blockade of postsynaptic mGluR5 decreased nicotine taking and nicotine seeking. mGluR7 is another presynaptic inhibitory receptor critically involved in modulating synaptic responses. We assessed the role of mGluR7 in the reinforcing and motivational aspects of nicotine and cue-induced reinstatement of nicotine-seeking behavior in rats. Intravenous self-administration under fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement was used to study the positive reinforcing and motivational effects of nicotine. Cue-induced reinstatement of nicotine-seeking behavior was used as a model of relapse to nicotine consumption. Activation of mGluR7 was achieved by pharmacological manipulation with the allosteric agonist AMN082 or genetic manipulation with lentiviral vector-induced overexpression of mGluR7. Systemic AMN082 attenuated nicotine self-administration under FR and PR schedules of reinforcement, as well as cue-induced reinstatement, indicating that mGluR7 activation inhibited the primary reinforcing and motivational effects of nicotine and nicotine-associated cues. AMN082 injections in the ventral tegmental area (VTA), but not the dorsal striatum, decreased nicotine taking and seeking, suggesting the involvement of VTA mGluR7 in nicotine dependence. Similarly, overexpression of mGluR7 in the VTA decreased nicotine self-administration and cue-induced reinstatement of nicotine seeking. Thus, activation of mGluR7 attenuated nicotine taking and seeking in rats through a neural circuitry involving the VTA within the mesocorticolimbic system. Therefore, mGluR7 may be a promising target for the treatment of nicotine dependence.

P38. Visualization of oxytocin release in the brainstem upon photoactivation of ChR2 expressing fibers originating from parvocellular neurons in the paraventricular nucleus of the hypothalamus

David Mendelowitz, Ramon Pinol, Heather Jameson*

In addition to the classic effects of the hormone oxytocin (OXT) on uterine contraction and milk ejection, recent work has suggested OXT can act as a neuromodulator upon synaptic release from parvocellular neurons originating in the paraventricular nucleus of the hypothalamus (PVN). One such target of PVN neurons is the parasympathetic neurons in the brainstem that generate parasympathetic activity to the heart. Recent studies using optogenetic stimulation of the PVN neurons that express channelrhodopsin (ChR2) revealed a direct pathway from these PVN neurons to brainstem parasympathetic cardiac vagal neurons (CVNs). Photoactivation of ChR2 containing PVN fibers elicited paired-pulse facilitation of glutamatergic neurotransmission to CVNs and this enhancement was diminished after application of the OXT receptor antagonist OTA indicating facilitation by endogenous OXT release from these synaptic terminals. In order to further test this hypothesis we engineered and dispersed within an in-vitro brainstem sniffer CHO cells highly sensitive to oxytocin. These sniffer CHO cells were stably transfected to express the human recombinant OXT receptor, and calcium changes within these cells could be visualized as these cells also express the red fluorescent calcium indicator, R-GECO1. Our data shows optogenetic stimulation of ChR2 expressing hypothalamic PVN fibers in the brainstem evoked large, reproducible, and transient increases in Ca2+ within sniffer CHO cells in close proximity to OXT fibers. The photostimulation-elicited increase in Ca2+ in the sniffer CHO cells upon PVN fiber activation was abolished by application of the oxytocin receptor antagonist OTA. These results support and extend the hypothesis that excitation of parvocellular PVN fibers releases OXT at their brainstem CVN targets, and this approach can be used as a highly sensitive assay for endogenous oxytocin release from PVN neurons and synapses.

P39. Changes in neuronal dopamine homeostasis following MPP+ exposure

Eugene Mosharov

MPP+, the active metabolite of neurotoxin MPTP, selectively kills dopaminergic neurons in vivo and in vitro exhibiting a variety of toxic mechanisms, including mitochondrial dysfunction, generation of peroxynitrite, induction of apoptosis, and oxidative stress due to disruption of vesicular dopamine (DA) storage. To investigate the effects of acute MPP+ exposure on neuronal DA homeostasis, we measured stimulation-dependent DA release and non-exocytotic DA efflux from mouse striatal slices, and extracellular, intracellular and cytosolic DA levels in cultured mouse ventral midbrain neurons. In acute striatal slices, MPP+ exposure gradually decreased stimulation-dependent DA release, followed by massive DA efflux that was dependent on MPP+ concentration, temperature and DA uptake transporter (DAT) activity. Similarly, in mouse midbrain neuronal cultures MPP+ depleted vesicular DA storage accompanied by an elevation of cytosolic and extracellular DA levels. In neuronal cell bodies, increased cytosolic DA was not due to transmitter leakage from synaptic vesicles but due to competitive MPP+ dependent inhibition of monoamine oxidase (MAO) activity. Accordingly, MAO blockers pargyline and L-deprenyl had no effect on cytosolic DA levels in MPP+ treated cells and had only a moderate effect on the survival of dopaminergic neurons treated with the toxin. In contrast, depletion of intracellular DA by blocking neurotransmitter synthesis resulted in ~30% reduction of MPP+-mediated toxicity, whereas overexpression of vesicular monoamine transporter 2 (VMAT2) completely rescued DA neurons. These results demonstrate the utility of comprehensive analysis of DA metabolism using various electrochemical methods and reveal the complexity of the effects of MPP+ on neuronal DA homeostasis and neurotoxicity.

P40. Intellectual abilities, memory, and behavioural problems in children and adolescents previously treated with glucocorticoids

Olaf B Paulson, Sara Krøis Holm, Martin Vestergaard, Kathrine Skak Madsen, William FC Baaré, Trine Bjørg Hammer, Alfred Peter Born, Hartwig T Siebner, Peter V Uldall*

Aim: To examine intellectual abilities, memory, and behavioural problems in two paediatric disease groups previously treated with glucocorticoids compared to healthy controls.

Methods: Thirty-eight children previously treated with glucocorticoids because of rheumatic disease or nephrotic syndrome aged 7-16 years and 42 healthy

children with comparable age, gender and parent education participated. Median cumulative dose in prednisolone-equivalents was 158 mg/kg (range 21–723) and the mean time elapsed since treatment was 3.5 years (SD 2.2). The verbal comprehension and perceptual organization indices of the Wechsler Intelligence Scale for Children III were estimated to assess intellectual abilities. A Pattern Recognition Memory test was used to measure memory performance. Behavioural problems were captured by the Child Behaviour Check List. Multiple linear regression models were used to analyse group differences.

Results: Patients did not significantly differ from controls in pattern recognition memory, perceptual organization index, or behavioural problems. However, patients had significant lower verbal comprehension indices (adjusted mean difference -14.6 95%CI (-21.3—-8.0), p=0.00004). This difference was present in both disease groups. There were no significant dose-response relationships with respect to intellectual abilities.

Conclusion: Children and adolescents previously treated with glucocorticoids seems to have lower intellectual verbal abilities compared to healthy controls.

P41. Disruption of relative reward value by reversible disconnection of orbitofrontal and rhinal cortex using DREADDs in rhesus monkeys

Richard Saunders, Mark Eldridge, Walter Lerchner, Takafumi Minamimoto, Yuji Nagai, Barry Richmond*

Rhinal cortex (Rh) is essential to stimulus-reward association learning in monkeys. Orbitofrontal cortex (OFC) is essential to relative value judgments. Thus disrupting the connections between Rh and OFC ought to produce a performance impairment in a task that requires both stimulus-reward association and comparisons between relative values.

Two monkeys received unilateral Rh aspiration lesions. They were then trained to perform a visually-cued reward size task. At the beginning of each trial, a visual cue signaled the amount of reward (1, 2, 4 or 8 drops—picked at random) available for correctly detecting when a red visual target turned green. The error rates of the monkeys decreased with increasing drop size, and were indistinguishable from unoperated controls. The operant demands were trial invariant, so we interpret the differences in performance across reward size as reflecting the subjective valuation of the expected reward by the monkey as signaled by the cue.

The OFC contralateral to the hemisphere with the Rh removal was injected with a modified lentiviral vector expressing a Gi-coupled receptor, hM4Di, (DREADD—Designer Receptor Activated by Designer Drug) that, when

activated by systemically delivered clozapine-N-oxide (CNO), causes neuronal silencing. If effective, activation with CNO should lead to a functional disconnection of Rh from OFC. Receptor occupancy studies via PET scanning were used to determine the concentration of CNO required to produce maximal receptor occupancy.

In behavioral testing sessions begun with systemic injection of CNO there was a marked reduction in the discrimination between expected reward sizes, and an overall reduction in error rate for both monkeys. These results demonstrate the necessity of the functional connection between OFC and Rh in stimulus-reward coding and relative reward evaluation, using the CNO-DREADD system.

P42. Alterations of ESCRT protein CHMP2B contribute to the pathogenesis of PD/DLB by impairing α-synuclein clearance

Brian Spencer, Kori Kosberg, Christina Patrick, Edward Rockenstein, Anthony Adame, Seung-Jae Lee, Changyoun Kim, Paula Desplats, Eliezer Masliah*

α-synuclein (α-syn) has been implicated in neurological disorders with parkinsonism including Parkinson's disease (PD). Recent studies have shown α-syn oligomers can be released from neurons and propagate from cell-to-cell in a prion-like fashion exacerbating neurodegeneration. In this report, we examined the role of the endosomal sorting complex required for transport (ESCRT) pathway on the cell-to-cell spread of α-syn propagation. We show that endocyosed extra-cellular α-syn can be transported via the ESCRT pathway through the multi-vesicular bodies to the autophagosome for degradation. This transport mechanism can be disrupted by the targeted degradation of the ESCRT protein CHMP2B by intra-cellular α-syn aggregates, thus generating a roadblock of endocytosed α-syn. Conversely, delivery of a lentiviral vector over-expressing CHMP2B rescued the neurodegenerative phenotype in α-syn tg mice. Thus, better understanding of the mechanisms of intracellular trafficking of α-syn might be important for understanding the pathogenesis and developing new treatments for DLB/PD.

P43. Dissecting the mesocortical dopamine pathway and its role in aversive motivation

Caitlin Vander Weele, Gillian Matthews, Romy Wichman, Craig Wildes, Kay Tye*

Dopamine (DA) neurotransmission from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) has been shown to be critically involved in appetitive motivation and DA has therefore been extensively studied in the context of reward. However, the role of DA in aversive motivation remains

unclear and vastly understudied. Multiple lines of converging evidence suggest that DA release in the medial NAc shell is primarily involved in appetitive behavior, while DA release in the medial prefrontal cortex (mPFC) mediates aspects of aversion. While stressful stimuli have been shown to preferentially elevate tonic levels of DA in the mPFC, the rapid neurotransmission dynamics have not been characterized. We show that the classical aversive stimulus, a tail pinch, rapidly increases in vivo catecholamine release in the mPFC as measured with fast-scan cyclic voltammetry. Further we show that this catecholamine signal is dopaminergic, rather than noradrenergic, using a combination of pharmacological and optogenetic approaches. Next, we wish to determine which downstream targets of the mPFC causally produce aversion. Here we use behavioral optogenetic approaches to investigate the projections to the lateral habenula (LHb) and paraventricular nucleus of the thalamus (PVT) in the generation of aversively motivated behavioral responses. Indeed, activation of the pathway is actively avoided. These studies aim to further our understanding of the mesocortical DA pathways and its role in aversive motivation through its actions in the mPFC.

P44. Adolescent social behavior, social defeat, and housing conditions impact cocaine self-administration in adulthood

Andrew Burke, Klaus Miczek*

Adolescent stress increases sensitivity to drugs of abuse in rodents, in agreement with increased illicit drug use after adolescent bullying. In a preclinical model, adolescent male Long Evans rats were socially defeated on an intermittent schedule, a protocol that increases cocaine taking in adult rats. On postnatal day (P) 21 rats were single (SH) or pair housed (PH). Adolescents were confronted with a novel male aggressor on P35, 38, 41, and 44, while controls were undisturbed. A separate group of adults were defeated, but not tested in adulthood. All resident and intruder behavior was recorded and subsequently quantified. We assessed locomotion in a novel open field (P57) and after a cocaine challenge (10 mg/kg, ip; P60). Rats were fitted with indwelling intravenous catheters (P61-63) and acquired cocaine self-administration (0.75 mg/kg/inf) on P66-68. Subsequently, rats were given access to cocaine (0.30 mg/kg) according to a progressive ratio schedule of reinforcement and then during a 24-hour continuous access binge. Adolescents more often froze when attacked, whereas adults displayed defensive and supine postures. Adolescent SH intruders decreased freezing from P35 to P44, whereas PH intruders increased freezing. Greater attack-induced freezing after repeated defeats predicted escalated cocaine self-administration in adulthood. A greater percentage of SH rats and PH defeated rats acquired cocaine self-administration. Defeated PH rats consumed more cocaine during progressive

ratio schedules and during the continuous access binge compared to both PH controls and SH defeated rats. Thus, adolescent social defeat, while different than adult defeat, still increases cocaine taking in PH, but not SH rats.

P45. Neto proteins: Exploring kainate receptor functional modulation

Theanne Griffith, Geoffrey Swanson*

Kainate receptors (KARs) are members of the ionotropic glutamate receptor (iGluR) family. They have diverse physiological roles in the brain that include modulation of neurotransmitter release and intrinsic neuronal excitability. Unlike other iGluRs, which primarily mediate direct signaling, KARs also play a modulatory role in the brain and are important for maintaining the balance of excitation and inhibition. KARS have also been implicated in pathological states such as epilepsy, pain and stroke. KARs associate with the auxiliary subunits Neto1 and Neto2. Neto proteins are CUB-domain containing, single-pass integral membrane proteins, which modulate receptor function and trafficking in a KAR subunit and Neto isoform specific manner. However, the structural determinants responsible for modulation of KAR function by Neto proteins are unknown. In this study, we focused our investigation on the structural basis of Neto2 modulation of GluK2 homomeric receptor gating mechanisms using whole-cell recordings from lifted HEK cells. Using chimeric Neto2 and GluK2 constructs, we have identified the extracellular domain of Neto2 as a critical determinant responsible for slowing GluK2 receptor desensitization kinetics. We also determined that Neto proteins are likely modulating GluK2 receptor desensitization via the M3S2 linker region, a region previously shown to influence iGluR desensitization. We are currently in the process of determining whether Neto2 interactions with the GluK2 M3S2 linker induce structural changes within the ligand binding domain to produce the observed effects on receptor desensitization. Our study sheds light on the structural basis of Neto modulation of KAR function and provides important insights for the development of small molecules to allosterically modulate KAR activity.

P46. Associations between Gender Identity and Traditional Gender Roles in Indian and British Women

Samuel Kane*, Meenakshi Menon

The aim of this study was to explore the association between gender identity and the endorsement of traditional gender ideologies in a sample of women in India and UK. Participants were a sample of female college students (N = 168, M age 19.7 years) in Britain (n = 102) and India (n = 66). They completed self-report scales that measured gender identity and endorsement of traditional gender ideologies in different domains (work sexism, parenting sexism, dating sexism, ambivalent sexism).

In this study, gender identity was assessed in adults using adaptations of the Egan and Perry (2001) scales. The felt contentedness scale was renamed acceptance of gender oppression, as the original scale more accurately reflects feelings of resignation to inflexible gender norms (Bigler, 2006). We examined whether a strong gender identity (high felt typicality, high felt oppression, and high felt pressure) is associated with traditional beliefs about gender roles.

There were cross-national differences in many of the measures. Women in India reported significantly greater felt pressure, and greater endorsement of sexist ideologies in the domains of work, parenting, and dating, than women in Britain. Partial correlations (controlling for country) revealed that felt typicality was significantly associated with more ambivalent sexism; and, acceptance of oppression and felt pressure were each significantly associated with more work sexism, parenting sexism, dating sexism, and ambivalent sexism.

Hierarchical regression analyses were run to explore whether country of testing moderates these associations further. Country of testing moderated the influence of felt typicality and acceptance of oppression on dating sexism ($F = 5.701$, $p = .018$, and $F = 7.244$, $p = .008$, respectively). Follow-up analyses revealed that felt typicality predicted ambivalent sexism only in UK ($B = .222$, $p = .022$) and that acceptance of oppression predicted ambivalent sexism more strongly in UK than in India ($B = .406$, $p = .000$, and $B = .280$, $p = .026$, respectively).

P47. Human Postmortem Brain Collection: Brain Donations from a Diverse Population

Michelle Mighdoll*, Amy Deep-Soboslay, Daniel Weinberger, Joel Kleinman, Thomas Hyde

The Lieber Institute for Brain Development began collecting postmortem human brains from the Maryland Office of Chief Medical Examiner in September 2012. Since inception, of 834 families contacted, the success rate is 56.8% (n=474), with only 26.6% (n=224) declining (and 16.3% being unreachable). Of the cases collected, 66% (n=316) are male and 34% (n=161) are female, with equal rates of donation (~56%). Our collection is comprised of cases across the lifespan, with the largest cohorts between 36-50 and 51-65 years of age. It is well-documented that African-American participants are significantly under-represented in biomedical research. The lack of adequate research on African-American participants has the potential to impede treatment and prevention of neuropsychiatric disorders, since research findings may not necessarily be generalizable from Caucasian samples. Of the referrals, while 63.9% (n=368) of Caucasian families consented, 49.2% (n=92) of all African-American referrals also agreed to postmortem human brain donation, a

rate which refutes the belief that African-Americans are unwilling to participate in biomedical research studies. All psychiatric and neurological diagnoses are confirmed by two board-certified psychiatrists according to DSM-V criteria. Of the 474 cases collected to date, 275 have completed curation and diagnostic evaluation. Primary diagnostic distribution includes: controls (n=70), major depressive disorder (n=54), bipolar disorder (n=31), schizophrenia (n=17), anxiety (n=7), dementia/Alzheimer's disease (n=15), and substance abuse (n=29). We also have the largest postmortem brain collection of Post-Traumatic Stress Disorder (n=19) in the world, as well as 10 eating disorder cases. The collection of postmortem human brains from large medical examiners' offices provides a unique resource for the rapid accrual of samples from normal controls and a diverse population of psychiatric disorders, encompassing all age, sex, and racial boundaries.

P48. Delineation of rostromedial tegmental nucleus (RMTg) in rats and mice via nociceptin/OFQ expression and anatomical connectivity

Rachel J. Smith, Thomas C. Jhou*

The rostromedial tegmental nucleus (RMTg), or tail of the ventral tegmental area (tVTA), has a strong inhibitory influence on midbrain dopamine neurons. Accordingly, RMTg has been implicated in drug reward and withdrawal, as well as aversive behaviors. Previously, RMTg has been identified anatomically using retrograde tracing from VTA, GABA expression, and psychostimulant-induced Fos activation in rats. However, it is unclear whether RMTg neurons are neurochemically distinct from GABA neurons in the midbrain, or whether RMTg is a caudal extension of GABAergic neurons in VTA. Further, the anatomical location of RMTg has not been well-characterized in the mouse. Here, we show that RMTg neurons in rats and mice express mRNA for prepronociceptin (PNOC), the precursor for nociceptin/orphanin-FQ. In situ hybridization labeling of PNOC was observed in the vast majority of RMTg neurons projecting to VTA (those double-labeled with the retrograde tracer CTB) but only in a minority of neurons outside RMTg or within VTA. In mouse, we show that RMTg is defined via PNOC expression, GABA expression (via reporter gene), retrograde tracing from VTA, and location of lateral habenula afferent fibers (via AAV-mediated mCherry expression). These data delineate RMTg in mice and rats, and show that RMTg is neurochemically distinct from neighboring GABAergic neurons, indicating it may play a distinct functional role as well.

P49. Examining protein synthesis in the nucleus accumbens after withdrawal from extended-access cocaine self-administration

Michael T. Stefanik, Mike Milovanovic, Marina Wolf*

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

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

P50. Synphilin-1 in neuronal housekeeping- targeting protein inclusions to the lysosomes

Esther Wong, Sijie Tan*

Collapse in proteostasis is seen in aging and neurodegeneration that results in perturbation of the cellular functional proteome. Autophagy is a lysosomal degradative pathway that plays a critical role in neuronal homeostasis. Autophagy has been shown to be effective in recognizing cytosolic protein aggregates and targeting them to lysosomes for degradation (aggrephagy).

However, some protein inclusions fail to be recognized by the autophagic system. In our study, we have found that basal and inducible autophagy target different types of protein inclusions. Furthermore, we have recently identified synphilin-1, a highly abundant neuronal protein with yet unknown function, to be necessary and sufficient to recruit the autophagic machinery to protein aggregates otherwise unrecognized by autophagy to promote their clearance by autophagy. The autophagic function of synphilin-1 is dependent on its ankyrin-1 domain and is regulated by posttranslational modifications. Posttranslational modifications via specific ubiquitin chains in this region contribute to diminish protein mobility on the surface of aggregates thereby allowing the stable assembly of the protein nucleation complexes required for autophagosome formation on the aggregates to facilitate aggrephagy. Our ongoing studies indicate that E3 ligase parkin may act as the molecular switch in cooperation with other kinase(s) to regulate synphilin-1 mediated aggrephagy. The findings highlight the versatility of cells to cope with different types of protein inclusions by directing their preferred disposal via different types of autophagy through activation of different post-translational modifications of aggrephagy mediating proteins.

P51. The neurophysiology of stress-related impairment of prefrontal cognitive function

David Devilbiss, Craig Berridge*

The prefrontal cortex (PFC) plays a critical role in the regulation of goal-directed behavior. PFC neurons display persistent discharge during delayed-response tasks when information must be retained across time. Persistence of delay-related activity may involve recurrent/self-excitatory neuronal activation. PFC neurons also code outcome (reward and error) information and events that involves recurrent activation. Stress impairs PFC function, as measured in these delayed-response tasks, and may involve degradation of persistent and recurrent activation during delay intervals. However, the neurophysiological mechanisms responsible for stress-related impairment in PFC-dependent function remain poorly understood. The current study examined the effects of stress on discharge activity of medial PFC (mPFC) neurons in rats tested in a T-maze delayed-response task. Stress potently suppressed the discharge rates of neurons strongly tuned to specific task events, including, delay reward and error, while simultaneously increasing the activity of weakly tuned neurons. Collectively, this effectively collapses normally robust patterns of task-related activity across functional groups of PFC neurons. Stress increased recursive activation of PFC neurons with strong, delay-related tunings, while suppressing recursive activation of neurons weakly tuned to delay-related information. Finally, stress suppressed the ability of individual PFC neurons to multiplex

multiple task events (e.g. reward neurons that also respond to the delay; delay neurons that also respond to error or reward). Stress-related suppression of discharge outside a neuron's preferred tuning predicted task performance, especially neurons tuned to the delay interval. These latter findings provide further support for the hypothesis that successful goal attainment involves multiplexing of task-related events across multiple populations of PFC neurons, including outcome evaluation signals coded by delay-tuned neurons.

P52. MDMA reduces markers for GABAergic neurons in the hippocampus and increases seizure susceptibility: Role of cyclooxygenase-dependent glutamate release

Gary Gudelsky, Courtney Huff, John Anneken, Jacobi Cunningham, Stuart Collins, Bryan Yamamoto*

MDMA is a unique psychostimulant that continues to be a popular drug of abuse. It is well documented that MDMA produces persistent reductions in markers of 5-HT axon terminals in rodents, as well as humans. To date, there has been little recognition of potential MDMA neurotoxicity to neuronal populations beyond 5-HT axon terminals in brain regions, such as the hippocampus, in which damage may account for the neurologic/cognitive effects associated with repeated exposure to MDMA. In the present study, we examined the hypothesis that MDMA produces glutamate-dependent damage to GABAergic neurons, as assessed from parvalbumin (PV) immunoreactive- and GAD67-positive neurons, in the hippocampus that results in an increase in seizure susceptibility. Repeated exposure to MDMA (4 x 10 mg/kg, ip) resulted in a 35% reduction in the number of PV-immunoreactive neurons in the dentate gryrus and a 50% reduction in the number of GAD67-positive cells in the dentate gyrus, as well as in the CA1 and CA3 regions. MDMA-induced reductions in markers of GABAergic neurons was attenuated in rats treated with the cyclooxygenase inhibitor ketoprofen. MDMA produced a sustained increase in the extracellular concentration of glutamate in the hippocampus that was also suppressed in animals treated with ketoprofen. Finally, repeated administration of MDMA resulted in an increase in susceptibility to kainic acid-induced seizures. Kainic acid (9 mg/kg,sc) produced seizures in approximately 20% of control animals, whereas approximately 85% of MDMA-treated rats exhibited kainate-induced seizures. An increase in the incidence of evoked seizures was not evident in animals treated concomitantly with the glutamate antagonist MK-801 and MDMA. The results support the view that repeated exposure to MDMA results in damage to hippocampal GABAergic neurons and a subsequent increase in seizure vulnerability that result from a cyclooxygenase dependent increase in the release of glutamate.

P53. The phosphodiesterase-4 (PDE4) inhibitor roflumilast decreases ethanol intake in C57BL/6J mice

Xin Liu, Pi-da Hao, Ming-feng Yang, Da-wei Li, Zong-yong Zhang, Han-ting Zhang, Bao-liang Sun*

Alcoholism has become one of the most damaging psychiatric disorders in the world, yet there are no ideal treatments in clinic. Phosphodiesterase-4 (PDE4), an enzyme that specifically hydrolyzes intracellular cyclic AMP (cAMP), may play an important role in the regulation of ethanol consumption. This is supported by the findings that inhibition of PDE4 by rolipram, a prototypic PDE4 inhibitor, reduces ethanol intake and self-administration. Roflumilast, another selective PDE4 inhibitor, has been approved for treatment of chronic obstructive pulmonary diseases (COPD) in clinic. It was of interest to know whether roflumilast altered ethanol consumption. The two-bottle choice paradigm was used to assess ethanol intake and preference in C57BL/6J mice treated with roflumilast (1, 3, or 10 mg/kg) or rolipram (0.5 mg/kg; positive control). The effect of roflumilast was verified using ethanol drinking-in-dark (DID). Locomotor activity was determined using the open-field test (OFT). Roflumilast decreased ethanol intake and preference in two-bottle choice in a dose-dependent manner, with the significant change at the highest dose (10 mg/kg) of roflumilast, similar to rolipram. Neither roflumilast nor rolipram affected sucrose or quinine drinking, although roflumilast at the highest dose decreased locomotor activity. These data provide additional demonstration for the role of PDE4 in ethanol intake and suggest that roflumilast may be beneficial for treatment of alcoholism.

P54. Cognition and hippocampal gene expression changes in mice challenged with mild physical- and blast-traumatic brain injury—models for drug development

Nigel Greig, David Tweedie, Lital Rachmany, Barry Hoffer, Chaim Pick*

The treatment of traumatic brain injury (TBI) represents an unmet medical need, as no effective pharmacological treatment currently exists. The development of such a treatment requires a fundamental understanding of the pathophysiological mechanisms that underpin the sequellae resulting from TBI, particularly the ensuing neuronal cell death and cognitive impairments. To aid in this endeavor two distinct types of mild TBI (mTBI), both with high face validity, were evaluated in anesthetized mice. One involved a closed-head weight drop representative of a common fall or accident, the other a high velocity blast shock wave generated by the detonation of an explosive device emulating blast-mTBI common to warfare. While both forms of trauma are distinctly different regarding the mechanism of trauma induction, there are striking similarities in the cognitive and emotional status of survivors. We examined indices of cognition and anxiety-like behavior and the hippocampal gene transcriptome

of mice subjected to both forms of mTBI. We identified common behavioral deficits and gene expression regulations, in addition to unique injury-specific forms of gene regulation. Molecular pathways presented a pattern similar to that seen in gene expression. Interestingly, pathways associated with Alzheimer's disease displayed a markedly different form of regulation depending on the type of TBI. While these data highlight similarities in behavioral outcomes after trauma, the divergence in hippocampal transcriptome observed between models suggests that, at the molecular level, the TBIs are quite different. These models provide tools to help define therapeutic approaches for the treatment of physical- and blast-TBIs, and data relating to experimental drugs of immediate translational potential is discussed.

P55. Anti-methamphetamine vaccine induces robust antibody response and attenuates the behavioral effects of methamphetamine in mice

Colin Haile, Kosten Therese, Xiaoyun Shen, Ramakrishnan Muthu, Berma Kinsey, Arora Reetakshi, Frank Orson, Kosten Thomas*

Here we characterized the immunogenicity, binding affinity and behavioral effects of an anti-methamphetamine (MA) conjugate vaccine (succinyl-methamphetamine-tetanus-toxoid, SMA-TT) following MA. The immunogenicity of SMA-TT was assessed in combination with two adjuvants, aluminum hydroxide (Alum, 1.5mg) and the novel Toll 4-like receptor agonist E6020 (3μg). Anti-MA antibody affinity was determined using equilibrium dialysis with radiolabeled MA. The impact of anti-MA antibodies on MA-induced locomotor activation was determined using passive immunization. Actively immunized mice were assessed on MA-induced locomotor activation and conditioned place preference. MA blood and brain concentrations were also evaluated using gas chromatography/mass spectrometry. Results showed that vaccination with SMA-TT (32μg)+Alum co-administered with E6020 produced 2-fold greater levels of anti-MA antibodies than SMA-TT with either adjuvant alone. Antibody affinity assays identified two population groups of anti-MA antibodies: high (Kd 7nM) and intermediate (Kd 90nM) affinity. Passively administered sera from animals immunized with SMA-TT significantly attenuated MA-induced locomotor activation in mice ($p<0.001$) and anti-MA antibody levels negatively correlated with activity ($r2=0.477$). MA-induced conditioned place preference was significantly attenuated in vaccinated mice that generated high anti-MA antibody levels. Immunized mice had significantly lower MA brain (75%, $p=0.008$) and higher blood (30%, $p=0.02$) levels following MA injection. Data suggest that SMA-TT in combination with adjuvants Alum and E6020 produces a robust antibody response with high to intermediate affinities that results in attenuated behavioral responses to MA. Effects on MA-induced behavior are likely due to the vaccine's ability to prevent entry of MA into the brain.

SPECIAL POSTER SESSION— HIGHEST RANKING POSTERS

P56. Alcohol triggers dopamine D1 receptor- and mTORC1-dependent synaptic plasticity in a subset of nucleus accumbens neurons

Jacob Beckley, Khanhky Phamluong, Scott Wegner, Dorit Ron*

Alcohol (EtOH) is intrinsically reinforcing, due to its ability to increase dopamine (DA) levels and alter signaling in the nucleus accumbens (NAc). We previously showed that mTORC1, which controls activity-dependent dendritic translation and synaptic plasticity, is activated in the NAc following acute EtOH, and that mTORC1 inhibition reduces binge EtOH drinking (Neasta et al, 2010, PNAS). NAc medium spiny neurons (MSNs) are subdivided into two populations that are stratified by their expression of either Gs-coupled DA D1 receptors (D1R MSNs) or Gi-coupled D2 receptors (D2R MSNs). Thus, we first determined how D1R or D2R activation affects mTORC1 signaling in the NAc. Similarly to EtOH and in contrast to D2R activation, D1R stimulation activates the mTORC1 pathway in the NAc, resulting in increased protein levels of the AMPA subunit GluA1 and scaffolding protein Homer. We then tested whether a single EtOH challenge alters synaptic transmission in NAc D1R or D2R MSNs. We found that systemic administration of EtOH (2g/kg) or 24 hours of access to EtOH (20%) leads to a long-lasting enhancement of the AMPA/NMDA ratio selectively in NAc D1R MSNs, and this effect is blocked by inhibiting either D1Rs or mTORC1. EtOH increases miniature excitatory postsynaptic current (mEPSC) amplitude and alters AMPA rectification, suggesting that the D1R/mTORC1-dependent plasticity is due to increased postsynaptic AMPA activity and a shift towards more GluA2-lacking AMPA receptors. Collectively, our data imply that EtOH enhances synaptic strength on NAc D1R MSNs via D1R-mediated activation of mTORC1, which results in synaptic protein translation and remodeling. We further propose that EtOH-induced plasticity in the NAc after a single EtOH experience reflects a neural imprint of EtOH's rewarding properties.

P57. Effects of maternal opioid maintenance therapy on neonatal outcomes: Methadone vs. Buprenorphine

Laura Brandt, Stephanie Fischberger, Reinhold Jagsch, Gabriele Fischer*

Objectives: Opioid maintenance therapy (OMT) with methadone (METH) and buprenorphine (BUP) during pregnancy bears the risk of neonatal abstinence syndrome (NAS) since opioids as other medications cross the placenta. Previous studies reported favourable NAS and neonatal outcomes for BUP compared to METH. The aim of the present study was to assess effects of maternal OMT (METH vs. BUP) on NAS duration and severity as well as neonatal outcomes and to evaluate differences of therapy methods and neonatal outcomes over the past decade. Methods: A prospective, standardized, observational study design was used for analysis of 68 mothers in multidisciplinary treatment and their neonates. 39 women were maintained with METH (mean dose at delivery: 58,62 mg/day) and 29 with BUP (9,60 mg/day). NAS was assessed by a modified Finnegan scale and treated with standardized pharmacological intervention. Results: BUP showed a significant benefit in reducing the medication dose needed for treatment of NAS (mean morphine dose 8.65mg vs. 22.80mg, p=0.008) and length of NAS treatment (12.38 days vs. 18.86 days, p=0.040). No significant differences between METH and BUP exposed neonates were observed for neonatal outcomes (birth weight, length, head circumference and gestational age; all p>.1). Comparison to data gathered in a comparable study design 10 years ago showed that for both groups duration of pregnancy could be prolonged from 38th to 39th week of gestation (p=0.033) and length of hospital stay was shortened from 27 to 18 days (p=0,024) for all children and from 33 to 22 days (p=0.024) for children in NAS treatment. Conclusions: OMT with BUP compared to METH during pregnancy has several advantages in terms of NAS parameters. However, a broader concept of medical treatment is important for both medications and enables a multidisciplinary care approach. A standardized pharmacological approach in pregnant women and their neonates reduces treatment costs.

P58. Cell subtype transcriptional regulation of mitochondrial biogenesis by chronic cocaine

Ramesh Chandra, T. Chase Francis, Prasad Konkalmatt, Michel Engeln, Ariunzaya Amgalan, Leah Jensen, Ashley La, Amy M. Gancarz, Sam A. Golden, Gustavo Turecki, Scott J. Russo, David M. Dietz, Mary Kay Lobo*

Altered brain energy homeostasis is a hallmark adaptation occurring in the cocaine-addicted brain. One such mechanism, which is a fundamental component of energy homeostasis and has not been addressed in cocaine abuse is mitochondrial biogenesis (MB). Here we examine transcriptional

regulation of MB in the two main nucleus accumbens (NAc) projection medium spiny neuron (MSN) subtypes, those enriched in dopamine D1 vs. D2 receptors, due to their critical but antagonizing roles in cocaine abuse. Using the RiboTag methodology, we observe an upregulation of ribosome-associated mRNA of many MB genes in D1-MSNs but a decrease in MB genes in D2-MSNs after repeated cocaine (20 mg/kg). In parallel we find that MB genes are upregulated in NAc of rodents that self-administer cocaine (FR1 schedule, 1mg/kg/infusion) and postmortem NAc of cocaine dependent individuals. Using chromatin immunoprecipitation (ChIP), we found that repeated cocaine (20mg/kg) leads to enrichment of the transcription factor early growth response 3 (Egr3) on MB gene promoters in NAc. To investigate the functional role of Egr3, we used a Cre-inducible AAV to overexpress Egr3 in NAc of D1-Cre and D2-Cre mice. Increasing Egr3 levels in D1-MSNs potentiated cocaine (7.5mg/kg) conditioned place preference (CPP) and cocaine (10mg/kg)-mediated locomotion, while enhancing Egr3 in D2-MSNs blunts these behaviors. Egr3 overexpression in D1-MSNs and repeated cocaine both significantly increased mitochondria number in D1-MSNs. We next directly altered MB in MSN subtypes by overexpressing peroxisome proliferator-activated receptor-gamma coactivator-1α (Pgc1α), a transcriptional coactivator of MB genes, using a Cre-inducible AAV. Overexpression of Pgc1α in NAc D1-MSNs enhanced cocaine CPP and cocaine-induced locomotion, while Pgc1α expression in D2-MSNs reduced these behaviors. Collectively, our findings demonstrate a novel role for altered MB in select cell subtypes in cocaine abuse.

P59. Varenicline improves motor, cognitive and psychiatric symptoms in the YAC128 mouse model of Huntington's Disease

Gary D'Souza, Malcolm Tingle, Ailsa McGregor*

Huntington's Disease (HD) is a fatal, inherited neurodegenerative disorder characterized by progressive movement, cognitive and psychiatric symptoms. Post-mortem and genetic mouse model studies report a significant loss of acetylcholine and choline acetyl transferase activity in the HD brain, but no change in the number of nicotinic receptors. This suggests impaired cholinergic neurotransmission may contribute to HD pathology. To determine whether chronic treatment with the nicotinic agonist varenicline reduced motor, cognitive and affective symptoms in the YAC128 transgenic mouse model of HD, the performance of 15 month old YAC128 mice (n=14) and age-matched wild type littermates (n=13) was assessed in the rotarod, T maze, novelty suppressed feeding (NSF) and forced swim test (FST) before and after treatment with varenicline for 4 weeks (5mg/kg/day). Thymidine analogues

were used to assess progenitor cell proliferation and survival. DARPP32 immunohistochemistry was performed to visualize medium spiny neurons in the striatum, hippocampus and cortex. Chronic varenicline treatment significantly increased fall latency in the rotarod (14±3s vs 50±7s, p=0.004) and increased rewarded alternation in the T maze in YAC128 mice (65±2% vs 79±3%, p=0.045). Varenicline also decreased latency to feed in the NSF test and reduced floating time in the FST in both YAC128 and wild type animals. Immunohistochemical analysis revealed increased progenitor cell proliferation and survival, as well as increased DARPP32 immunoreactivity in the striatum and cortex of varenicline-treated animals. Chronic treatment with varenicline significantly improved motor coordination and spatial memory in late-stage YAC128 mice. Varenicline also produced genotype-independent improvements in recognition memory, anxiety and depressive-like behavior. Improved performance in YAC128 mice may be attributed to increased striatal and cortical neurogenesis.

P60. Disruption of relative reward value by reversible disconnection of orbitofrontal and rhinal cortex using DREADDs in rhesus monkeys

Mark Eldridge*, Walter Lerchner, Takafumi Minamimoto, Yuji Nagai, Richard Saunders, Barry Richmond

Rhinal cortex (Rh) is essential to stimulus-reward association learning in monkeys. Orbitofrontal cortex (OFC) is essential to relative value judgments. Thus disrupting the connections between Rh and OFC ought to produce a performance impairment in a task that requires both stimulus-reward association and comparisons between relative values.

Two monkeys received unilateral Rh aspiration lesions. They were then trained to perform a visually-cued reward size task. At the beginning of each trial, a visual cue signaled the amount of reward (1, 2, 4 or 8 drops—picked at random) available for correctly detecting when a red visual target turned green. The error rates of the monkeys decreased with increasing drop size, and were indistinguishable from unoperated controls. The operant demands were trial invariant, so we interpret the differences in performance across reward size as reflecting the subjective valuation of the expected reward by the monkey as signaled by the cue.

The OFC contralateral to the hemisphere with the Rh removal was injected with a modified lentiviral vector expressing a Gi-coupled receptor, hM4Di, (DREADD—Designer Receptor Activated by Designer Drug) that, when activated by systemically delivered clozapine-N-oxide (CNO), causes neuronal silencing. If effective, activation with CNO should lead to a functional

disconnection of Rh from OFC. Receptor occupancy studies via PET scanning were used to determine the concentration of CNO required to produce maximal receptor occupancy.

In behavioral testing sessions begun with systemic injection of CNO there was a marked reduction in the discrimination between expected reward sizes, and an overall reduction in error rate for both monkeys. These results demonstrate the necessity of the functional connection between OFC and Rh in stimulus-reward coding and relative reward evaluation, using the CNO-DREADD system.

P61. Egr3 Expression in Nucleus Accumbens Medium Spiny Neuron Subtypes Alters Outcomes to Social Defeat Stress

T. Chase Francis, Ramesh Chandra, Michel Engeln, Mary Kay Lobo*

The Nucleus Accumbens (NAc) is a critical mediator of depression-like outcomes to chronic stress. Medium spiny neurons (MSNs) are the projection neurons of the NAc, which are distinguished by efferent targets and enrichment in dopamine 1 (D1) vs. dopamine 2 (D2) receptors. We recently found that repeated optogenetic stimulation of NAc MSN subtypes, using an adeno-associated virus (AAV) expressing ChR2(E123A), oppositely mediates behavioral outcomes to social defeat stress (SDS). Repeated high frequency (≥50Hz) optogenetic stimulation of NAc D1-MSNs in susceptible mice (mice displaying depression-like behaviors) after chronic (C)SDS reversed social avoidance and enhanced sucrose preference. In contrast, repeated stimulation of NAc D2-MSNs produced susceptibility to a subthreshold (S)SDS. To explore the molecular plasticity mechanisms of stimulation-induced alterations in SDS outcomes, we probed gene expression of plasticity-related molecules in NAc using quantitative real-time PCR. Following repeated stimulation of D1-MSNs or D2-MSNs, we observed a decrease in the transcription factor early growth response 3 (Egr3) in the NAc. In parallel, we are examining ribosome-associated Egr3 mRNA levels selectively in each MSN subtype after CSDS and after repeated stimulation of each MSN. We are also using cell-type specific AAVs to overexpress or knockdown Egr3 levels in MSN subtypes during SDS. We found that miRNA-mediated knockdown of Egr3 in D2-MSNs promoted susceptibility to SSDS. In contrast, AAV Egr3 overexpression in D2-MSNs enhanced resilience following CSDS. Preliminary whole-cell recordings imply this effect may be mediated by a decrease in excitatory synaptic strength at MSN synapses following Egr3 overexpression. These results suggest Egr3 manipulation in D2-MSNs is sufficient to mimic stimulation-induced susceptibility outcomes. Taken together, our findings provide insight into the molecular mechanisms mediating depression-like outcomes to social defeat stress.

P62. Characterizing subsecond dopamine during ethanol self-administration

Andrew Haack, Sharif Taha*

Recent evidence has demonstrated a role for subsecond release of dopamine (DA) in the nucleus accumbens (NAcc) in food (Roitman et al, 2004) and cocaine-seeking (Phillips et al, 2003). However, the contribution of rapid DA release during ethanol-seeking remains poorly understood. Infusion of DA receptor antagonists into the NAcc reduces ethanol self-administration (Czachowski et al, 2001), while drugs that potentiate DA levels in the NAcc conversely increase operant responding for ethanol (Samson et al, 1999). In addition, microdialysis studies have shown that NAcc DA levels are elevated during ethanol self-administration (Doyon et al, 2001). However, it remains unclear which task-related stimuli evoke DA. To date, no investigation has identified how ethanol predictive cues, operant ethanol behavior and the pharmacological effect of ethanol affect rapid DA release in the NAcc. In this study, we employed fast scan cyclic voltammetry (FSCV) to study subsecond DA release in the NAcc during ethanol self-administration. Adult Wistar rats first received 5 weeks of intermittent access to 20% ethanol in their home cage (Simms et al, 2008). Rats that drank in excess of 3 g/kg/24 hours were implanted with chronic carbon fiber electrodes to the NAcc core. After implantation, rats received training sessions in a FR1 scheme in which each lever press delivered 100 μL of 20% ethanol after a 1 s delay. After performance stabilized, DA in the NAcc was measured in the same paradigm using FSCV. Our results (n = 8 rats) indicate that DA levels increased with the presentation of a cue predictive of ethanol delivery. In addition, DA levels increased during approach to the lever and peaked ~200 ms after lever press. These results resemble prior observations of dynamic DA modulation during food- and cocaine-seeking and suggest a general role for subsecond DA release in facilitating cue-driven learning and/or behavior, as well in motivating reward-seeking operant behavior.

P63. Establishing a role for the paraventricular nucleus of the thalamus in Pavlovian conditioned approach behavior

Joshua Haight, Kurt Fraser, Huda Akil, Susan Ferguson, Shelly Flagel*

Evidence has recently emerged suggesting a role for the paraventricular nucleus of the thalamus (PVT) in the processing of reward-associated cues, but much of this previous work is confounded by the fact that Pavlovian conditioned reward cues can act as both predictive and incentive stimuli. Using a unique animal model, we are able to parse the incentive from the predictive properties of reward cues. When rats are exposed to a Pavlovian conditioning paradigm,

wherein a discrete cue predicts food reward, some rats, termed sign-trackers (STs), attribute incentive salience to the cue. Others, termed goal-trackers (GTs), treat the cue as a predictor. Here we investigated the role of the PVT in the expression and acquisition of these conditioned responses (CRs). Outbred rats were first trained on a Pavlovian conditioning task, and then ibotenic acid was used to lesion the PVT. We found that PVT lesions attenuated the expression of the goal-tracking response, and increased the sign-tracking response, selectively in GTs. Next, to assess the effects of PVT lesions on the acquisition of goal-and sign-tracking CRs, we used selectively bred rats for which it is known a priori whether they will acquire a goal- or sign-tracking CR. Similar to the expression study, PVT lesions attenuated the development of a goal-tracking response in rats with an inherent tendency to goal-track. In contrast, PVT lesions prior to training enhanced the sign-tracking response in rats with a predisposition to sign-track. These data demonstrate a role for the PVT in the attribution of incentive properties to reward cues and suggest that the PVT differentially regulates goal- and sign-tracking behaviors. We are currently using chemogenetic tools to parse the role of specific afferent projections to the PVT in mediating these conditioned responses.

P64. Posttraining optogenetic control of basolateral amygdala projections to the ventral hippocampus modulates the consolidation of emotional, but not contextual, learning in rats

Mary Huff, Ryan LaLumiere*

The basolateral amygdala (BLA) modulates memory consolidation for multiple types of learning, whereas other brain regions play more specific roles in different kinds of learning. The ventral hippocampus (VH), an efferent target of the BLA, has been suggested to selectively process emotion-related aspects of learning, yet whether the BLA→VH pathway modulates memory consolidation, and does so in a learning-specific manner, is unknown. Therefore, in the present study, the BLA efferents in the VH were optogenetically stimulated or inhibited immediately after training in a modified contextual fear conditioning (CFC) task that permits separation of the context and footshock learning. The BLA of male Sprague-Dawley rats was bilaterally transduced to express either the cation channel channelrhodopsin-2 [ChR2(E123A)] or the outward proton pump eArchT3.0. Fiber optic probes were implanted dorsal to the VH to provide illumination of the BLA fibers innervating the VH. For the CFC task, rats received 3 min of pre-exposure to the apparatus on day 1. On day 2, rats were placed into the apparatus, received an immediate footshock, and were then quickly removed. Retention was tested on day 4. Optical stimulation of the BLA→VH pathway after context pre-exposure had no effect on retention.

In contrast, optical stimulation of the BLA→VH pathway following footshock training, using trains of 40, but not 20 or 80, Hz light pulses enhanced retention. Similar light pulses given to eYFP-control rats following footshock training had no effect on retention. Preliminary work also suggests 15 min of optical inhibition of this pathway following footshock training impairs retention. These findings indicate that BLA→VH projections influence the consolidation for the footshock, but not context, learning for a modified CFC task and provide direct evidence that BLA projections to other brain regions modulate memory consolidation differently depending on the kind of learning.

P65. Corticotropin-releasing factor (CRF) signaling in the prefrontal cortex impairs cognitive function

Sofiya Hupalo, Robert Spencer, Craig Berridge*

The prefrontal cortex (PFC) regulates 'executive' cognitive processes critical for goal-directed behavior. Dysregulation of PFC-dependent cognition is posited to underlie a variety of psychopathologies including ADHD and stress-related disorders. Corticotropin-releasing factor (CRF) and CRF1 receptors are prominent in the PFC. However, despite decades of research on the neurobiology of CRF, the degree to which CRF acts in the PFC to modulate PFC-dependent cognition is currently unknown.

To test whether CRF signaling in the PFC exerts stress-like actions on working memory, we examined the effects of CRF infusion (25, 50, 100, 250 ng/hemisphere) into the rat medial PFC on performance in a delayed response task of spatial working memory. CRF infusion into the caudal dorsomedial PFC (dmPFC) elicited a robust and dose-dependent impairment in task performance. In contrast, infusion into the rostral dmPFC did not impact performance. This rostrocaudal topography of CRF action is similar to noradrenergic α1/β-receptor modulation of sensorimotor gating and differs from that seen with catecholamines, which modulate working memory via actions in the rostral medial PFC. Thus, these results provide further evidence for a topographic functional organization of the PFC across the rostrocaudal and dorsoventral axes.

Additional studies using intra-PFC infusion of the CRF antagonist, D-Phe-CRF (50, 200 ng/hemisphere), examined whether endogenous CRF signaling in the PFC modulates working memory. Intra-PFC infusion of this CRF antagonist elicited a dose-dependent improvement in working memory performance, similar to FDA-approved treatments for ADHD. Collectively, these results indicate that CRF signaling in the PFC impairs PFC-dependent cognition as measured in this working memory task. Thus, pharmacological agents targeting CRF signaling may be effective in the treatment of PFC cognitive dysfunction associated with a variety of behavioral disorders.

P66. Neurokinin 1 receptor signalling from endosomes: a key source of pain signalling

Dane Jensen, TinaMarie Lieu, Michelle Halls, Nicholas Veldhuis, Quynh Mai, Nicholas Barlow, Christopher Porter, Meritxell Canals, Nigel Bunnett*

G-protein coupled receptors (GPCRs) are the largest class of membrane bound receptors and are involved in the majority of pathophysiological signalling pathways. Upon activation, most GPCRs traffic to endosomes. Although GPCRs can continue to signal from endosomes, the mechanisms of endosomal signalling and its importance in complex pathophysiological processes are unknown. The substance P (SP) neurokinin 1 receptor (NK1R) is a mediator of pain and inflammation and is rapidly internalized to, and signals from, endosomes. However, the role of endosomal signalling in NK1R mediated pain is not understood.

Here we investigated the importance of internalization and endosomal signalling of NK1R on pain and inflammation. Dynamin-1 and clathrin inhibitors as well as dynamin-1 siRNA were used to block NK1R endocytosis and trafficking to endosomes in cell lines and intact rats and mice. NK1R internalization and trafficking were quantified using BRET and immunofluorescence. Endosomally-mediated ERK, PKC and cAMP signalling were measured in cell lines using FRET biosensors and by immunofluorescence in rats. Capsaicin-evoked mechanical hyperalgesia was evaluated following intrathecal injection of dynamin, clathrin, NK1R, or MEK inhibitors in mice.

Here we show that in HEK293 cells, dynamin and clathrin disruption blocked SP stimulated NK1R endocytosis and inhibited SP-induced activation of nuclear pERK, cytoplasmic PKC, and cytoplasmic cAMP. Intrathecal injection of clathrin and dynamin inhibitors and dynamin-1 siRNA blocked capsaicin-evoked endocytosis of the NK1R and activation of ERK in spinal neurons, and suppressed capsaicin-evoked mechanical hyperalgesia. Dynamin inhibitors also blocked the prolonged excitation of NK1R spinal neurons when challenged with SP. Our results demonstrate a critical role for the endosomal signalling of the NK1R in pain transmission. These results also open new therapeutic targets for the treatment of NK1R mediated pain and inflammation.

P67. Identification of human SLC1 transporters that mediate transmembrane flux of D-serine

Genevieve Lind, Jill Farnsworth, Brent Lyda, Nicholas Natale, Alan Foster, Michael Kavanaugh*

ASCT1 and ASCT2 are sodium-dependent neutral amino acid transporters belonging to the solute carrier 1 (SLC1) gene family, which also includes the excitatory amino acid transporters EAAT1-5. As obligate exchangers,

these transporters have the potential to regulate homeostastic flux of many neutral amino acids including L-Ala, L-Ser, and L-Cys. However, many details regarding the cellular localization and functional roles of the ASCT transporters in the central nervous system are unknown. The molecular species involved in mediating transport of D-Ser in CNS have yet to be identified despite the fact that D-Ser is well-established as a co-agonist at NMDARs and it has been suggested to play critical roles in modulating signaling and synaptic plasticity. In this study, we expressed ASCT-1 and ASCT-2 in Xenopus laevis oocytes and found that in addition to broad recognition of many neutral L-amino acids, both transporters selectively transported the D-isomer of serine but not other D-amino acids tested. The Km values for D-serine at ASCT-1 and ASCT-2 were 105 μM and 182 μM, respectively. Other D-amino acids tested were not recognized, indicating enantiomeric specificity and suggesting that ASCTs may play a role in influencing D-serine concentrations in the CNS through exchange-mediated uptake or release. Additionally, we have synthesized and explored the properties of novel ASCT1/2 blockers that inhibit transport of D-serine through both transporters at nanomolar concentrations. These compounds may be useful for modulating D-serine concentrations in the CNS and could prove to be therapeutically relevant for such conditions as AD, stroke, and schizophrenia.

P68. Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy

Witold Lipski, Tom Wozny, Vincent DeStefino, Scott Stanslaski, Arun Antony, Donald Crammond, Judy Cameron, Mark Richardson*

Epilepsy is a debilitating condition affecting 1% of the population worldwide. Medications fail to control seizures in at least 30% of patients, and deep brain stimulation (DBS) is a promising alternative treatment. However, poor understanding of the mechanisms underlying the effects of electrical stimulation on seizure networks remains a significant barrier to improving efficacy. A modified clinical DBS hardware platform was recently described (PC+S) allowing long-term recording of electrical brain activity such that effects of DBS on neural networks can be examined. This study reports the first use of this device to characterize idiopathic epilepsy and assess the effects of stimulation in a non-human primate (NHP). Clinical DBS electrodes were implanted in the hippocampus of an epileptic NHP bilaterally, and baseline local field potential (LFP) recordings were collected for seizure characterization using the PC+S. Real-time automatic detection of ictal events was demonstrated and validated by concurrent visual observation of seizure behavior. Seizures consisted of large-amplitude 8-25Hz oscillations originating from the right hemisphere and quickly generalizing, with an average duration of 55.3±2.0 seconds and occurrence of 0.98±0.23 seizures per day. Variable

stimulation parameters resulted in suppression of local neural activity or in seizure induction during stimulation under ketamine anesthesia. Chronic stimulation in the awake animal was studied to evaluate how seizure activity was affected by stimulation configurations that suppressed broadband LFPs in acute experiments. This is the first electrophysiological characterization of epilepsy using a next-generation clinical DBS system that offers the ability to record and analyze neural signals from a chronically stimulating electrode. These results will direct further development of this technology and ultimately provide insight into therapeutic mechanisms of DBS for epilepsy.

P69. Underlying mechanisms and functional consequences of autonomous firing loss in the parkinsonian subthalamic nucleus

Eileen McIver, Jeremy Atherton, D. James Surmeier, Mark Bevan*

The motor symptoms of Parkinson's disease (PD) are associated with abnormally synchronous cortico-basal ganglia-thalamo-cortical activity. In animal models, parkinsonian activity emerges slowly, several days to weeks following loss of dopamine, implying a critical contribution of neuronal plasticity. The subthalamic nucleus (STN) is a key component of the movement-suppressing indirect and hyperdirect pathways of the basal ganglia. Following dopamine depletion in the 6-hydroxydopamine (6-OHDA) mouse model, the autonomous activity of STN neurons ex vivo was profoundly disrupted (control: 9.3 Hz; 6-OHDA: 3.0 Hz), and the proportion of inactive cells increased from 18 to 40%. Disrupted autonomous activity was caused by an increase in ATP-sensitive potassium (KATP) channel current because antagonism of KATP channels with 100nM glibenclamide ex vivo fully rescued firing.

In the absence of dopamine, the STN is disinhibited due to hyperactivity of the indirect pathway and consequently more powerfully patterned by hyperdirect cortical excitation. We hypothesized that following dopamine depletion, excessive activation of STN NMDA receptors (Rs) at cortico-STN synapses triggers KATP channel-dependent disruption of STN activity. Indeed, pre-incubation of control slices in 25μM NMDA mimicked KATP channel-mediated firing disruption in the 6-OHDA model. Conversely, knockdown of STN NMDARs through viral expression of cre recombinase in 6-OHDA-treated GRIN1lox/lox mice prevented activity disruption ex vivo and ameliorated motor dysfunction in vivo. Because autonomous STN activity renders excitatory synaptic integration phase-dependent, we further hypothesized that its disruption following loss of dopamine promotes abnormal, synchronous activity and motor dysfunction. In order to test this hypothesis we are developing a pharmacogenetic approach to restore intrinsic STN activity and assess its impact on motor dysfunction.

P70. Interactions between chronic stress and methamphetamine on the blood-brain barrier: Role of neuroinflammation

Nicole Northrop, Amy Ferng, Nicole Harless, Reka Natarajan, Bryan Yamamoto*

Acute exposure to stress causes neuroinflammation and a possible transient opening of the blood-brain barrier (BBB) to potentially harmful molecules. However, it is unknown if chronic exposure to stress produces sustained neuroinflammation and breach of the BBB. Therefore, we examined if exposure to 21 days of chronic unpredictable stress (CUS) produced neuroinflammation and disrupted BBB structure and function. Male Sprague-Dawley rats exposed to 21 days of CUS exhibited increased cyclooxygenase-2 (COX-2) and hyper-ramified microglia, 1 day post CUS, and decreased structural proteins of the BBB, claudin-5 and occludin, and increased BBB permeability, 7 days post CUS, indicating that stress-induced BBB disruption is associated with neuroinflammation. Since stress and drug abuse are comorbid and it is known that high doses of methamphetamine (Meth) cause BBB damage, we hypothesized that exposure to a shorter CUS paradigm would potentiate the effects of a subsequent exposure to a moderate dose of Meth on BBB disruption, via neuroinflammation. Rats were exposed to 10 days of CUS and treated with Meth (7.5 mg/kg, q2hr, x4, i.p.) or saline on day 11. Serial exposure to CUS and Meth decreased occludin and claudin-5 and increased BBB permeability to 10,000 Da FITC- dextran, 7 days after treatment. Furthermore, treatment with the COX inhibitor, ketoprofen (5 mg/kg, x2/day), after exposure to CUS and Meth, prevented BBB disruption. These results illustrate that chronic stress on its own and through its interactions with Meth produces a long-lasting disruption of BBB structure and function through a neuroinflammatory mechanism. A sustained breach in BBB function suggests increased vulnerability of the brain to subsequent insults. Since we've observed an interaction with chronic stress and investigator administered Meth on BBB function, ongoing experiments are focused on the interactions of contingent Meth intake and stress on BBB disruption.

P71. Doxazosin XL reduces Post-traumatic stress disorder (PTSD)checklist-military-scored(PCL-M) ratings in veterans with PTSD

Christopher Rodgman, Christopher Verrico, Manuela Holst, Francisco Franco, Daisy Thompson-Lake, Colin Haile, Richard De La Garza, II, Thomas Newton*

Post-traumatic stress disorder (PTSD) is common among veterans of Iraq and Afghanistan. Psychotherapy is helpful, but medications are often needed, and norepinephrine reuptake inhibitors (SSRI, SNRI) are first line agents, but has troublesome side effects. Prazosin, an α1 noradrenergic antagonist,

is effective for nightmares, but limited by short half-life. Doxazosin XL is more advantageous with 24 hour half-life and has proven effective in our lab to blunt subjective effects of cocaine and meth. To determine if doxazosin xl was superior to placebo in reducing Posttraumatic Stress Disorder Checklist-Military (PCL-M) scores, we ran a double-blind, within subjects trial at the Michael E. DeBakey Veterans Affairs Medical Center. Participants were screened (N=8) using the Clinician Administered PTSD Scale (CAPS). Following this, participants were asked to fill out the Beck Anxiety Index (BAI), Beck Depression Inventory II (BDI II), Pittsburgh Sleep Quality Index (PSQI), and PCL-M. Meeting criteria, they were randomly selected to either doxazosin xl or placebo, scheduled and brought back on day 1 to receive 4 mg doxazosin xl vs placebo Participants were asked to return upwards of once every four days to fill out the data batteries (PCL-M, PSQI, BAI, BDI-II) and obtain vitals, as doxazosin xl dose was raised every four days by 4 mg (8mg, 12 mg, 16 mg) to 16 mg. On day 16, the CAPS was repeated, and the PCL-M, PSQI, BAI, and BDI-II were given. After two-week washout, procedures repeated with the alternative agent (doxazosin xl vs placebo). On analysis, data sets met normality and equal variance assumptions, total DF = 12, F = 16.279, with a statistical significant difference ($p = 0.007$). This demonstrates a clear trend indicating doxazosin xl lowered PCL-M scores in veterans with PTSD in 16 days. Furthermore, a crossover effect arose, with lower baseline PCL-M scores in the group starting the placebo in phase 2 after taking doxazosin xl in phase 1.

P72. Brain mapping of neurons with a dual glutamatergic-GABAergic phenotype

David H Root, Shiliang Zhang, Hui-Ling Wang, Marisela Morales*

Glutamate is both an amino acid and an excitatory neurotransmitter. As an amino acid, glutamate participates in the synthesis of proteins and also as a substrate for the enzyme glutamic acid decarboxylase (GAD) to produce the inhibitory neurotransmitter GABA. Glutamate is accumulated in synaptic vesicles by one of three known vesicular glutamate transporters (VGluT1, 2, and 3), while GABA is accumulated in synaptic vesicles by the vesicular GABA transporter (VGaT). VGluTs, GADs and VGaT are associated to membranes of vesicles that are shuttled to axon terminals, vesicles that upon depolarization and calcium entry, release either glutamate or GABA. Accumulating evidence indicates that VGluTs are in different neurons from those containing GAD and VGaT. Thus glutamate is used as signaling molecule by a set of neurons different from other neurons that use GABA as signaling molecule. However, we had identified a group of neurons within the ventral tegmental area that co-express transcripts encoding VGluT2 and GAD (Root et al., 2014; Nat Neurosci). In order to determine if VGluT2+ GAD+ neurons exist in other

brain regions, we used a combination of double in situ hybridization to map neurons co-expressing VGluT2 mRNA and GAD mRNA across the entire brain. VGluT2+ GAD+ neurons were observed in a select group of subcortical regions. VGluT2+ GAD+ neurons were observed in the entopeduncular nucleus that resides within the internal capsule. VGluT2+ GAD+ neurons were also found in the lateral supramammillary nucleus, near the mammilothalamic tract. Finally, VGluT2+ GAD+ neurons were observed in the anterior and medial parts of the ventral tegmental area, within the rostral linear, interfascicular, medial paranigral, and medial parabrachial pigmented nuclei. As all three regions in which VGluT2+ GAD+ neurons were identified have well-established projections to limbic structures, VGluT2+ GAD+ neurons may play unique roles in learning, memory, and emotionality.

P73. Neurocircuitry and Receptor Mechanisms Underlying the Differential Sensitivity of Prefrontal Cognitive Processes to Psychostimulants

Robert Spencer, Jed Shmusky, Barry Waterhouse, Craig Berridge*

Psychostimulants, including methylphenidate (MPH), improve cognitive and behavioral processes dependent on the prefrontal cortex (PFC) and extended frontostriatal circuitry in both Attention Deficit Hyperactivity Disorder (ADHD) patients and healthy subjects. In humans and rats, systemic MPH improves working memory (WM) and response inhibition in a narrow inverted-U shaped manner. In contrast, MPH improves sustained attention (SA) and attentional set shifting over a broader and right-shifted dose range, similar to that seen with classroom behavior. To better understand the potential neural mechanisms underlying the divergent dose-dependent effects of MPH across cognitive processes we first identified neurocircuitry involved in WM and SA tasks. In these studies, temporary inactivation of the dorsomedial PFC (dmPFC), dorsomedial striatum (dmSTR), and ventromedial striatum (vmSTR) impaired performance in both tasks. Nonetheless, additional studies demonstrate that MPH action in the dmPFC, but not dmSTR or vmSTR, was sufficient for improvement in both WM and SA tasks. Interestingly, the dose-dependent effect of intra-PFC MPH on SA was broader and right-shifted relative to WM, identical to that seen with systemic administration. Prior studies demonstrate that PFC α2 receptors promote WM while α1 receptors promote attentional set shifting. Consistent with this, we observed that blockade of α2, but not α1, receptors in the PFC prevent the WM enhancing effects of MPH. Collectively, these studies indicate the divergent dose sensitivity to psychostimulants observed across PFC-dependent cognitive processes reflect differential actions of α1 vs α2 receptors in the PFC. Clinically these results raise the possibility that higher doses that maximally control

attention may impair processes important for other domains of academic/social functioning and suggest α1-antagonists as a potential adjunct treatment for ADHD.

P74. Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala

Joseph Stujenske, Ekaterina Likhtik, Mihir Topiwala, Joshua Gordon*

Theta oscillations synchronize the basolateral amygdala (BLA) with the hippocampus (HPC) and medial prefrontal cortex (mPFC) during fear expression. The role of gamma-frequency oscillations in the BLA is less well characterized. We examined gamma- and theta-frequency activity in recordings of neural activity from the BLA-HPC-mPFC circuit during fear conditioning, extinction, and exposure to an open field. In the BLA, slow (40-70 Hz) and fast (70-120 Hz) gamma oscillations were coupled to distinct phases of the theta cycle and reflected synchronous high-frequency unit activity. During periods of fear, BLA theta-fast gamma coupling was enhanced, while fast gamma power was suppressed. Periods of relative safety were associated with enhanced BLA fast gamma power, mPFC-to-BLA directionality, and strong coupling of BLA gamma to mPFC theta. These findings suggest that switches between states of fear and safety are mediated by changes in BLA gamma coupling to competitive theta frequency inputs.

P75. Lateral habenula excitatory activity as a neural mechanism underlying ethanol-induced aversion

Shashank Tandon, Sharif Taha*

Ethanol has both rewarding and aversive properties. Clinical studies suggest that sensitivity to ethanol's aversive effects plays a role in vulnerability to developing alcohol use disorders. We have shown recently that electrolytic lesion of the Lateral Habenula (LHb) significantly attenuates conditioned taste aversion (CTA) induced by a single ethanol injection in rats (Haack et al., 2014). In this study, we recorded neural firing in the LHb of behaving rats before and after an ethanol-induced CTA. Water-deprived rats (n=6) were trained to perform an operant response (FR1) to receive a saccharin reward (0.2 mL). Neural activity in the LHb during operant responding for saccharin was recorded in two sessions: after pairing saccharin with saline injection ("Pre-CTA" session) and after pairing saccharin with a 20% ethanol solution injection (1.5 mg/kg, i.p.; "CTA" session). Behaviorally, rats showed a highly significant ethanol-induced aversion to saccharin. Relative to pre-CTA sessions, rats completed significantly

fewer successful trials in the CTA session. Comparison of LHb neural firing in pre-CTA and CTA sessions revealed four main changes in firing properties. First, baseline (not event-related) firing in CTA sessions was significantly higher than that occurring in pre-CTA sessions. Second, cue-evoked firing shifted from a pattern of primarily inhibition during pre-CTA sessions to primarily excitation during CTA sessions. Third, lever press-evoked firing showed a similar shift toward higher firing rates after CTA induction. Fourth, firing rates were significantly higher during consumption of the devalued saccharin solution in CTA sessions. Our results demonstrate that ethanol-induced CTA leads to consistently higher LHb firing rates (both baseline and event-evoked) which is associated with decreased operant responding. Our data are consistent with the idea that LHb is a significant node in regulating drug-seeking behaviors.

P76. Sign- and goal-tracking rats learn differently in the face of changing reward value

Sam Bacharach, Alex Kawa, Donna Calu*

During a simple autoshaping procedure, where the extension of a lever precedes the delivery of food pellets, rats show individual differences in conditioned responding; some rats approach and contact the lever (sign-tracking (ST)), whereas other rats approach and contact the food cup (goal-tracking (GT)). Here we use an unblocking procedure to examine whether ST and GT rats show differences in learning about changing reward value. After characterizing rats as ST or GT, we trained them in an unblocking task that uses odor cues as predictors of sucrose reward. During initial conditioning, rats learned to nose poke into an odor port, where they sampled odor cue (A), after which responding in a fluid well below resulted in the delivery a fixed quantity of sucrose. During compound conditioning, the previously learned odor cue (A) was followed by one of three novel odor cues (X, Y, or Z), which was predictive of the same (X), more (Y), or less (Z) reward than expected from (A) alone. During a probe test, rats received X, Y, and Z in extinction conditions and time spent in the sucrose well was an indicator of reward expectancy. ST rats learned about increases, but not decreases in reward value, whereas the opposite was true for GT rats. Individual differences in conditioned responding during autoshaping correlated with the rats' ability to learn about changing reward value. Presently, we use in vivo electrophysiology in rats performing in this unblocking task to examine the neural correlates underlying these individual differences in learning.

P77. Site specific knockdown of D2 autoreceptors alters dopamine kinetics, behavior and sensitivity to dopamine based drugs

Caroline Bass, Kimberly Bernosky-Smith, Brian M, Michael J, Evgeny Budygin*

Regulation of dopamine (DA) neurotransmission can occur by altering the firing rate of dopaminergic neurons, the synthesis and release of DA, and reuptake through the DA transporter (DAT). D2 autoreceptors interact with all of these processes, however, their role(s) in behavior and drug responses are not particularly clear. This is due in large part to their complex neuroanatomical localization in multiple brain regions, on different types of neurons, and at both pre- and postsynaptic sites. To address this complexity, we use viruses encoding short hairpin RNAs (shRNA) targeting the D2 receptor to manipulate populations in specific brain regions in rats. By injecting the virus into the substantia nigra (SN) or ventral tegmental area (VTA), only the cell bodies will be transduced, resulting in knockdown of either nigrostriatal or corticomesolimbic D2 autoreceptors, respectively. Using fast scan cyclic voltammetry we show that D2 autoreceptor knockdown from the SN results in decreased DA released per pulse and Vmax in the dorsal striatum, indicating that both release and reuptake are inhibited. In addition these rats exhibit enhanced locomotor activity, lack of habituation, less robust locomotor responses to high doses of cocaine and decreased sensitivity to haloperidol-induced catalepsy. Knockdown of mesolimbic D2 autoreceptors does not alter spontaneous activity, but does shift a delayed discounting curve to the left. Together these data suggest that D2 autoreceptor feedback inhibition mediates key aspects of behavioral and drug responses in addition to neurochemical control over DA neurotransmission.

P78. Optogenetic and pharmacogenetic dissection of STN-GPe in vivo network activity in experimental Parkinson's disease

Joshua Callahan, Ryan Kovaleski, Mark Bevan*

The glutamatergic subthalamic nucleus (STN) and reciprocally connected GABAergic external globus pallidus (GPe) are key components of the hyperdirect and indirect pathways of the cortico-basal ganglia-thalamo-cortical circuit, which together suppress movement by increasing basal ganglia inhibition of thalamo-cortical activity. In Parkinson's disease (PD) loss of substantia nigra dopamine neurons leads to increased activity of these pathways and the emergence of abnormal, synchronous neuronal activity. In order to determine the mechanisms underlying parkinsonian STN-GPe network activity, we are using silicon tetrodes/optrodes to simultaneously record unit

and LFP activity from the cortex, STN and GPe in the 6-OHDA mouse model of PD. Under urethane anesthesia, STN neurons are normally phase-locked to slow cortical oscillations (~1 Hz) while prototypic GPe neurons discharge tonically with minimal entrainment. However, following loss of dopamine, prototypic GPe neurons discharge in antiphase while a subset of GPe neurons (arkypallidal) discharge in-phase with cortical and STN activity. Furthermore, STN activity is more intensively driven by cortical input. Optogenetic inhibition of ArchT expressing GPe neurons confirmed their prototypic nature. Optogenetic inhibition of the STN largely abolished the phase-locked activity of arkypallidal neurons but had minimal impact on the activity of prototypic GPe neurons. We hypothesize that the firing pattern and minimal impact of STN inhibition on prototypic GPe activity is due to hyperexcitability of D2 striatal projection neurons (D2-SPNs) during cortical excitation. We will therefore pharmacogenetically inhibit D2-SPNs through activation of Gi-DREADDs to determine whether reducing excessive D2-SPN activity restores tonic firing in prototypic GPe neurons.

P79. Novel mGluR5 positive allosteric modulator attenuates neurodegeneration and alters microglial polarization after TBI

Alan Faden, Bogdan Stoica, Jeffrey Conn, Alok Kumar, Boris Sabirzhanov, David Loane*

Traumatic brain injury (TBI) causes microglial activation and related neurotoxicity that contributes to chronic neurodegeneration. Activation of metabotropic glutamate receptor 5 (mGluR5) by the orthosteric agonist CHPG) is neuroprotective in experimental TBI models, and has strong anti-inflammatory effects in vivo and in vitro. However, the therapeutic potential of CHPG is limited by its weak potency and limited brain permeability. Potent, selective positive allosteric modulators (PAMs) of mGluR5 have been developed, which show good brain penetration after systemic administration. We evaluated the mGluR5 PAM VU0360172 (VU), in a mouse model of controlled cortical impact (CCI). Vehicle, VU or VU plus the mGluR5 antagonist MTEP were administered systemically to CCI mice at 3 h post-injury; lesion volume, hippocampal cell counts, microglial activation, and functional recovery were assessed through 28 days post-injury. Anti-inflammatory effects of VU were also examined in vitro using BV2 and primary microglia. VU treatment significantly reduced the lesion, attenuated hippocampal neurodegeneration, and improved motor function recovery after CCI. Co-administration of MTEP blocked the protective effects of VU. This mGluR5 PAM significantly reduced CD68 and NOX2 expression in activated microglia at 28 days post-injury, as well as modulating inflammatory

related miRs. In addition, VU treatment shifted the balance between M1/M2 microglial activation states towards an M2 phenotype. Thus, VU0360172 provides neuroprotection after experimental TBI through mechanisms that likely include modulation of posttraumatic neuroinflammation.

P80. A Clinical Trial of Gene Therapy to Prevent Neuropathy

David Fink, Marina Mata*

Chemotherapy-induced polyneuropathy (CIPN) is a common, dose-limiting complication of chemotherapy for cancer. Prevention of neuropathy by neurotrophin administration is limited by off-target effects of these pleiotropic bioactive peptides. To overcome this limitation we have constructed a series of nonreplicating herpes simplex virus (HSV)-based vectors that efficiently target gene delivery to dorsal root ganglia (DRG) from skin inoculation. In rodents, an NT3-expressing HSV vector prevents CIPN caused by cisplatin, and we have completed FDA-enabling toxicology and biodistribution studies. We are now proposing an open-label phase 1/2a randomized, double-blind, placebo-controlled trial. Phase 1 stage objectives. To complete an escalating dose safety evaluation of the NT3-expressing vector (PGN-703) in patients with colorectal or bladder cancer slated to receive cisplatin or oxaliplatin-based adjuvant chemotherapy; Safety will be determined by medical history, physical examination and laboratory tests. Dosing will advance from the lowest dose to the maximum tolerated dose based on evaluation of dose limiting toxicity. Phase 2a stage objectives. To extend the clinical assessment of PGN-703 with a randomized, double-blind, placebo-controlled phase 2a efficacy and safety analysis of PGN-703 at the maximum tolerated dose in subjects with colorectal or bladder cancer slated to receive cisplatin or oxaliplatin-based adjuvant chemotherapy. The primary outcome will be prevention of neuropathy, determined by electrodiagnostic testing 3 months after the conclusion of treatment. The key secondary outcome measure will be prevention of a clinically-relevant neuropathy, defined by the emergence of 2 out of 3: 1. symptoms of neuropathy (any one of numbness, tingling, dead feeling or burning); 2. decreased vibration or touch/pressure sensation by examination; 3. absent ankle reflexes, at 3 months after the conclusion of treatment. Details of the proposed trial will be presented.

P81. Calcium Flux is associated with Synaptotagmin-1's Promotion of the Formation of Axonal Filopodia in developing Neurons

Karen Greif, Anna Brandtjen, Claire Weichelsbaum, Nikitha Ashok*

Synaptotagmin-1 (syt1), a Ca2+-binding protein that functions in regulation of vesicle exocytosis at the synapse, is expressed in many types of neurons well before synaptogenesis begins both in vivo and in vitro. We recently demonstrated that syt1 plays a role in regulating axon branching and filopodial dynamics in developing embryonic chick forebrain neurons. Overexpression of syt1 increased the formation of axonal filopodia and branches. Conversely, knockdown of syt1 decreased the numbers of axonal filopodia and branches. The mechanism by which syt1 exerts its influence on axon development is unknown. In order to investigate whether syt1 accomplishes its effects on filopodia using a mechanism similar to its role at the synapse, we manipulated Ca2+ levels using calcium blockers and calcium ionophores. A 15-minute exposure to the calcium ionophore, A23187, significantly increased axonal filopodia; blockade of calcium channels using La3+ or Cd2+ decreased filopodia number. These findings are consistent with the well-defined role of Ca2+ in filopodial dynamics. Overexpression of syt1 using adenovirus-mediated transfection was coupled with La3+ treatment to examine whether blocking Ca2+ influx would reverse Syt1-mediated increases in axonal filopodia. Embryonic chick forebrain neurons were transfected with a syt1-YFP construct or GFP. After 48 hrs, cells were treated with La3+ or vehicle for 15 minutes. Treatment with La3+ reversed the increase in filopodia stimulated by syt1 overexpression. Taken together these data suggest that syt1 regulates the formation of axonal filopodia using its Ca2+-binding functions, prior to engaging in its conventional functions at the synapse. Future experiments involve site-directed mutagenesis of syt1's C2 domains, to directly study our hypothesis. This research was supported by grants from Bryn Mawr College.

P82. Estrogen increases cocaine choice under concurrent reinforcement in castrated male rats

Tod Kippin, Jared Bagley, Kyle Ploense, Lana Bubalo*

Steroid hormones regulate motivation for drugs and a range of natural reinforcers. We have shown that female rats exhibit an estrogen-dependent choice of cocaine reinforcement over food reinforcement whereas gonadectomy in males failed to impact cocaine choice. Here, we examine the impact of estrogen on the cocaine-food choice in castrated male rats. Castrated male Sprague-Dawley rats were trained to respond on different levers for food (3 x 45 mg pellets) or cocaine (1.0 mg/kg IV) reinforcement and then allowed

to choose between the two reinforcers under concurrent reinforcement. Throughout training and testing, one group of males received daily estrogen (5 microg) and another received vehicle (0.1 ml of peanut oil). A third group of intact male rats received the same cocaine and food reinforcement training and testing. All rats readily acquired responding for food and for cocaine. Intact males and castrated males receiving vehicle exhibited approximately equal choice for cocaine and food reinforcement whereas castrated males treated with estrogen exhibited elevated cocaine relative to the other groups. Further, the estrogen-treated castrates exhibited higher cocaine motivation when tested on a progressive ratio schedule of reinforcement compared to their food motivation as well as to that exhibited by vehicle controls. These data indicate that estrogen increases the choice for cocaine over a natural reinforcer in males but that castration does not alter this choice. These findings indicate that, as in females, estrogen increases cocaine choice and motivation in males and suggest that the lack of effect of castration may be due to the concurrent loss of estrogen and androgen receptor stimulation. Supported by NIDA (1R01DA027525).

P83. Understanding the neural dynamics of motivational encoding in the subthalamic nucleus and premotor cortex of the Parkinsonian brain

Mark Richardson, Witold Lipski, Donald Crammond, Michael Randazzo, Stathis Kondylis, Ahmad Alhourani, Robert Turner*

Parkinson's disease (PD) is a neurodegenerative disorder affecting midbrain dopamine neurons that results in dysregulation of basal ganglia circuitry. Motor dysfunction, including tremor, bradykinesia, and rigidity is a prominent symptom of this aberrant signaling, and most amenable to conventional treatment. This has lead to a tendency to perceive PD as strictly a movement disorder, and to understand the neural circuits underlying its pathophysiology strictly in terms of their motor function. Bradykinesia, however, has been suggested to represent an implicit decision not to move fast, rather than an inability to do so. In addition, apathy is among the most common and debilitating non-motor manifestations of PD, and is characterized by diminished motivation, decreased goal-directed behavior, and flattened affect. Recent studies suggest that impaired incentive processing is involved, but the underlying mechanisms are still poorly understood. In order to elucidate potential mechanisms for the neural encoding of motivation in cortico-basal ganglia circuits, we studied PD patients undergoing awake STN mapping during deep brain stimulation (DBS) electrode implantation while they performed a monetary incentive force task. On each trial, subjects were asked

to respond to visual cues by squeezing grip force levers in order to maximize reward or minimize loss. Single-unit (SU) recordings from the STN and electrocorticography (ECoG) in pre-motor cortex (PMC) during the task were used to understand the motivational encoding in these networks. In addition to movement-responsive STN neurons (9/19), SU activity was modulated during incentive cue presentation (1/19). ECoG recordings showed a movement-related decrease in beta oscillatory power in PMC, increase in PMC-STN coherence, as well as PMC beta-gamma cross-frequency coupling; and these measures were modulated during the incentive task. These findings may support a role for STN-PMC interaction in the encoding of motivation.

P84. Characterization of c-Jun N-terminal kinase (JNK)-mediated mechanisms of cannabinoid and opioid tolerance

Daniel Morgan, David Marcus, Michael Zee, Ken Mackie*

Mice expressing a desensitization-resistant form of the cannabinoid 1 receptor (CB1) receptor were produced to investigate the role of CB1 receptor desensitization on tolerance to delta-9-THC in vivo. Desensitization-resistant S426A/S430A mutant mice exhibit a significant but modest delay in tolerance to delta-9-THC suggesting that other mechanisms for cannabinoid tolerance exist in these mutants lacking the "classic" GRK/arrestin mechanism of desensitization. Pre-treatment of S426A/S430A mutant mice with either 3 or 10 mg/kg SP600125, a selective JNK inhibitor, causes a block in the development of tolerance to the analgesic effects of delta-9-THC. This finding demonstrates that coordinated action of both JNK and GRK/arrestin signaling is responsible for chronic tolerance to delta-9-THC. The role of JNK signaling in the development of chronic tolerance to morphine and fentanyl has also been examined. Pre-treatment with either 3 or 10 mg/kg SP600125 attenuates tolerance to the antinociceptive effects of 10 mg/kg morphine but not 0.3 mg/kg fentanyl in the tail-flick and hotplate tests. Interestingly, pre-treatment with SP600125 attenuates tolerance to the hypothermic effects of both morphine and fentanyl suggesting that JNK signaling is involved in tolerance for certain physiological responses to fentanyl. Previous reports demonstrated that the JNK 2 isoform is responsible for acute tolerance to the antinociceptive effect of 10 mg/kg morphine. Surprisingly, tolerance to chronically administered (10 once daily injections) 10 mg/kg morphine was abolished in JNK 1 knock-out mice raising the possibility that different JNK isoforms may be responsible for different types of morphine tolerance. Taken together these results demonstrate the important role that JNK signaling plays in chronic tolerance for agonists acting at two different G protein-coupled receptors.

P85. Hot and cold: Temperature effects on neural circuits from therapeutic hypothermia to febrile seizures

David Naylor

Hypothermia benefits severe neurological insults such as hypoxic ischemic injury, trauma, and status epilepticus. Inversely, fever worsens stroke outcome and is common with childhood seizures. Seizures also are common with re-warming after therapeutic cooling. We explore the effects of temperature on synaptic inhibition, drug action, and the firing properties of circuits with whole-cell patch-clamp in hippocampal slices and computational modeling. Temperature markedly affects synaptic function and circuit activity. GABAergic synaptic inhibition increases with hypothermia and progressively increases as temperature is lowered well below 32 C, the standard treatment post-cardiac arrest. Lowering from 34 C to < 26 C increases mIPSC decay-time (11.7 +/– 4.0 to 21.2 +/– 6.4 ms; p<.05) and Area-Under-the-Curve (–705 +/– 85 to –1170 +/– 331 pA ms; p<.05). Elevating temperature decreases synaptic inhibition, but plateaus above 37 C. Unlike IPSC AUC, frequency continues to increase above 40 C, but plateaus at 32 C for low temperatures. Differential effects on IPSC size vs. event frequency indicate temperature's alteration of circuit activity is not fully explained by changes in magnitude of synaptic inhibition. Hypothermia alters effects of pharmacological agents such as barbiturates, with phenobarbital (200uM) having a modest 27% increase in AUC during hypothermia, but a strongly significant 165% under more normothermic conditions. Benzodiazepines such as diazepam continue to have strong effects at low temperature, though. Receptor kinetic computational models suggest the temperature-specific modulation of GABA-AR channel properties may overlap dissimilarly with the pharmacological action of different GABAergic agents. In conclusion, hypothermia has direct effects on GABA-ARs and hippocampal circuits. The enhancement and diminution of inhibition at low and high temperatures, respectively, helps explain both therapeutic as well as injurious, pro-convulsive mechanisms.

P86. The role of putative stem and neural progenitor cell populations in adult zebrafish axon regeneration following injury

Jeffery Plunkett, Haydee Torres, Abdiel Badillo, Aileen Hernandez, Alcides Lorenzo Gonzalez, Martin Oudega*

Although post-embryonic neurogenesis is limited in the mammalian brain, zebrafish (Danio rerio) retain multiple proliferative neurogenic and stem cell niches throughout adult life. The focus of our research is to study how CNS injury affects the induction of neurogenic progenitor cell fates in the adult zebrafish brain. It has been well documented that in contrast to mammals,

adult zebrafish recover functionally from a complete spinal cord transection injury. Damaged axons deriving from specific neuronal populations within the brainstem are able to regenerate across and beyond a spinal cord transection site. We hypothesize that spinal cord injury will induce an endogenous, quiescent population of brainstem progenitor cells that act to integrate and enable the regenerative response seen following spinal cord injury in the fish. Preliminary data have shown prior to injury, nestin immunoreactivity was observed near ventricular areas, as well as in ventral brainstem regions, which contain nuclei of descending brainstem projection neurons. Furthurmore, an increase in Nestin immunoreactivity was observed in similar brainstem regions following spinal cord injury. We are currently examining regenerative brainstem regions for nestin, sox-2. and Neurod1 expression pre- and post-spinal cord injury utilizing a combination of RT-PCR, in-situ hybridization and immunohistochemical techniques. Analysis of specific gene targets within the stem/neural progenitor pathway will provide us with a better understanding of the role of stem cells in the CNS axon regeneration response seen in teleost fishes.

P87. Dependence receptors and retrograde neuronal death after spinal cord injury

Michael Shifman, Cynthia Laramore, James Shahoud, Jie Chen*

Following injury, axons in the mammalian spinal cord do not regenerate and functional recovery further impeded by retrograde neuronal death. The retrograde cell death appears to be apoptotic, but little is known about its specific mechanisms. Recently, a new type of apoptosis-inducing mechanism, so-called "dependence receptors", was described. Dependence receptors induce apoptosis when unoccupied by their ligands, but block apoptosis when bound by their ligand. Unlike in mammals, spinal cord injury (SCI) in the lamprey is followed by axon regeneration, but only about 50% of the severed reticulospinal(RS) axons regenerate, while the fates of unregenerated neurons is unknown. We report previously that in animals allowed to survive 16 weeks after SCI, many of those neurons were TUNEL and activated caspase—positive, suggesting that cells were dying by apoptosis. The majority of these neurons also expressed Neogenin (axonal guidance receptors for RGM) and simultaneously, expression of RGM was downregulated near the transection. Thus we hypothesize that after SCI, Neogenin function as "dependence receptor," inducing delayed apoptotic neuronal death. To test this hypothesis, we downregulated Neogenin expression by in vivo delivery of antisense morpholino oligonucleotides (MOs) to RS neurons by retrograde transport at the time of spinal transection. Downregulation of Neogenin expression in lamprey RS neurons enhance their survival and prevent Caspases 3, 8 and 9 activation.

P88. Tonic vs. phasic retrograde synaptic modulation by endocannabinoids: differential astrocytic control of anandamide and 2-AG

Jeffrey Tasker, Shi Di*

Recent evidence suggests that different endocannabinoids (eCBs) may be responsible for the effects of tonic and evoked eCB release at some synapses. Thus, activity-dependent eCB effects are often dependent on 2-arachidonoylglycerol (2-AG) synthesis and tonic CB1 receptor activation is mediated by anandamide (AEA) at some GABA synapses in hippocampal slice cultures. Here, we tested for the differential dependence on 2-AG of evoked vs. tonic eCB actions at GABA synapses onto magnocellular neurons using whole-cell patch clamp recordings in acute brain slices. We tested for the 2-AG dependence of both depolarization- and glucocorticoid-induced suppression of GABA release in vasopressin (VP) and oxytocin (OT) neurons recorded in slices from dehydrated rats, in which reduced astrocytic coverage of neuronal membranes allows eCBs to spill over from glutamate synapses onto GABA synapses. Bath application of tetrahydrolipstatin (THL), a diacylglycerol lipase antagonist that blocks 2-AG synthesis, blocked both the depolarization- and glucocorticoid-induced suppression of GABA release in both VP and OT neurons, suggesting that evoked eCB actions are mediated by on-demand 2-AG synthesis in these cells. We next tested for the dependence of tonic CB1 receptor activation on 2-AG synthesis. Unlike the evoked eCB actions, tonic CB1 receptor activation was insensitive to changes in glial coverage and to blockade of 2-AG synthesis, suggesting that it was mediated by constitutive AEA release. Thus, AEA is released tonically at GABA synapses and is insensitive to glial buffering, while 2-AG is released phasically in an activity-dependent manner and its access to GABA synapses is regulated by astrocytes. Supported by NIH 2R01 MH066958 and the Pierson Endowment.

P89. Sex and species differences in effects of chronic intranasal oxytocin

Karen Bales

Oxytocin (OT) is a neuropeptide which has been widely implicated in social cognition in animal species and humans. As such, it is already in clinical trials for use in treating autism, schizophrenia, and social anxiety, among other disorders. This has occurred without previous long-term animal testing. My current program of research examines the effects of chronic developmental exposure to intranasal OT in prairie voles (Microtus ochrogaster) and titi monkeys (Callicebus cupreus), two socially monogamous species; as well as BTBR T+ Itpr3tf/J (an inbred mouse strain with social deficits) and

C57BL/6J mice. In male (but not female) voles, intranasal OT administered once daily from postnatal days 21-42 resulted in acute increases in contact behavior, but persistent deficits in pair-bonding tested at day 60. The same doses which impaired pair-bonding also reduced endogenous OT protein in the paraventricular nucleus of the hypothalamus. In both strains of mice treated with a similar dose to that used in human studies (and which caused pair-bonding deficits in the voles (0.8 IU/kg), OT caused little to no long-term effects, either positive or negative, in both sexes. Preliminary data from monkeys suggests that OT at this weight-adjusted dose is causing a reduction in interactions with parents, an increase in interactions with strangers, and sex-specific responses to novelty. Taken as a whole, these results suggest that long-term exposure to intranasal OT has the potential for negative effects, which may be strongly sex- and dose-dependent, and which may be mediated through changes in the endogenous OT system. This research is supported by HD071998.

P90. Differentiated antidepressant-like profiles of ketamine, fluoxetine and vortioxetine in Flinders Sensitive Line rats depleted of endogenous 5-HT—An approach to gain new mechanistic insights?

Kristian Gaarn du Jardin, Nico Liebenberg, Heidi Müller, Gregers Wegener, Connie Sanchez, Betina Elfving*

Consistent with clinical results, a single ketamine dose exhibits acute and protracted antidepressant-like effects in Sprague Dawley (SD) rats (Gigliucci et al. 2013). One hypothesis ascribes ketamine's antidepressant effect to enhanced glutamate transmission via NMDA receptors on GABA interneurons (Duman 2014). Recent research showed that 5-HT depletion abolished its protracted effect in SD rats (Gigliucci et al. 2013). Vortioxetine, a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and 5-HT transporter inhibitor, is thought to exert its antidepressant activity through modulation of several neurotransmitter systems including 5-HT, glutamate and GABA (Sanchez et al. 2014). Here, we investigate the acute and protracted antidepressant-like effect of ketamine (15 mg/kg, IP, 1 or 48 hr), and acute effects of vortioxetine and fluoxetine (both 10 mg/kg, IP, 1 hr) in Flinders Sensitive Line (FSL) rats, a genetic model of depression, using the forced swim test. Studies were conducted under normal and low 5-HT tone (> 90 % hippocampal reduction) achieved after treatment with p-chlorophenylalanine (100 mg/kg/day for 3 days, IP).

FSL rats exhibited similar depressive-like phenotypes under normal and low 5-HT tone. At normal 5-HT tone, ketamine had acute and protracted antidepressant-like effects. Both effects were abolished under low 5-HT tone,

indicating a critical role of endogenous 5-HT tone for these effects in FSL rats. The 5-HT receptors involved remain to be identified. Acute fluoxetine had an antidepressant-like effect only at normal 5-HT tone. In contrast, vortioxetine displayed an acute antidepressant-like effect under normal and low 5-HT tone. The latter effect may potentially be ascribed to its agonistic activity at 5-HT1A and/or 5-HT1B receptors, since these receptors are engaged at the dose tested (Sanchez et al. 2014). This hypothesis remains to be substantiated experimentally.

P91. Cocaine-induced alterations in calcium signaling in the striatum

Aaron Garcia, Susan Ferguson*

The striatum is a key node in the limbic system and underlies many important functions, including motivation, reward, and learning. Dysfunction in striatal signaling has been heavily implicated in drug addiction. Medium spiny projection neurons (MSNs) in the striatum can be subdivided into two types that differ in their neuropeptide composition and receptor expression as well as their projection patterns. Specifically, MSNs expressing D1 receptors form part of the direct pathway whereas MSNs expressing D2 receptors form part of the indirect pathway. Dysregulation of these two cell types and their relative balance has been posited to play a role in a number of neuropsychiatric diseases, including addiction. While studies have examined how neurons in these pathways respond to cocaine, little is known about how calcium signaling in these two cell types is affected by cocaine exposure. Through the use of the genetically encoded calcium indicator, GCaMP6, and 2-photon imaging in a slice preparation we have found that in some MSNs calcium signaling increases in response to cocaine exposure while in others it decreases. Given that the direct and indirect pathway MSNs of the striatum express D1 and D2 dopamine receptors, which are coupled to Gs and Gi/o signaling cascades, respectively, it is likely that this difference in dopamine receptor expression could be responsible for the variation in the observed effects. We are currently performing additional experiments in which GCaMP6 is restricted to direct or indirect pathway MSNs in subcompartments of the striatum to determine if the diversity of our effects can be attributable to cell type. We will determine if there are different responses in dorsal and ventral striatum given that there are functional and anatomical differences in these areas. Additionally, we are performing experiments to determine how calcium signaling is altered in direct and indirect pathway MSNs in animals with different amounts of exposure to cocaine.

P92. From GWAS to function in schizophrenia: The role of Akt3 in neurocognitive development and conditioned learning

Kristy Howell, Amanda Law*

Akt cell signaling consists of three independently encoded, yet homologous genes (AKT1-3) whose roles include cell survival, proliferation, and migration. Biological and genetic studies suggest aberrant AKT1 signaling in schizophrenia and recent Genome Wide Association studies (GWAS) have identified risk loci in and around the AKT3 gene. AKT3 plays a role in attainment of normal brain size, but the neural mechanisms and its potential role in schizophrenia are unknown. This project examines a novel mouse model deficient in Akt3 on the C57BL6 background to determine its role in neurodevelopment and neurobehavioral function. A comprehensive battery of behavioral tasks in adult male wildtype (Akt3 +/+), heterozygous

(Akt3 +/–), and knockout (Akt3 –/–) mice evaluating sensorimotor gating, anxiety, learning and memory, cognitive deficits and social cognition were performed. Significant deficits in a prefrontal cortical (mPFC) mediated temporal order object recognition task with an allelic dose dependent response were observed. Akt3–/– mice also exhibit altered contextual fear conditioning while cued conditioning was intact. Furthermore, normal sensorimotor gating, novel object, and sociability were observed with no anxiety phenotype detected. Additional behavioral and molecular studies are underway to disentangle the role of Akt3 in frontal cortical and hippocampal mediated cognitive function. Female mice are also being incorporated for a comprehensive approach to determine if Akt3 mediates sex-specific differences. Our studies suggest that Akt3 plays distinct roles in neurodevelopment and neurobehavioral function as it relates to specific domains of learning and memory and identify Akt3 as a novel potential pharmacological target for treating cognitive dysfunction in schizophrenia.

P93. Parkinsonian subthalamic nucleus-external globus pallidus network activity during stereotyped cortical activity states

Ryan Kovaleski, Joshua Callahan, Mark Bevan*

The reciprocally connected subthalamic nucleus (STN)-external globus pallidus (GPe) network is a key component of the movement suppressing hyperdirect and indirect pathways of the basal ganglia. To determine the mechanisms underlying parkinsonian STN-GPe activity during stereotyped cortical activity states, we recorded STN-GPe unit activity concurrently with the motor cortex electrocorticogram in control and 6-hydroxydopamine (6-OHDA)-injected mice under urethane anesthesia.

Although STN firing was consistently entrained to the active phase of cortical slow wave activity (SWA), discharge intensified after dopamine depletion (control = 6.4 Hz; 6-OHDA = 11.2 Hz). Dopamine loss had no effect on firing during activated cortical states (ACS) evoked by tail pinch. GPe neurons exhibiting SWA-correlated firing increased after dopamine depletion (control = 61%; 6-OHDA = 85%). GPe neurons fired out-of-phase (control = 14%; 6-OHDA = 75%) or in-phase with SWA (control = 47%; 6-OHDA = 10%) or were uncorrelated (control = 39%; 6-OHDA = 15%). Published data together with optogenetic manipulations (see Callahan poster) indicate that following dopamine loss, out-of-phase neurons correspond to prototypical GPe-STN neurons, whereas in-phase neurons are arkypallidal GPe neurons that project to striatum only. During ACS, out-of-phase GPe discharge rate increased in control mice (SWA = 14 Hz; ACS = 17 Hz) but decreased in 6-OHDA mice (SWA = 31 Hz; ACS = 22 Hz), whereas in-phase GPe discharge increased in control and 6-OHDA mice (control: SWA = 12 Hz, ACS = 19 Hz; 6-OHDA: SWA = 10 Hz, ACS = 18 Hz). Finally, elevated beta band (13-30 Hz) activity, a motor suppressing activity pattern in Parkinson's disease, was only observed in the STN LFP during ACS (control = 2281 uV2; 6-OHDA = 4678 uV2). Because anesthesia may inhibit beta band activity across the circuit, we have recently initiated recordings in head-fixed, awake mice.

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P94. Chronic stress causes behavioral deficits and decreases serotonin afferents to the medial prefrontal cortex

Reka Natarajan, Nicolas Chiaia, Nicole Northrop, Bryan Yamamoto*

Chronic stress exposure causes persistent mood and cognitive dysfunction. However, little is known about the mechanisms and pathways mediating these lasting behavioral deficits. Previously, we have shown that chronic unpredictable stress (CUS) decreases serotonin (5HT) cells specifically in the interfascicular region of the dorsal raphe (DRI). The DRI projects to the medial prefrontal cortex (mPFC) but it is unknown if there is a decreased 5HTergic innervation of the mPFC by the DRI that may underlie CUS induced persistent deficits in mood and cognition. We tested the hypothesis that the prevention of CUS dependent elevations in corticosterone (CORT) through CORT synthesis inhibition would block the decrease in DRI innervation of the mPFC and the deficits in behavior. Adult male Sprague-Dawley rats underwent 21 days of CUS and received i.p. injections of the CORT synthesis inhibitor Metyrapone (Mety) or vehicle, 15 min before each stressor. To determine if CUS decreased DRI afferents to the mPFC, retrograde tracer TrueBlue was injected bilaterally into the mPFC after CUS and tracer positive cells in the DRI were counted 1 week post CUS. Results show that CUS induced decreases in TrueBlue

positive soma in the DRI were blocked by Mety treatment after CUS. To test for dysfunction in mood regulation, rats underwent a forced swim test 4 days after CUS. Results show that stress induced increases in the duration of time spent immobile were blocked by Mety treatment after CUS. Furthermore, Barnes maze assessment for cognitive function 1 month after CUS exposure showed that Mety treatment blocked CUS induced deficits in reversal learning, indicating that CORT mediates CUS induced enduring deficits in cognitive flexibility. These results are the first to identify that CUS dependent decreases in DRI 5HTergic afferents to the mPFC underlie protracted mood and cognitive dysfunction. Future experiments will focus on the mechanism mediating these behavioral deficits.

P95. High yields of oligodendrocyte lineage cells from human embryonic stem cells at physiological oxygen tensions for evaluation of translational biology.

Sybil Stacpoole, Sonia Spitzer, Bilada Bilican, Alastair Compston, Ragnhildur Karadottir, Siddharthan Chandran, Robin Franklin*

We have established an efficient system to specify NG2/PDGF-Rα/OLIG2+ oligodendrocyte precursor cells (OPCs) from human embryonic stem cells (hESCs) at low physiological (3%) oxygen levels. This was achieved via both forebrain and spinal cord origins, with up to 98% of cells expressing NG2. Developmental insights reveal a critical role for fibroblast growth factor 2 (FGF-2) in OLIG2 induction via ventral forebrain pathways. The OPCs mature in vitro to express O4 (46%) and subsequently become galactocerebroside (GALC), O1 and myelin basic protein-positice (MBP+) multibranching oligodendrocytes. These were cultured alongside hESC derived neurons. The electrophysiological properties of human OPCs are similar to those of rat OPCs with large voltage-gated sodium currents and the ability to fire action potentials. Exposure to a selective retinoid X receptor agonist increased the proportion of O4+ oligodendrocytes that express MBP from 5 to 30%. Thus we have established a developmentally engineered system to investigate the biological properties of human OPCs and test the effects of putative remyelinating agents prior to clinical application.

P96. Phosphodiesterase inhibition and Impulsivity

Marlies van Duinen, Pim Heckman, Arjan Blokland, Jan Ramaekers, Jos Prickaerts*

Impulsivity is a multifaceted concept that comes in many different forms. Impulsive behavior is generally divided into impulsive actions, i.e. an inability to inhibit a response, impulsive choices, i.e. a distorted judgment with respect to choosing between two different outcomes, and reflection impulsivity, ability

to evaluate available information prior to deciding. All concepts of impulsivity seem to find their origin in frontostriatal circuitry. Within this circuitry the extracellular effect of dopamine is largely mediated through the cAMP/PKA signaling cascade. Importantly, the cGMP/PKG signaling cascade is known to modulate the cAMP/PKA cascade in both the direct D1 and indirect D2 pathway neurons. These cascades are thus a potential target for pharmacological intervention of dopaminergic signaling in impulse control disorders, like addiction or ADHD. Phosphodiesterase type 2 (PDE2A), which degrades both the intracellular messenger cAMP and cGMP, is known to be present in both dopaminergic pathway neurons and the prefrontal cortex.

In the current project we investigated whether the PDE2A inhibitor BAY60-7550 (0.03, 0.1, 0.3 and 1.0mg/kg) could reverse both a systemic amphetamine-induced deficit in impulse control, as well as impulsivity caused by induction of 6-OHDA lesions in medial prefrontal cortex (mPFC), in operant chambers in adult rats by means of conditioned reaction time task schedules of reward.

Results showed no effect of BAY60-7550 on premature responses in the amphetamine-induced deficit model. In the 6-OHDA lesion model, BAY60-7550 decreased the number of premature responses only in the 6-OHDA-lesioned rats. In conclusion, these results form an indication of an equal distribution of the PDE2A enzyme in both direct and indirect pathway neurons. Most likely, BAY 60-7550 induces its effects via dopaminergic neurons in the mPFC, making it an interesting target for treatment of ADHD.

P97. Circadian variation of alertness and subjective sleep quality in a brain trauma patient

Diane B. Boivin, Jenny Guo, Ari Shechter*

The central circadian clock governs the daily pattern of several physiological, hormonal, and behavioral processes such as the sleep-wake cycle, melatonin levels, and alertness. The endogenous circadian clock has a period of approximately 24 hours and is entrained to the 24-hour day by exposure to the light-dark cycle. Non-24-hour sleep-wake syndrome, or hypernychthemeral syndrome, is characterized by the absence of entrainment to the normal day length and is rare in sighted individuals. One such patient is a 45-year-old sighted woman diagnosed with hypernychthemeral syndrome following a traumatic brain injury sustained in a car accident. The circadian variation of melatonin, subjective alertness (SA), and subjective sleep quality (SSQ) were investigated during a four-day experiment in a time-isolation laboratory. The subject underwent a 24-hour ultra-rapid sleep-wake cycle (URSW) procedure consisting of alternating 60-minute periods of wake and nap opportunity

under constant semi-recumbent posture. Plasma melatonin, SA, and SSQ were measured throughout the URSW. Non-linear regression analysis was used to determine the relationship between melatonin, SA, and SSQ. The patient's data was compared to those of 8 healthy women aged 26 ± 2.67 (mean ± SD), who underwent an URSW in 2009 during their mid-follicular phase. Patient's melatonin phase occurred significantly earlier than controls', and no circadian rhythm was detected in her SA and SSQ. Her SA and SSQ scores were abnormally elevated and low, respectively, throughout the URSW. Results suggest a disrupted circadian control of sleep propensity, and a potentially abnormal perception of sleepiness. This study provides insight into the pathophysiology of hypernychthemeral syndrome in sighted individuals and may inform future management of the patient.

P98. Diet-induced increases in NAc CP-AMPARs and enhanced sensitivity to cocaine in obesity-prone vs. obesity-resistant rats

Carrie Ferrario, Cameron Nobile*

Alterations in mesolimbic circuits contribute to aberrant motivation for food, drugs, and cues associated with them. Human neuro-imaging studies show that activation of the nucleus accumbens (NAc) in response to food-cues is enhanced in obese people. Furthermore, individual differences in susceptibility to diet-induced obesity may be mediated in part by alterations in NAc function. The NAc receives convergent glutamate and dopamine input. AMPA type glutamate receptors provide the main source of excitation to the NAc, and repeated activation of dopamine systems can enhance AMPAR-mediated transmission. To date, no studies have examined potential alterations in NAc glutamatergic transmission in any preclinical model of obesity. Thus, we have begun a series of studies to determine the effect of eating a junk-food diet on mesolimbic function and glutamatergic transmission in rats that are susceptible vs. resistant to diet-induced obesity. We found that rats that became obese on a junk-food diet are sensitized to the locomotor activating effects of cocaine after junk-food diet deprivation compared to non-obese rats given the same diet. This was associated with a selective increase in NAc surface expression of the AMPAR GluA1, but not GluA2, subunit only obese rats. Junk-food diet deprivation also increased GluA1 surface expression in selectively bred obesity-prone vs. obesity resistant rats. These data suggest diet-induced increases in NAc calcium permeable-AMPARs (CP-AMPARs) in susceptible rats. Preliminary electrophysiological data provide further support for this conclusion. Overall, our data suggest that exposure to junk-food diet enhances NAc glutamatergic transmission and sensitivity to cocaine-induced locomotion only in individuals susceptible to diet-induced obesity. These data will be

discussed in light of the role for CP-AMPARs in cue-induced drug-seeking behavior and our recent work suggesting that motivation for sucrose-cues is enhanced in obesity-prone rats.

P99. The neural chaperone proSAAS blocks synuclein fibrillation and neurotoxicity

Iris Lindberg, Hua Lam, Michael Helwig, Akina Hoshino, Nikolai Lorezen, Daniel Otzen, Nigel Maidment*

Emerging evidence strongly suggests that chaperone proteins are cytoprotective in neurodegenerative proteinopathies involving protein aggregation, for example the accumulation of aggregated alpha-synuclein into the Lewy bodies present in Parkinson's disease. Of the various chaperones that have been explored in neurodegenerative disease, the small secretory chaperone known as proSAAS has many attractive properties. ProSAAS, widely expressed in neurons throughout the brain, is capable of blocking both the aggregation of beta amyloid into fibrils as well as blocking beta amyloid neurotoxicity. Additional experimental evidence strongly implicates the proSAAS chaperone protein in Parkinson's disease. First, three separate proteomics studies have identified proSAAS as a potential biomarker in various neurodegenerative diseases, including Parkinson's disease. Second, we have found that immunoreactive proSAAS is associated with aggregated proteins in the substantia nigra of Parkinson's disease patients. Our data also show that proSAAS potently inhibits the fibrillation of alpha-synuclein in an in vitro assay. Lastly, we have shown that proSAAS-encoding lentivirus can block alpha-synuclein-induced cytotoxicity in primary cultures of nigral dopaminergic neurons. Collectively, these studies support the idea that neuronal proSAAS represents a potential therapeutic target in neurodegenerative disease.

P100. Huntington's disease CSF seeds mHTT aggregation

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disease that results in progressive motor, cognitive and psychiatric impairment and ultimately death. There is no effective therapy in part because of the lack of a biomarker to measure target engagement and disease progression. We report preliminary data for such a biomarker. The disease is caused by an abnormal CAG trinucleotide repeat expansion within exon 1 of the HD gene that produces a mutant Huntingtin protein (mHTT) containing an expanded polyglutamine (poly(Q)n, n≥ 36) tract. The repeat expansion confers an increased misfolding and aggregation propensity to mHTT, leading to buildup of soluble and insoluble mHTT aggregates and a corresponding deficit in

the intracellular quality control of protein folding. We used an inducible PC12 cell model of HD (Htt14A2.6) as an assay system, The Htt14A2.6 cells inducibly expresses a fragment of mHTT (truncated exon 1) epitope tagged with enhanced green fluorescence protein (mHttex1-GFP) in the presence of ponasterone A. This seeding assay measures and contrasts the percentage of cells with aggregates. Autopsy CSF from HD subjects and BACHD transgenic rats effectively seeds aggregation in a HD cell model. Addition of exogenous peptides containing the HD sequence and immunodepletion studies demonstrate that seeding is mHTT template-specific and may reflect an underlying disease propagation mechanism. Abeta and alpha syneculin do not enhance mHTT aggregation. This seeding assay distinguishes living HD subjects from healthy and non-HD dementia controls. Seeding measures in gene-positive subjects without clinical symptoms fall between HD patients and controls. This quantifiable seeding property in HD CSF may serve as a HD molecular biomarker assay to monitor disease progression and evaluate therapies that target mHTT protein.

P101. Allosteric regulation of phosphodiesterase-2 controls dopamine-induced GluA1 membrane insertion in medium spiny neurons

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The strength of glutamatergic synaptic transmission depends on the number of post-synaptic AMPA receptors. Modulation of synaptic strength is achieved by changing surface AMPAR numbers in a process that requires active trafficking from intracellular vesicles to the plasma membrane and is regulated by PKA, a cAMP-dependent kinase. Phosphodiesterase-4 (PDE4), an enzyme that degrades cAMP, regulates PKA activity and controls dopamine-induced GluA1 membrane insertion (Nishi et al., 2008; Song et al., 2013). Here we asked whether additional PDEs expressed in D1 medium spiny neurons (MSNs) also regulate membrane insertion of GluA1-containing AMPARs. Our approach combines live-cell imaging of cAMP and cGMP dynamics, along with GluA1 trafficking measurements with computational modeling of signaling to explore the contribution of each PDE to GluA1 trafficking in MSNs. Inhibition of PDE2, a highly expressed striatal PDE, increases GluA1 membrane insertion in D1 MSNs. To examine if the cGMP-allosteric activation of PDE2 regulates GluA1 trafficking, cGMP levels were enhanced using NO-donors or PDE inhibitors. We found that treatment with SNAP, a NO donor, decreased GluA1 membrane insertion. Inhibition of PDE1, a cAMP/cGMP PDE, also resulted in a decrease in dopamine-induced cAMP levels and GluA1 membrane insertion. This decrease was due to the allosteric activation of PDE2 by cGMP, as simultaneous inhibition of PDE2, or expression of PDE2 mutants abolished the decrease in GluA1 membrane insertion. These results are proof of concept

that we can modulate the directionality and magnitude of GluA1 trafficking in MSNs by either activating or inhibiting PDE2.

References:

Nishi et al., ; Distinct Roles of PDE4 and PDE10A in the Regulation of cAMP/PKA Signaling in the Striatum. J Neurosci. 2008; 28(42): 10460.

Song et al., ; ERK regulation of phosphodiesterase 4 enhances dopamine-stimulated AMPA receptor membrane insertion. Proc Natl Acad Sci U S A. 2013; 110(38): 15437.

P102. Sensory neuron-induced CSF1 triggers microglial DAP12-dependent neuropathic pain

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Although microglia are major contributors to the mechanical hypersensitivity produced by peripheral nerve injury, there is little consensus as to how nerve injury activates spinal cord microglia. Importantly, activation of microglia requires an intact connection between the injured sensory neurons in dorsal root ganglia (DRG) and the spinal cord. Thus, injured DRG neurons must transmit signals that communicate with the microglia. Here we focused on the cytokine, colony-stimulating factor 1 (CSF1), which is critical to the differentiation and maintenance of the myeloid lineage population, including microglia, and its receptor, CSF1R, which is also required for microglia development and in the adult CNS is only expressed in microglia. We also studied the microglial membrane adaptor protein DAP12, which lies downstream of CSF1R and is central to microglia functionality. We demonstrate that nerve injury-induced CSF1 in sensory neurons is required not only for the activation of dorsal horn microglia, but also for the mechanical hypersensitivity that is the hallmark of the neuropathic pain condition. Finally, we also demonstrate a critical contribution of DAP12 to the nerve injury-induced mechanical hypersensitivity.