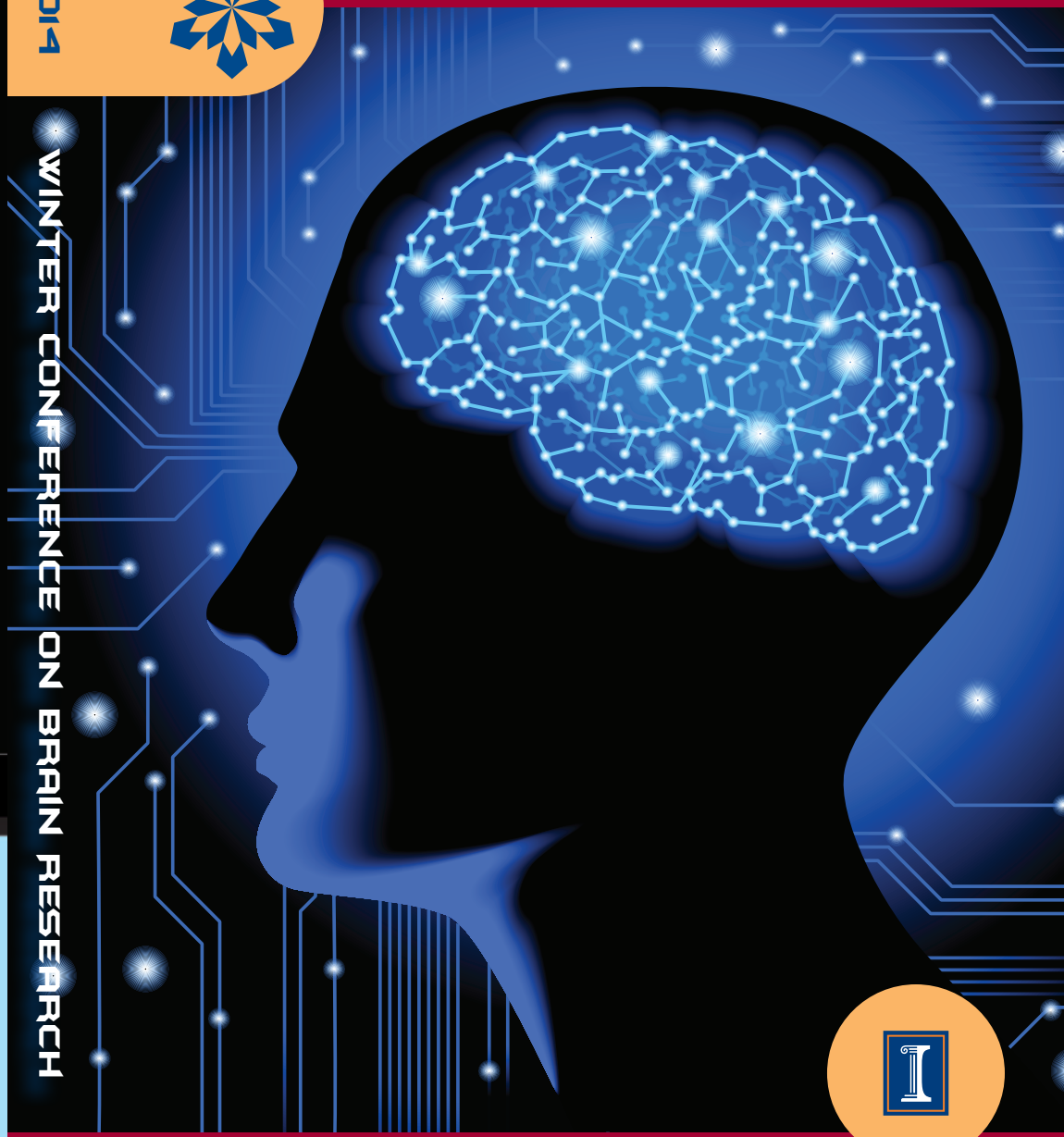
47TH ANNUAL WCBR
JANUARY 25–30, 2014
STEAMBOAT SPRINGS, COLORADO

WINTER CONFERENCE ON BRAIN RESEARCH

2014



WELCOME TO THE FORTY-SEVENTH ANNUAL WINTER CONFERENCE ON BRAIN RESEARCH

Whether you are a first-time participant or have been coming for years, welcome to Winter Brain! The Winter Conference on Brain Research (WCBR) has been around for almost 50 years. The first meeting took place in Lake Tahoe in 1968, organized by neuroscientists from UCLA. From an initial attendance of around 60, the meeting grew to around 400-500 participants. One aspect that makes our meeting unique is the casual atmosphere and opportunities for interactions with colleagues. WCBR includes scientists from a variety of fields, and it is always a week full of formal and informal discussions, at the conference center and in the ski slopes. As an example of what WCBR can provide, many of the most productive collaborations I have set were arranged at this meeting; some even at a chair lift! This year we have a fantastic program.

We begin the week with a **Welcome Reception** on Saturday, where you can meet with friends and colleagues and welcome new attendees (they will wear peach badges) and Travel Fellows (they have a peach dot in their badge). On Sunday, we kick off with an **Opening Breakfast** during which we feature our keynote speaker, Dr. **Karl Deisseroth**, D.H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University. Karl has transformed modern neuroscience with his crucial role in developing optogenetics and more recently with the clarity technique. Dr. Deisseroth has not only developed revolutionary tools, but has used them in very clever ways to solve long-standing issues in the neurobiology of reward and decision-making. His presentation will cover the general aspects of technique development and the CLARITY project in particular. In addition, we will have a **Brain Talk Town Meeting** on Monday, during which a panel that includes Dr. Larry Parsons (Scripps Research Institute), Kyle Frantz (Georgia State University) and Thomas Crowley (University of Colorado, Denver) will discuss "Drug Use in Teens". The Town Meeting is a traditional component of WCBR Outreach Program; its targeted audience is the local school population, and WCBR participants are welcome to join. I will encourage everyone to check out and volunteer in our **Outreach Program**, in which we present sessions at local schools throughout the week. 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** 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 (NASTAR) Race for skiers and snowboarders, followed by a Mountain Lunch. Please be sure to attend the **Business Meeting** on Wednesday following the afternoon sessions, as we will hold elections for Conference Chair-elect and board members. Additionally, we will 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. We thank you all for your contributions.

I am sure you will have a great time and realize what a fantastic scientific program we have this year. Enjoy the meeting!

Conference Chair
Patricio O'Donnell

Contents

General Information

HEADQUARTERS is the Sheraton Steamboat Resort. All scientific activities will be held there.

WCBR INFORMATION DESK AND MESSAGE CENTER are in the conference area, first floor, Sheraton Steamboat Resort.

The desk hours are as follows:

	Morning	*Afternoon*
Saturday 1/26	8:00 a.m.–12:00 p.m.	3:30–8:30 p.m.
Sunday 1/27	6:30–10:00 a.m.	3:30–7:00 p.m.
Monday 1/28	7:00–10:00 a.m.	3:30–6:45 p.m.
Tuesday 1/29	7:00–10:00 a.m.	3:30–6:00 p.m.
Wednesday 1/30	7:00–10:00 a.m.	3:30–5:30 p.m.
Thursday 1/31	7:00–10:00 a.m.	

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

POSTER SESSION 1, 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.

Posters can be set up after 12:00 p.m. on Sunday.

POSTER SESSION 2, 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.

Posters can be set up after 8:00 a.m. on Monday.

POSTER SESSION 3, 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.

Posters can be set up after 8:00 a.m. on Tuesday.

POSTER SESSION 4, 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.

Posters can be set up after 8:00 a.m. on Wednesday.

Please refer to pages 24–31 for a listing of poster sessions.

EXHIBITS AND LOUNGE are in Sunshine Peak. Refreshments are provided 3:30 to 4:30 p.m., Sunday through Wednesday. Exhibitor setup is Sunday, January 26, 12:00–3:00 p.m. All exhibitors should be packed up by 2:00 p.m. on Thursday, January 30.

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

Monday through Thursday breakfast will be available from 6:30–9:00 am, in Saddles/Sevens. ***The tickets in your registration packet are required for admission.***

SKI LIFT TICKETS will be available from the WCBR Information Desk. Daily tickets can be purchased or prepaid tickets can be picked up only during desk hours.

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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Michelle Chappell
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Phone 217-333-2880
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Travel Fellowship Program

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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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South Windsor, CT 06074
Contact: Michael Mohammadi
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ASSOCIATION BOOK EXHIBIT

9423 Old Mt Vernon Rd
Alexandria, BA 22309
Contact: Mark Trocchi
Tel 703-619-5030
Fax 703-619-5035
info@bookexhibit.com

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Special Events

SATURDAY, JANUARY 25

Welcome Wine and Cheese Reception • 6:00–7:30 p.m. • Grand Ballroom

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

SUNDAY, JANUARY 26

Conference Breakfast and Plenary Address • Grand Ballroom

7:00–8:30 a.m. • Breakfast

8:00–9:30 a.m. • Plenary Address

The plenary keynote address is presented by:

Karl Deisseroth, M.D., PhD, D.H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University

Optical deconstruction of fully-assembled biological systems

Karl has transformed modern neuroscience with his crucial role in developing optogenetics and more recently with the CLARITY technique. Dr. Deisseroth has not only developed revolutionary tools, but has used them in very clever ways to solve long-standing issues in the neurobiology of reward and decision-making. His presentation will cover the general aspects of technique development and the CLARITY project in particular.

MONDAY, JANUARY 27

First Meeting of the Board of Directors • 6:30–8:30 a.m. • Villas Gallery

Brain Talk Town Meeting • 6:45–8:00 p.m. • Storm Peak

Attendance is open to all.

Drug Use in Teens

Experts in adolescence and addiction will discuss drug use in teenagers. Although many teenagers are exposed to potentially addictive drugs, most don't suffer serious complications. Panel members will discuss risk factors for addiction, worrisome signs and symptoms and describe how the adolescent brain differs from the adult brain.

John Mendelson, California Pacific Medical Center Research Institute **(Moderator)**, *Loren Parsons, The Scripps Research Institute, Kyle J. Frantz, Georgia State University, Thomas J. Crowley, University of Colorado, Denver*

TUESDAY, JANUARY 28

Breakfast for Travel Fellows Meeting • 6:30–7:30 a.m. • Saddles/Sevens

Look for the reserved signs

Special Poster Session • 6:30–8:30 p.m. • Sunshine Peak

The 22 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 30.

WEDNESDAY, JANUARY 29

Smitty Stevens Memorial Ski Race • 10:00–11:30 a.m. • Lower Bashor

Registration cards must be completed no later than Monday, January 27, 8:00 a.m. at the WCBR Information Desk.

Mountain Lunch • 11:30 a.m.–2:00 p.m. • Hazies (top of the Gondola)

Skiers can take the Gondola from the base to Hazies with their lift ticket. All **non-skiers** will need to present their WCBR name badge for complimentary access on the Gondola.

Required lunch ticket is in your registration packet.

Business Meeting • 6:30 p.m. • Mt. Werner

Attendees will vote on the Program and Facilities 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 30

Second Meeting of the Board of Directors • 6:30–8:30 a.m. • Villas Gallery

Reception • 6:30 p.m. • Grand Ballroom Foyer

Banquet and Dance • 7:30 p.m. • Grand Ballroom

Required ticket is in your registration packet.

Program

PREAMBLE TO THE PROGRAM

The 2014 WCBR Program consists of panels 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.

SUNDAY, JANUARY 26

7:00 A.M.

Breakfast • Grand Ballroom

8:00 A.M.

Plenary Address • Grand Ballroom

Karl Deisseroth

Optical deconstruction of fully-assembled biological systems

3:30–4:30 P.M.

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM

1. **Panel** • Storm Peak

   Oxidative tress in psychiatric disorders

   Elliot Hong, Ana C. Andreazza, Akira Sawa, ***Patricio O'Donnell (Chair)***

2. **Panel** • Mt. Werner

   Neural mechanisms of drug-altered decision-making

   Kate Wassum (Chair), *Geoffrey Schoenbaum, Sean Ostlund, Benjamin Saunders*

3. **Panel** • Twilight

   Endocannabinoid function in the brain reward system and the continued pursuit of bliss

   Carl Lupica (Chair), *Loren (Larry) Parsons, Joseph Cheer, Stephanie Borgland*

4. **Panel** • Rainbow

   Putting the ice on stress, aging and CNS trauma

   Monika Fleshner, Nicole Berchtold, Monica Siegenthaler, ***Kelli Sharp (Chair)***

5. **Panel** • Sunset

   Regulation of cytoskeletal and membrane functions during growth cone guidance

   Paul Letourneau (Chair), *Jonathan Terman, Yimin Zou, John Henley*

6. **Panel** • Skyline

   Gonadotropin releasing hormones: A comparative approach to multiple forms and functions

   Yonathan Zohar (Co-Chair)**, Nancy Sherwood, Jean Harry, **Mary Ann Ottinger (Co-Chair)

8:30–10:00 P.M.

7. **Panel** • Storm Peak

   Neural antecedents to adolescent and adult antisocial and substance-use disorders

   ***Thomas Crowley (Chair)**, Sophia Schneider, Stuart White, Jean Liu*

8. **Panel** • Mt. Werner

   Cortical dysfunction in Rett Syndrome: Opportunities for new treatment development

   ***Frank Menniti (Chair)**, Michela Fagiolini, Alysson Muotri, Lucas Pozzo-Miller*

9. **Panel** • Twilight

   Ion channel subunit interactions: Combinations and consequences

   *Chen Gu, Leonard Kaczmarek, **Ian Forsythe (Chair)***

10. **Panel** • Rainbow

    Non-conventional modes of neurotransmission in the CNS : Do we need a new vocabulary?

    ***Louis-Eric Trudeau (Chair)**, Alex Hoffman, Javier Stern, Vladimir Parpura*

11. **Panel** • Sunset

    The light and dark of mu and delta opiod receptor heterodimerization: Analgesia versus analgenic tolerance

    *Lakshmi Devi, Wakato Fujita, **George Wilcox (Chair)**, Helene Beaudry*

12. **Panel** • Skyline

    Mechanisms which may mediate depression

    *Minh-Hu Han, Rosemary Bagot, Ronald Seese, **Fritz Henn (Chair)***

MONDAY, JANUARY 27

7:30–9:30 AM

13. **Panel** • Storm Peak

    Midbrain systems and the regulation of aversion and reward

    *Elyssa Margolis, Thomas Jhou, **Ryan LaLumiere (Chair)**, Mitchell Roitman*

14. **Panel** • Mt. Werner

    Regulation of the dendritic spine actin cytoskeleton and membrane trafficking in health and disease

    ***Mark Dell'Acqua (Chair)**, Gareth Thomas, Peter Penzes, Scott Soderling*

15. **Panel** • Twilight

To amphetamine and beyond! Exploring neural mechanisms of drug and non-drug reinforcers

Luis de Lecea, Ralph DiLeone, ***Chris Olsen (Chair)****, Lique Coolen*

16. **Panel** • Rainbow

Immune regulation in neurovascular unit in cerebrovascular disorders and MS

Jaroslaw Aronowski (Chair)*, Gregory del Zoppo, Dale Pelligrino, Douglas Feinstein, Paula Dore-Duffy*

17. **Panel** • Sunset

Connectivity in the psychoses: From genes to neural circuitry

Miklos Argyelan, Steven Potkin, James Kennedy, ***Anil Malhotra (Chair)***

18. **Panel** • Skyline

Individual variation in development of compulsive behaviors: The search for a common mechanism

Jill Becker, ***Laura O'Dell (Chair)****, Gretchen Neigh, Kelly Klump*

3:30–4:30 P.M.

Exhibits and Posters • Sunshine Peak

4:30–6:30 P.M.

19. **Panel** • Storm Peak

Juvenile social isolation and risk for psychiatric disorders

Gabriel Corfas (Chair)*, Patricio O'Donnell, J. Amiel Rosenkranz, Kazutoshi Nakazawa*

20. **Panel** • Mt. Werner

Traversing the translation of target-based hypotheses in psychostimulant addiction

Kathryn Cunningham, Athina Markou, Phil Skolnick, ***Amy Newman (Chair)***

21. **Panel** • Twilight

NMDA-receptor signaling in plasticity and death

Karl Ulrich Bayer (Chair)*, Steve Traynelis, Haruhiko Bito, Ulli Bayer, Suzanne Zukin*

22. **Panel** • Rainbow

Aggregate prone proteins in neurodegenerative disorders: Uncovering new mechanisms and discovering novel therapeutics

Warren Hirst (Chair)*, Anurag Tandon, Ai Yamamoto, X. William Yang*

23. **Panel** • Sunset

Evolvability of behavior: Genes, development, and neural circuits

Hillery Metz, Barbara Finlay, Bruce Carlson, ***Paul Katz (Chair)***

24. **Panel** • Skyline

When ski helmets aren't enough: Emerging therapies for TBI and post-traumatic epilepsy

Bret Smith, Amy Brooks-Kayal, Ivan Soltesz, ***Edward Hall (Chair)***

6:45–8:30 P.M.

Brain Talk Town Meeting • Storm Peak

Drug Use in Teens

John Mendelson (Chair), *Loren Parsons, Kyle J. Frantz, Thomas J. Crowley*

All are welcome and encouraged to attend.

8:30–10:00 P.M.

25. **Panel** • Storm Peak

    Genetic and non-genetic contributions to abusive rodent alcohol drinking

    ***John Crabbe (Chair)**, Steve Boehm, Paula Hoffman, Sarah Leibowitz*

26. **Panel** • Mt. Werner

    New vistas in post-mortem studies in schizophrenia: Implications for etiology and novel therapeutics

    *Amanda Law, Schahram Akbarian, Joel Kleinman, **Larry Siever (Chair)***

27. **Panel** • Twilight

    Slices, cells, circuits, and steroids: Insights on estrogen action in the brain using *ex vivo* techniques

    ***Bradley Cooke (Chair)**, John Meitzen, Deepak Srivastava, Eniko Kramár*

28. **Panel** • Rainbow

    Interindividual variations in major depression pathology: Effects of age and the placebo response

    ***Jon-Kar Zubieta (Chair)**, Sara Weisenbach, Olusola Ajilore*

29. **Panel** • Sunset

    Modern brain banking for modern times

    ***Barbara Lipska (Chair)**, Cristian Achim, Brent Harris, Piotr Kozlowski*

30. **Panel** • Skyline

    The role of GABAergic interneurons in Huntington's Disease

    ***Michael Levine (Chair)**, Anton Reiner, Carlos Cepeda, Michelle Day*

TUESDAY, JANUARY 28

7:30–9:30 A.M.

31. **Panel** • Storm Peak

    The "inflamed" dire consequences of TBI: Exploiting novel mechanisms and treatments for battling neuroinflammation

    *Jonathan Godbout, Susanna Rosi, Cesar Borlongan, **Nigel Greig (Chair)***

32. **Panel** • Mt. Werner

    Impulsivity and psychiatric disorders: Clinical and preclinical perspectives

    *Harriet de Wit, Jack Smathells, Daniel Claassen, **Nathan Holtz (Chair)***

33. **Panel** • Twilight

    Why can't a woman be more like a man? Interactions between sex and stress and responses to stimulants and toxins

    *Debra Bangasser, Cheryl Conrad, **Vicky Luine (Chair)**, Diane Miller*

34. **Panel** • Rainbow

It's all in the timing…

Patrick Simen, Marshall Hussain Shuler, ***Matthew Matell (Chair)****, Martin Wiener*

35. **Panel** • Sunset

Spike timing-dependent plasticity in cortical learning

Robert Froemke, ***Alfredo Kirkwood (Chair)****, Harel Shouval, Pablo Celnik*

36. **Panel** • Skyline

Kv2.1 potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration

Elias Aizenman (Chair)*, Michael Tamkun, D.P. Mohapatra, Niyathi Hegde Shah, Federico Sesti*

3:30–4:30 P.M.

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM.

37. **Panel** • Storm Peak

Risk factors and predictors of human drug abuse

Jim Bjork, Patricia Conrod, ***Hugh Garavan (Chair)****, Sharon Morein-Zamir*

38. **Panel** • Mt. Werner

Addressing cognition impairment in schizophrenia: Taking aim on emerging intracellular and receptor-based targets

Gretchen Snyder (Chair)*, Christopher Shaffer, Sven Akkerman, Sean Smith, James Bibb*

39. **Panel** • Twilight

Mitochondrial ion channels and transporters in the regulation of synaptic plasticity and neuronal survival

Yuriy Usachev (Chair)*, Gavriel David, Nickolai Brustovetsky, Elizabeth Jonas*

40. **Panel** • Rainbow

BDNF modulation of neural circuits and behavior: New insights and translational implications

Alexei Morozov, Maribel Rios, Jacqueline McGinty, ***Vinay Parikh (Chair)***

41. **Panel** • Sunset

The central role of parvalbumin interneurons in critical period plasticity

Aaron McGee (Chair)*, Hirofumi Morishita, Elizabeth Quinlan, Joshua Trachtenberg*

42. **Panel** • Skyline

Neuronal excitability in function and dysfunction

Jerry Yin (Chair)*, John Disterhoft, Edi Barkai, Susan Tsunoda*

6:30–8:30 P.M.

Special Poster Session & Reception • Sunshine Peak

WEDNESDAY, JANUARY 29

7:30–9:30 A.M.

43. **Panel** • Storm Peak

    Functionally characterizing the transcriptional landscape of the developing human brain

    ***Thomas Hyde (Chair)**, Andrew Jaffe, James Knowles, Ed Lein, Brady Maher*

44. **Panel** • Mt. Werner

    Neural circuitry underlying feeding

    ***Paul Phillips (Chair)**, Matthew Carter, Luis de Lecea, Yexica Aponte, Michael J. Krashes*

45. **Panel** • Twilight

    Targeting cyclic nucleotide phosphodiesterases for the treatment of Huntington's Disease

    *Christopher Schmidt, **Anthony West (Chair)**, Hai Lin, Nicholas Brandon*

46. **Panel** • Rainbow

    AMPA receptor regulation at postsynaptic sites

    ***Johannes Hell (Chair)**, Susumu Tomita, Jose Esteban, Terunaga Nakagawa*

47. **Panel** • Sunset

    The role of CK1 and its regulation in multiple CNS disease states

    ***Marc Flajolet (Chair)**, Louis Ptacek, Paul Vezina, Camron Bryant, Cristina M. Cruciat*

48. **Panel** • Skyline

    Developing treatments for Spinal Cord injury

    *Roman Giger, Herbert Geller, **James Fawcett (Chair)**, John Steeves*

10:00–11:30 A.M.

Smitty Stevens Memorial Ski Race • Lower Bashor

11:30 A.M.–2:00 P.M.

Mountain Lunch • Hazie's (Top of the Steamboat Gondola–Thunderhead Lodge)

3:30–4:30 P.M.

Exhibits and Posters • Sunshine Peak

4:30–6:30 P.M.

49. **Panel** • Storm Peak

    Clinical application of stem cell technologies for CNS Disease

    ***Hans Keirstead (Chair)**, Monica Siegenthaler, Aileen Anderson, Matt Blurton-Jones, Brian Cummings*

50. **Panel** • Mt. Werner

    Clinical effectiveness and mediating factors of modafinil in substance dependence and sleep disorders

    *Gianluigi Tanda, Jed Black, Thomas Newton, **Peter Morgan (Chair)**, Charles O'Brien*

51. **Panel** • Twilight

    Molecular regulation of excitatory synapses

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

52. **Panel** • Rainbow

New functions for new neuropeptides: From feeding/ body weight regulation to drug abuse to chaperone function in neurodegenerative disease

Lloyd Fricker (Chair), *Lakshmi Devi, Dan Morgan, Iris Lindberg*

53. **Panel** • Sunset

Isolation no more: Cross-modal and multisensory influences on cortical function

Matthew Banks, Sarah Pallas, ***Hey-Kyoung Lee (Chair)***, *Patrick Kanold*

54. **Panel** • Skyline

Neuroscience is looking for a few good brains: Funding neuroscience research and training in difficult times

Kathie Olsen, Elliott Albers, ***Kyle Frantz (Chair)***

6:30 P.M.

Business Meeting • Mt. Werner

All are welcome and encouraged to attend.

THURSDAY, JANUARY 30

7:30–9:30 AM

55. **Panel** • Storm Peak

Novel treatments for drug and alcohol dependence

Christopher Rodgman, Colin Haile, ***Thomas Newton (Chair)***, *Steven Brimijoin*

56. **Panel** • Mt. Werner

Location, location, location: Approaches to determining the function of dopamine and dopamine receptors in particular brain regions and cell types

Lauren Dobbs, ***Kim Neve (Chair)***, *Martin Darvas, John Williams*

57. **Panel** • Twilight

Adaptive timing: Coordinating temporal precision across the synapse

Paul Manis, Samuel Young, ***George Spirou (Chair)***, *Leonard Kaczmarek*

58. **Panel** • Rainbow

Neuroactive steroid therapeutics–translational advances on the slopes

Roberta Brinton, Wenbin Deng, Christine Marx, ***A Leslie Morrow (Chair)***

59. **Panel** • Sunset

Impulsivity: What is the underlying circuitry?

Mark Geyer, Ross Baker, ***Steven Potkin (Chair)***, *Mark Hamner*

60. **Panel** • Skyline

The habenula and beyond: New questions, circuits, and roles in motivated behavior

Thomas Jhou (Chair), *Carlos Mejias-Aponte, Eric Turner, Alice Stamatakis*

3:30–4:30 P.M.

Refreshment break • Ballroom Foyer

4:30–6:30 PM

61. **Panel** • Storm Peak

    Navigating the tree line run of drug development over the next decade

    ***David Devilbiss (Chair)**, Daniel Hutcheson, Carrie Jones, Steven Leiser, Paul McCracken*

62. **Panel** • Mt. Werner

    Corticostriatal plasticity and reward-related learning

    ***Jacqueline McGinty (Chair)**, Donna Calu, Susan Marie Ferguson, Alexxai V Kravitz, Colleen Hanlon*

63. **Panel** • Twilight

    Methods to explore the brain: Peptides, light and toxins

    *Leslie Sombers, Ream Al-Hasani, **Stewart Clark (Chair)**, Ines Ibanez-Tallon*

64. **Panel** • Rainbow

    Seizures, autism, neuronal injury and the plasticity of the immature brain: From bench to bedside

    ***Claude Wasterlain (Chair)**, Angus Wilfong, F. Edward Dudek, Jeffrey Ekstrand, Anne Anderson*

65. **Panel** • Sunset

    45 years of motor control: Accounts of where we were and where we are

    Lawrence Young, Jim Bloedel, Ed Keller, **Andrew Schwartz *(Chair)***

66. **Panel** • Skyline

    COMT: From fantasy to fact

    *Amanda Law, **Elizabeth Tunbridge (Chair)**, Daniel Weinberger*

6:30 P.M.

Reception • Ballroom Foyer

7:30 P.M.

Banquet and Dance • Grand Ballroom

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

POSTER SESSION I

SUNDAY, JANUARY 26, 2014 • SUNSHINE PEAK

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. Grouping central serotonin neurons by their networks
Kathryn Commons

P2. Aberrant organization of presynaptic active zones in a Drosophila model of amyotrophic lateral sclerosis
Hong Fei

P3. Defects in synaptic transmission precede motor neuron degeneration in Drosophila models of amyotrophic lateral sclerosis
Mohammad Shahidullah

P4. Prolonged inhibition of RhoA by HSV-mediated gene transfer of C3 transferase enhances corticospinal tract regeneration after spinal cord injury
David Fink

P5. LTD requires "autonomous" CaMKII and involves phosphorylation of S567 on the AMPA Receptor GluA1 subunit
Steven Coultrap

P6. Measuring absolute concentrations of neurotransmitters in vivo with fast-scan controlled-adsorption voltammetry
Christopher Atcherley

P7. Recruitment of serotonergic responses in cardiac vagal neurons during hypoxia and hypercapnia
Peter Byrne

P8. A primate specific and brain enriched miRNA, is involved in major depression and antidepressant treatment
Gustavo Turecki

P9. Genome-wide analysis of MeCP2-mediated transcriptional regulation in the brain
Harrison Gabel

P10. Fast-scan cyclic voltammetry; A new screening tool for anti-depressants
Parastoo Hashemi

P11. A proposed neuronal circuitry underlying reward prediction signaling by dopamine neurons
Tibor Koos

P12. NMDA receptors in primary afferents are potentiated by BDNF released by microglia during the induction of neuropathic pain
Juan Carlos Marvizon

P13. Hypothermia increases synaptic inhibition with effects on GABA-A receptor kinetic properties and drug interactions
David Naylor

P14. Directly testing the functional roles of resting state networks

Stephen LaConte

P15. Causal inference in multisensory speech perception

Michael Beauchamp

P16. Evidence for neuroinflammation in the NS-PTEN KO mouse model of cortical dysplasia with epilepsy

Amy Brewster

P17. Towards a possible animal model for late chronotypes

Sheng Zhou

P18. Brainstem stimulation augments information integration in the cerebral cortex of desflurane-anesthetized rats

Anthony Hudetz

P19. Roles of the unique α4:α4 agonist binding site in the (α4)(β2)2-nicotinic acetylcholine receptor isoform in a form of positive allosteric modulation and in desensitization of functional responses

Ronald Lukas

P20. Mathematical and voltammetric evidence for dual-transport of serotonin *in vivo*

Kevin Wood

P21. Activity of locus coeruleus norepinephrine neurons during behavioral response inhibition

Matthew Riedy

P22. Chronic intermittent hypoxia/hypercapnia diminishes excitatory glutamatergic, but does not alter inhibitory neurotransmission to cardiac vagal neurons in the dorsal motor nucleus

Ned Cauley

POSTER SESSION 2

MONDAY, JANUARY 27, 2014 • SUNSHINE PEAK

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.

P23. PDE5 inhibition does not improve object memory performance in rats after environmental enrichment

Sven Akkerman

P24. Discovery and characterization of a G protein-biased agonist that inhibits β-arrestin recruitment to the D2 dopamine receptor

David Sibley

P25. Hippocampal network disruptions after diffuse brain injury in swine

John Wolf

P26. Mitochondrial DNA: An early biomarker of preclinical Alzheimer's disease

Ramon Trullas

P27. Super-physiological pharmacology by mGlu4 receptor positive allosteric modulators

Robbin Brodbeck

P28. Circadian regulation of visual function: control of contrast sensitivity by a dopamine → NPAS2 → cyclic AMP signaling pathway in retinal ganglion cells

Michael Iuvone

P29. mTOR pathway hyperactivity in a mouse model of cortical dysplasia with epilepsy is associated with alterations in the Kv1.1 potassium channel

Anne Anderson

P30. Augmented inhibition from WIN55,212-2 sensitive interneurons diminishes CA1 output after traumatic brain injury

Akiva Cohen

P31. Photoactivation of fibers originating from parvocellular neurons in the paraventricular nucleus of the hypothalamus releases oxytocin in the brainstem

Heather Jameson

P32. GAT1 expression in human brain: alternate transcripts, expression in development, and potential relationships to brain function and schizophrenia

Michelle Mighdoll

P33. Dopaminergic resetting of circadian food anticipatory activity rhythms in the rat

Ralph Mistlberger

P34. Neuroticism scores predict the impact of acute tryptophan depletion in subgenual cortex

Olaf B. Paulson

P35. Up-regulation of mGlu5 receptors in brain—A new common feature of antidepressant drugs action

Andrzej Pilc

P36. *In vivo* and *in vitro* zebrafish models for CNS axonal regeneration after injury

Jeffery Plunkett

P37. Synaptic protein changes in the posterior cingulate in the progression of Alzheimer's disease

Stephen Scheff

P38. Optogenetic assessment of heterosynaptic suppression of inputs in the ventral striatum

Julie Brooks

P39. A general theory of intertemporal decision-making and time perception

Vijay Mohan K Namboodiri

P40. HspB1 silences translation of PDZ-RhoGEF by enhancing miR20a and miR128 expression to promote neurite extension

Marina Mata

P41. Optogenetic stimulation of locus coeruleus noradrenergic neurons increases inhibitory neurotransmission to parasympathetic cardiac vagal neurons in the nucleus ambiguus

David Mendelowitz

P42. Possible attenuation of the subjective effects of alcohol by the antiepileptic carisbamate in participants with alcohol-use disorder

Christopher Rodgman

P43. Circadian adaptation improves sleep, vigilance, and heart rate variability of night shift workers

Diane B. Boivin

P44. Neuroprotective effects of the natural compounds resveratrol and piceid

Jane Cavanaugh

POSTER SESSION 3

TUESDAY, JANUARY 28, 2014 • SUNSHINE PEAK

*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.*

P45. Long-term effects of estradiol on network-level activity in dissociated rat hippocampus

Alexander Calhoun

P46. Developmental antioxidant treatment prevents abnormalities in a rat model of schizophrenia

Gwendolyn Calhoon

P47. Genetic dissection of cerebellar circuitry in cognitive, social, and affective behavior

Erik Carlson

P48. Extrasynaptic NMDA receptor modulation of fast-spiking interneurons

Eastman Lewis

P49. Ryanodine receptor channels mediate critical sub-cellular calcium signals during normal and optogenetically enhanced neuronal regeneration in C. elegans

Christopher Gabel

P50. Influence of M1 and M4 muscarinic acetylcholine receptor activation on sleep/wake architecture, quantitative electroencephalography and cognition

Robert Gould

P51. Neuropeptide PACAP-induced modifications in Kv2.1 channel provides neuroprotection against cerebral ischemia/reperfusion injury

Raeesa Gupte

P52. Pharmacological and functional properties of triheteromeric GluN1/GluN2A/GluN2B NMDA receptors

Kasper Hansen

P53. Mu opioid receptors hyperpolarize respiratory-controlling Kölliker-Fuse neurons

Erica Levitt

P54. H3.3 nucleosomal dynamics regulate synaptic development and plasticity in post-replicative neurons

Ian Maze

P55. Activation of noradrenergic locus coeruleus neurons promotes anxiety- like and aversive behaviors

Jordan McCall

P56. Characterization of a novel JNK-mediated mechanism of cannabinoid tolerance

Daniel Morgan

P57. Effects of transient overexposure of Neuregulin-3 during early postnatal development on adult behaviors related to schizophrenia

Clare Paterson

P58. Non-vesicular release of dopamine by ventral tegmental area projections to the lateral habenula

David Root

P59. Molecular and circuit basis of impaired hippocampal-prefrontal synchrony in a mouse model of the 22q11-microdeletion

Andrew Rosen

P60. Imaging the ultra-structure of inositol trisphosphate receptors using super-resolution microscopy

Ian Smith

P61. Central glucagon-like peptide-1 receptors play a critical role in cocaine taking and seeking in rats

Heath Schmidt

P62. Locus coeruleus optoICSS: Selective noradrenergic activation's role in reinforcement

Karl Schmidt

P63. The somatodendritic K+ channel Kv2.1 regulates neuronal resilience and death in response to HIV-1 gp120

Andrew Shepherd

P64. Direct hippocampal-prefrontal input supports spatial working memory

Timothy Spellman

P65. NPCs cultured at physiologically relevant oxygen tensions have a survival advantage following transplantation

Sybil Stacpoole

P66. Acute but not chronic effects of NMDA receptor antagonism on EEG and ERPs in awake-behaving rats

Elyse Sullivan

POSTER SESSION 4

WEDNESDAY, JANUARY 29, 2014 • SUNSHINE PEAK

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.

P67. Nav1.6 somato-dendritic localization in hippocampal neurons is via an ankyrinG-independent mechanism

Elizabeth Akin

P68. Phosphodiesterase 4 inhibition differentially regulates GluN2B and GluA1 receptor phosphorylation *in vivo* and *in vitro*

Gretchen Snyder

P69. Clinical, genetic and cellular findings in Christianson Syndrome

Eric M. Morrow

P70. Changes in gene expression in the CNS of myostatin and insulin-like growth factor 1 genetically-modified mice

Sonsoles de Lacalle

P71. Chronic epileptic encephalopathy in adult patients with bilaterally synchronous frequent and/or prolonged subclinical epileptiform discharges

Denson Fujikawa

P72. Progesterone suppresses the development, but not expression, of cocaine choice under concurrent reinforcement in female rats

Tod Kippin

P73. Bidirectional control of lateral habenula neurons by release of glutamate and GABA from ventral tegmental area inputs

Carlos Mejias-Aponte

P74. Nucleus accumbens synaptic plasticity in a genetic mouse model of bipolar mania

Puja Parekh

P75. Induction of endoplasmic reticulum-plasma membrane contacts is a non-conducting function of the Kv2.1 voltage-gated potassium channel

Philip Fox

P76. The Rocky Mountain multiple sclerosis center tissue bank provides tissue to researchers around the globe

Kristina Bliss

P77. Impulsivity, perfectionism and serotonin regulation in anorexia nervosa

David Jimerson

P78. BDNF modulation of parasympathetic cardiac vagal neurons located in the nucleus ambiguus

Ryan Bateman

P79. Antagonism of lipopolysaccharide activation of nodose ganglion neurons by CP 55,940

Gaylen Edwards

P80. Effects of spinal cord injury on firing properties of identified neurons in the mouse spinal cord

Ronald Harris-Warrick

P81. Safety assessment of an intraspinal cell delivery system in yucatan mini-pigs

Tanya Wyatt

P82. Navigating the tree line run of drug development over the next decade

David Devilbiss

P83. Methadone maintenance and HIV risk in Ukraine

George Woody

P84. Examination of dopaminergic modulation of corticostriatal information processing in an animal model of Huntington's disease

Cameron Pollock

P85. Ablation of the inhibitor of DNA binding 4 (Id4) gene results in effects on circadian clock function

Giles Duffield

P86. FRET analysis of GluA2 AMPA receptors reveals structural rearrangement within the C-terminal domain during receptor activation

Anders S. Kristensen

Session Abstracts

PANEL • SUNDAY, 4:30–6:30 PM • STORM PEAK

1. Oxidative tress in psychiatric disorders

Chair: Patricio O'Donnell
Presenters: Elliot Hong, Ana Andreazza, Akira Sawa, Patricio O'Donnell

There is increasing evidence that oxidative stress may play a role in schizophrenia and bipolar disorder. In recent years, sophisticated clinical measures are unveiling links of oxidative stress markers with disease domains. In addition, preclinical work is converging in identifying oxidative stress as a key element in pathophysiological states in diverse animal models. This panel will overview these issues, presenting unpublished data that will move the field forward by identifying oxidative stress as a pathophysiological mechanism in these disorders. Elliot Hong will discuss clinical evidence of increased oxidative stress and evidence of endogenously low glutathione levels in schizophrenia patients, and will present new findings that oxidative stress negatively impacts brain pathophysiology as measured by clinical brain imaging and electrophysiology. Ana Andreazza will review the differences between mitochondrial dysfunction and oxidative stress pathways in moof disorders and schizophrenia and the link between peripheral oxidative damage to lipids and white matter abnormailities in the same disorders. Akira Sawa will present data of increased oxidative stress in genetic models as well as data from patient-derived lymphoblasts and olfactory neuronal cells showing indicating increased oxidative stress and a correlation with cognition and clinical phenotypes. Patricio O'Donnell will present data showing juvenile antioxidant treatment prevents oxidative stress (largely in parvalbumin prefrontal interneurons) and diverse neurochemical, electrophysiological, and behavioral deficits in a developmental rodent model (rats with a neonatal ventral hippocampal lesion). Overall, the panel will highlight oxidative stress as a cellular process possibly involved in the expression of behavioral traits characteristic of psychiatric disorders.

PANEL • SUNDAY, 4:30–6:30 PM • MT. WERNER

2. Neural mechanisms of drug-altered decision-making

Chair: Kate Wassum
Presenters: Kate Wassum, Geoffrey Schoenbaum, Sean Ostlund, Benjamin Saunders

A central hypothesis of recent addiction research is that drug addiction can be understood in terms of the brain's associative reward-learning and motivational

systems, that the effects of drug exposure must be interpreted in behavioral and cognitive terms if drug addiction is to be understood. In this panel we will discuss how chronic use of or repeated exposure to addictive substances can alter fundamental associative learning and motivational processes to produce aberrant drug-seeking and -taking behavior and how these behavioral effects are mediated by the brain. We will present mostly unpublished research wherein well-established behavioral paradigms designed to parse the discrete psychological components of reward-learning and motivation were used in combination with recording and interference methods in rodents with a history of drug exposure or self-administration. We focus on two substances: opiates and cocaine, and provide evidence that, although both are highly addictive, the underlying mechanisms through which they lead to addiction may be different. Kate Wassum (UCLA) will present data showing that withdrawal from chronic opiate exposure produces aberrant reward seeking by inflating reward value via a basolateral amygdala mu opioid receptor-dependent process. Geoffrey Schoenbaum (NIDA) will present data showing that orbitofrontal-dependent functions that support both inference-based behavior and learning are disrupted by experience self-administering cocaine. Sean Ostlund (UCLA) will present work on the role of mesolimbic dopamine signaling in Pavlovian incentive motivation and how this is impacted by repeated cocaine exposure. Lastly, Benjamin Saunders (UCSF) will discuss optogenetic and pharmacological evidence that dopamine contributes to both adaptive conditioned motivational processes and maladaptive drug craving.

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

3. Endocannabinoid function in the brain reward system and the continued pursuit of bliss

Chair: Carl Lupica

Presenters: Carl Lupica, Loren (Larry) Parsons, Joseph Cheer, Stephanie Borgland

Endocannabinoids (eCBs) are released in brain reward circuits to mediate long- and short-term changes in synaptic transmission and alter reward-related behavior during exposure to abused drugs. Cellular studies show that the eCB, 2-arachidonoylglycerol (2-AG), is released from midbrain dopamine (DA) neurons to act as a retrograde messenger and inhibit synaptic GABA and glutamate release onto these cells. Our understanding of eCBs in reward circuits has also recently expanded to include alterations in these pathways by natural rewards. This panel will explore mechanisms in which eCBs are released during intake and pursuit of drug and food rewards, and will examine their roles in regulating motivation. Carl Lupica (NIDA-IRP) will provide an overview of the sites of eCB action in brain reward circuits and will describe mechanisms for 2-AG release from ventral tegmental area (VTA) DA neurons

by psychostimulants. Larry Parsons (Scripps) will discuss sensitization of nicotine-induced increases in 2-AG formation in the VTA by nicotine, and how this increases DA neuron activity via reduced GABA release. He will also demonstrate that inhibition of 2-AG synthesis restores normal GABAergic signaling in the VTA of nicotine-dependent rats to attenuate nicotine self-administration. Joe Cheer (University of Maryland) will show that eCBs facilitate mesolimbic DA release to alter control of behavioral timing necessary for responding under fixed-interval schedules of reinforcement. Stephanie Borgland (University of Calgary) will describe synaptic alterations in the VTA initiated by consumption of sweetened, high-fat food, and increased insulin levels. These changes initially include a 2-AG-dependent form of long-term depression at glutamate synapses on VTA DA neurons, followed days later by an increase in glutamatergic synaptic strength. Together, the participants in this panel will describe novel roles for eCBs in the brain reward circuitry that impact motivated behavior.

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

4. Putting the ice on stress, aging and CNS trauma

Chair: Kelli Sharp
Presenters: Monika Fleshner, Nicole Berchtold, Monica Siegenthaler, Kelli Sharp

An extensive literature demonstrates that exercise and an enriched environment modulate the health and resilience of the brain and spinal cord. In this panel, we present new molecular and behavioral data revealing the potential of physical and cognitive activity to modulate resistance to stress across the lifespan, gene expression in the human brain, and efficacy of therapeutic interventions for SCI. Monika Fleshner (University of Colorado) will discuss recent findings that benefits of exercise for resisting stress are more enduring if exercise is initiated in juveniles versus as adults. The nature of neural and peripheral adaptations produced by adolescent running that result in stable changes in stress neurocircuitry and responsivity will be examined. Nicole Berchtold (University of California, Irvine) will present microarray data characterizing human brain gene expression profiles associated with cognitively/socially enriched versus isolated lifestyles, in aged individuals. Differences in regional responses will be presented, using data from the frontal cortex (BA9/46), posterior cingulate (BA23), hippocampus, and motor association region (BA6/8). Monica Siegenthaler (California Stem Cell, Inc) will discuss data that exercise acts as an adjuvant to enhance the regenerative potential of human embryonic stem cell-based therapies for neurodegenerative diseases. In particular, the differentiation, purity, and migration of transplanted oligodendrocyte progenitor cells into the spinal cord (SC) following SC injury (SCI) are enhanced by post-transplant exercise. Finally, Kelli Sharp (University of California, Irvine) will present data

from preclinical and clinical models that activity-dependent training paradigms modulate functional recovery following SCI. These findings will help elucidate underlying mechanisms of successful rehabilitation training, and will provide important guidance for future human clinical trials.

PANEL • SUNDAY, 4:30–6:30 PM • SUNSET

5. Regulation of cytoskeletal and membrane functions during growth cone guidance

Chair: Paul Letourneau

Presenters: Paul Letourneau, Jonathan Terman, Yimin Zou, John Henley

Motile growth cones lead growing axons along routes through embryonic tissues to targets where neural circuits are assembled. These growth cone behaviors subside as axons switch their activities from elongation to synaptogenesis. However, the return of growth cone motility after disease or injury may be critical to regenerate and repair damaged neural circuits. This panel will discuss research from four laboratories on the mechanisms that regulate growth cones. The speakers will focus on cytoskeletal and membrane functions as key components of the navigational behaviors of growth cones. These may also be potential targets for therapeutic innovations for axon regeneration. Paul Letourneau (University of Minnesota) will describe roles of three actin binding proteins, ADF, radixin, and Arp2/3, in mediating the regulation of growth cone actin dynamics by attractive and repulsive guidance cues. Jonathan Terman (University of Texas Southwestern Medical Center) will describe recently identified redox enzymes, MICALs, that specifically oxidize and disassemble actin filaments and mediate growth cone guidance by the semaphorin family of axon guidance cues. Yimin Zou (UC-San Diego) will describe how regulatory pathways for planar cell polarity and apical basal polarity interact with each other in mediating growth cone attractive responses to Wnt signaling proteins. Several Wnt proteins are re-expressed after spinal cord injury. John Henley (Mayo Clinic-Minnesota) will discuss signaling pathways that control the adhesive behaviors of growth cones. Integrin adhesive receptors are downregulated by inhibitory extrinsic ligands, while upregulation of integrin function promotes axonal regeneration.

6. Gonadotropin releasing hormones: A comparative approach to multiple forms and functions

Co-Chairs: Mary Ann Ottinger and Yonathan Zohar
Presenters: Yonathan Zohar, Jean Harry, Nancy Sherwood

Gonadotropin releasing hormone (GnRH) is an old gene phylogenetically, with complex actions including controlling reproductive function and signaling within the brain. There are remarkable differences in the genes encoding GnRH and variations in the 10 amino acid sequence across species, as well as in the number of GnRH forms per species. The cascade of neural events involved in GnRH actions transcends species, with critical developmental events that depend on specific modulators and signals. Early developmental events and exposure to toxins and other environmental challenges have the capacity to influence these processes. Using a range of vertebrate and invertebrate models to ask specific research questions allows us to gain an understanding of both developmental and functional processes. Additionally, transgenic models provide the ability to manipulate gene expression of selected genes in order to clarify their role. This session will examine novel comparative models and their utility in revealing key aspects of the function of the GnRH system. Speakers and the topic that they will address include: Yonathan Zohar, who will discuss fish models to unravel the functional significance of GnRH multiplicity and the regulation of the GnRH system. Nancy Sherwood will present studies that illuminate the evolution of GnRH structure and function. Jean Harry will discuss neuroinflammatory processes and aging as affected by exposure to environmental chemicals. Mary Ann Ottinger will address the impacts of endocrine disruptors on GnRH neurons and neuroendocrine systems. Discussion will focus on the attributes of each of these models and what each brings to understanding GnRH regulation of puberty, reproductive activity and neuronal aging.

PANEL • SUNDAY, 8:30–10:00 PM • STORM PEAK

7. Neural antecedents to adolescent and adult antisocial and substance-use disorders

Chair: Thomas Crowley
Presenters: Thomas Crowley, Sophia Schneider, Stuart White, Jean Liu

The addiction field has made vast advances by asking how drugs alter brain functions, thereby driving continued drug self-administration. However, substance use disorders and their frequently comorbid antisocial disorders have significant joint heritability, posing an additional, less-studied question: what heritable neural mechanisms establish in some brains—before any drug exposure—robust vulnerabilities to develop substance and antisocial problems? Members of this panel attempt to disentangle in human studies the antecedent from the drug-induced brain dysfunction. Thomas Crowley (Univ. of Colorado Denver) will review evidence for childhood predictors (familial, behavioral, electrophysiological) of adolescent and adult substance and antisocial problems. His fMRI studies show widespread hypoactivity during risky decision-making in adolescents with serious conduct and substance problems. Sophia Schneider (Univ. Med. Center Hamburg-Eppendorf) does fMRI studies in adolescents, who are often described as risk-taking, impulsive, and vulnerable to substance abuse. She relates greater adolescent risk-taking to hypoactive reward structures (as often seen in addicted adults), emphasizing those structures' role in individually different predispositions to addiction. Stuart White (NIMH/NIH) studies decision-making deficits in youths at risk for antisocial behavior. His model-based fMRI work shows dysfunction in these youths' decision-related prediction-error computations. He will discuss theoretical and potential clinical applications of his data with particular reference to DSM-5's new specifier for conduct disorder, "with limited prosocial emotions". Jean Liu (Mind Research Network) will present her findings on genetic copy-number variations and alcohol dependence, as well as brain activation patterns elicited by alcohol cues, smoking cues, and combined cues.

PANEL • SUNDAY, 8:30–10:00 PM • MT. WERNER

8. Cortical dysfunction in Rett Syndrome: Opportunities for new treatment development

Chair: Frank Menniti
Presenters: Frank Menniti, Michela Fagiolini, Alysson Muotri, Lucas Pozzo-Miller

Rett Syndrome (RTT) is a developmental disorder caused by disruptions in the X-linked transcriptional repressor MECP2. Carriers suffer developmental regression at 6-18 mo that leaves them without speech and hand control, autistic features, seizures, and autonomic deficits. Disruption of cortical/

hippocampal function in RTT underlies these symptoms and the panel will present new approaches to remediate these defects. Frank Menniti (Mnemosyne Pharmaceuticals) will review current treatments for RTT and the evidence that RTT symptoms result from loss of MeCP2 function in cortex. Michela Fagiolini (Children's Hospital, Boston) will speak about the regression of visual function in MeCP2 KO mice. These studies reveal NMDA receptor signaling defects mediates the effects of MeCP2 lesion and that manipulation of such signaling ameliorates defects in MeCP2 KOs. Alysson Muotri (UCSD) focuses on astrocyte dysfunction as a mediator of MeCP2 lesion in astrocytes and neurons derived from human RTT iPSCs. RTT astrocytes have altered gene expression, calcium wave propagation, cytokine regulation and glutamate uptake whereas RTT neurons have morphological and functional deficits similar to those observed in MeCP2 KOs and human pathological samples. Co-cultured of RTT-derived neurons with healthy astrocytes rescues neuronal deficits, demonstrating that astrocytes can restore RTT neuronal homeostasis. Lucas Pozzo-Miller (U. Alabama) will discuss MeCP2 deletion on hippocampal network excitability, synaptic structure, and plasticity in mouse brain slices. MeCP2 dysfunction impairs BDNF signaling through the TrkB-TRPC3/6 signaling cascade, which in turn prevents the proper development of GABAergic synaptic inhibition in area CA3. The panel will discuss how the growing understanding of the pathological basis for disruption in cortical activity in RTT will lead to new treatments that relieve symptoms or, ideally, prevent the developmental regression to slow or halt the disease course.

PANEL • SUNDAY, 8:30–10:00 PM • TWILIGHT

9. Ion channel subunit interactions: Combinations and consequences

Chair: Ian Forsythe
Presenters: Chen Gu, Leonard Kaczmarek, Ian Forsythe

Potassium channels play diverse roles in regulating neuronal excitability and various interactions influence subunit association, channel properties and physiological function. In this panel we will explore three different aspects of Kv3 subunit interaction which are critical in regulating neuronal excitability and in fast spiking and rapid repolarization at high firing rates. Chen Gu (Ohio State University) will describe Kv3 channel assembly, transport and activity are regulated by zinc through different sites: influencing subunit tetramerization, axonal transport and targeting through intracellular and extracellular zinc binding sites. Len Kaczmarek (Yale University) will describe experiments demonstrating that the cytoplasmic C-terminal domain of Kv3.3 interacts with WAVE3, a protein that regulates actin nucleation through the Arp2/3 complex, and with Hax-1 a protein that is required for the survival of cerebellar neurons and that also interacts with the actin cytoskeleton. Kv3.3 is expressed at high

levels in the cerebellum, and inherited human mutations in Kv3.3 result in cell death of cerebellar neurons, a condition known as Spinocerebellar Ataxia 13 (SCA13), causing widespread cerebellar degeneration. The experiments suggest that these protein-protein interactions link opening of the channel to assembly of actin filaments and to cell survival. Ian Forsythe (University of Leicester, UK) has examined the distribution of Kv3 currents in the auditory brainstem and used laser micro-dissection to identify the relative contribution of mRNA for each subunit within the key nuclei and combined this with evidence from knockout animals to test how the absence of Kv3.1 or Kv3.3 subunits changes the properties of native Kv3 currents. These different approaches illustrate the range of mechanisms and invite discussion about trafficking, activity and function of Kv3 channels which underlying physiological processing and neuronal survival.

PANEL • SUNDAY, 8:30–10:00 PM • RAINBOW

10. Non-conventional modes of neurotransmission in the CNS: Do we need a new vocabulary?

Chair: Louis-Eric Trudeau
Presenters: Louis-Eric Trudeau, Alex Hoffman, Javier Stern, Vladimir Parpura

The discovery and characterization of chemical neurotransmission in the nervous system initiated many decades ago lead to the establishment of a classical model describing a well-defined sequence of events, starting with the release of neurotransmitters from axon terminals, the diffusion of neurotransmitters across a narrow synaptic cleft and the action of these neurotransmitters on local receptors situated right across the cleft on the dendrite or cell body of the target cell (the postsynaptic density). Research in the past two decades has gradually expanded the repertoire of cell-to-cell signaling mechanisms in the nervous system to the point where previously well-defined terms such as « synaptic », « pre-synaptic » and « post-synaptic » have become limiting and confusing. In this panel, multiple examples of non-conventional modes of neurotransmission will be presented and a new vocabulary will be proposed in the hope of clarifying this issue and the language. First, Louis-Eric Trudeau (University of Montreal) will provide an overview of neurotransmitter release from dopamine neurons, including axonal dopamine release, but also synaptic glutamate release and somatodendritic dopamine release. Alex Hoffman (NIDA) will discuss new anatomical and electrophysiological data suggesting non-vesicular dopamine release in the lateral habenula. Javier Stern (Georgia Regents University) will then describe

new work on the mechanisms and functions of dendritic peptide release. Finally, Vladimir Parpura (University of Alabama) will provide an overview of chemical transmitter release from glial cells, a process that occurs without the need for an axon terminal.

PANEL • SUNDAY, 8:30–10:00 PM • SUNSET

11. The light and dark sides of mu and delta opioid receptor heterodimerization: analgesia versus analgesic tolerance

Chair: George Wilcox
Presenters: Lakshmi Devi, Wakako Fujita, Helene Beaudry, George Wilcox

Recent studies suggest that dimerization of G protein-coupled receptors, including opioid receptors, importantly impacts receptor maturation, signaling and/or trafficking. Heterodimerization among opioid receptors or between opioid receptors and other G protein-coupled receptors is thought to affect the pharmacological properties of opioids. The functional consequences of the heterodimerization between mu (MOR) and delta (DOR) opioid receptors is the subject of this panel, which features structural and functional probing of these heterodimers in mammalian central nervous system (CNS). Lakshmi Devi (Icahn School of Medicine at Mt Sinai, New York NY) will introduce the panel with a brief background on MOR and DOR anatomy, pharmacology and physiology. Wakato Fujita (Icahn School of Medicine at Mt Sinai) will describe the identification of compounds specifically targeting MOR-DOR heterodimers using high throughput screening of a library of small molecules. George Wilcox (Univ of Minnesota, Minneapolis MN) will present recent pre-clinical work demonstrating that MORs and DORs likely co-localize in peptidergic nociceptive afferent terminals and that the analgesic synergy between select MOR and DOR agonists in the spinal cord depends on the presence of the epsilon isoform of protein kinase C (PKC). This dependence reinforces the co-localization of the receptors in afferent terminals. Helene Beaudry (Univ of Sherbrooke, Sherbrooke, Quebec) will discuss her recent studies showing that, assuming delta-2 pharmacology mirrors that of MOR-DOR heteromers, those heteromers likely participate in the development of morphine analgesic tolerance; targeting DOR with antagonists may provide a valuable strategy to reduce analgesic tolerance accompanying repeated morphine administration in chronic inflammatory pain patients. Overall, attendees at this panel will gain an improved understanding of opioid receptor localization, heterodimerization, coupling and production of analgesia. coupling and production of analgesia.

PANEL • SUNDAY, 8:30–10:00 PM • SKYLINE

12. Mechanisms which may mediate depression

Chair: Fritz Henn

Presenters: Minh-Hu Han, Rosemary Bagot, Ronald Seese, Fritz Henn

Critical components in the circuit driving major depression appear to involve the prefrontal cortex, hippocampus—amygdala pathways and a summation of outputs from these areas in the l. habenula. Using two distinct well documented animal models of depression, chronic social defeat stress (CSDS) and congenital learned helplessness we found several pathological alterations. Initially Han showed that pathological alterations in animals that became depressed through CSDS could be made resilient by extending and increasing the pathological changes. Bagot using opticogenetics and sequencing examined the plasticity of glutaminergic neurons from the N. Accumbens and found opposing roles for ventral hippocampal projections and prefrontal cortical projections to the N. accumbens. Seese will discuss the consequences of increased glutaminergic activity on cortical synapses and will show in congenital learned helplessness there is as much as a 40 % decrease in synaptic contacts in some cortical areas. Henn will discuss the pathology in the l. habenula of congenital helpless animals as revealed by proteomics and briefly discuss the outcfome of the initial 4 cases of intractable depression to be treated with DBS to reduce the chronic overactivity in this structure initially found in learned helpless animals and substantiated in imaging studies of patients.

PANEL • MONDAY, 7:30–9:30 AM • STORM PEAK

13. Midbrain systems and the regulation of aversion and reward

Chair: Ryan LaLumiere

Presenters: Elyssa Margolis, Thomas Jhou, Ryan LaLumiere, Mitchell Roitman

Reward and aversion signaling are critical neural processes that guide an organism's ongoing behavior as well as alter neural plasticity to influence future behavior. The mechanisms by which reward and aversion are signaled in the brain have been of considerable interest for both normal behavioral processes and those related to drugs of abuse. Recent work has suggested that both types of signaling are mediated through midbrain systems, including the mesocorticolimbic dopamine pathway, though the precise mechanisms for how aversion and reward are differentially signaled remains a major area of investigation. This panel will discuss recent findings addressing this issue, both with "natural" rewarding and aversive stimuli and with drugs of abuse. First, Elyssa Margolis (Gallo Institute, University of California, San Francisco) will present data on how mu opioid receptor activation of ventral tegmental area (VTA) dopamine neurons, a necessary component for morphine reward,

can be mediated by P-type calcium channels and how the effects of such activation sort by projection targets of the VTA dopamine cells. Second, Thomas Jhou (Medical University of South Carolina) will discuss recent findings on the role of the rostromedial tegmental nucleus (RMTg) and its afferents in reward-seeking despite negative outcomes. This behavior is a key element of both addictive and manic behavior. Ryan LaLumiere (University of Iowa) will discuss findings on midbrain systems, including the RMTg and mesocorticolimbic dopamine projections, that play a role in the extinction and suppression of cocaine-seeking behavior. Finally, Mitch Roitman (University of Illinois at Chicago) will present recent work, using real-time recording techniques in behaving rats, showing how changes in motivational states modulate the differential dopamine signaling in the nucleus accumbens related to reward versus aversive taste stimuli.

PANEL • MONDAY, 7:30–9:30 AM • MT. WERNER

14. Regulation of the dendritic spine actin cytoskeleton and membrane trafficking in health and disease

Chair: Mark Dell'Acqua
Presenters: Mark Dell'Acqua, Gareth Thomas, Peter Penzes, Scott Soderling

Experience-dependent plasticity at excitatory synapses is controlled by signaling pathways that regulate dendritic membrane trafficking and the actin cytoskeleton to coordinately modify synaptic strength and dendritic spine structure. Importantly, structural and functional plasticity in spines supports normal learning and memory, and alterations in dendritic spine structure and postsynaptic function are associated with nervous system disorders including Alzheimer's, Down syndrome, Fragile X, autism, and schizophrenia. Mark Dell'Acqua (University of Colorado) will introduce the panel and highlight recent studies showing how palmitoylation of the postsynaptic scaffold protein AKAP79/150 by the palmitoyl acyltransferase DHHC2 controls dendritic endosomal trafficking pathways that regulate spine structure and synaptic potentiation. Gareth Thomas (Temple University) will then present new findings implicating direct palmitoylation of LIM Kinase-1 as a novel regulatory mechanism that is critical for spine-specific actin polymerization, structural plasticity and long-term spine stability. Importantly, recent clinical genetic studies have identified a number of synaptic proteins as genetic substrates of risk for mental disorders, including schizophrenia and autism. Accordingly, Peter Penzes (Northwestern University) will present new data on the roles of these synaptic mental disorder susceptibility genes in regulating postsynaptic structure and function. Finally, Scott Soderling (Duke University) will discuss recent findings showing how actin-regulatory signaling complexes control spine structure and synaptic function and how abnormalities in this pathway may be associated with specific features of Fragile-X Syndrome.

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

15. To amphetamine and beyond! Exploring neural mechanisms of drug and non-drug reinforcers

Chair: Chris Olsen

Presenters: Luis de Lecea, Ralph DiLeone, Chris Olsen, Lique Coolen

The focus of this panel will be to discuss recent developments in our understanding of reward processing and compare/contrast findings from non-drug reinforcers and drugs of abuse. We will explore rewards ranging from sugar, opiates, and sex, to amphetamine and beyond. Luis de Lecea (Stanford School of Medicine) will describe a new circuit linking the hypothalamus, norepinephrine and the parabrachial area with aversion to food. Ralph DiLeone (Yale School of Medicine) will talk about a novel role for vitamin D in modulating mesolimbic function, with consequences for both food and drug intake. Chris Olsen (Medical College of Wisconsin) will present data characterizing drug and non-drug reward-related behaviors in the leptin deficient obese (ob/ob) mouse. Lique Coolen (University of Mississippi Medical Center) will present data that demonstrate that methamphetamine exposure promotes compulsive sexual behavior, which can in turn trigger future drug seeking.

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

16. Immune regulation in neurovascular unit in cerebrovascular disorders and MS

Chair: Jaroslaw Aronowski

Presenters: Gregory del Zoppo, Dale Pelligrino, Douglas Feinstein, Paula Dore-Duffy

NVU play active roles in regulating immune homeostasis of diseased brain. Understanding the participation of glia in this process may help to identify new targets with therapeutic potential. Jaroslaw Aronowski will discuss the role neurons play in modulating the polarity of microglia toward M2 "healing" phenotype after stroke and how this neuron-mediated effect utilizes PPARg and RXR. Gregory del Zoppo—ICH during ischemic stroke necessitates leakage of the cerebral microvessel permeability barrier, a condition also seen with edema formation. The extravasation of the plasma matrix proteins vitronectin and fibronectin during edema formation and hemorrhage are associated with differential release of matrix proteases from microglia (by integrin-mediated processes), and are associated with microvessel basal lamina degradation. He will discuss these processes, and the role of integrin expression in the development of microvessel permeability. Paula Dore-Duffy will discuss the role of the pericytes in regulation of leukocyte infiltration and regulation of

T-cell polarity from THI and TH2 phenotypes—in particular the role of the pericyte in neurodegenerative disease models. Dale A. Pelligrino will explore the neuroinflammatory pathways and neuropathologic implications associated with extracellular release of S100β from astrocytes following subarachnoid hemorrhage. Treatment options and the role of RAGE will also be considered. Douglas Feinstein will discuss findings that the MS drug Tecfedera (DMF-dimethyl fumarate) not only acts to suppress T-cell, but has additional antiinflammatory effects in glial cells. DMF inhibits inflammation via Nrf2 activation and suppression of NF-kappaB. Also, DMF induces expression of M2 genes in glial cells and can exert long-term effects by reducing expression of several histone deacetylases. Thus treatment with drugs of this class may lead to long-lasting changes in gene expression that contribute to the beneficial effects seen in MS.

PANEL • MONDAY, 7:30–9:30 AM • SUNSET

17. Connectivity in the psychoses: From genes to neural circuitry

Chair: Anil Malhotra

Presenters: Miklos Argyelan, Steven Potkin, James Kennedy, Anil Malhotra

Conceptual and technical advances in brain imaging research have begun to identify abnormalities in brain connectivity as essential to the pathophysiology of severe psychiatric illness. Massive interconnectivity is a fundamental characteristic of human brains, and can be characterized at both the structural and functional level. Recent data suggests that certain indices of dysconnectivity may be common to schizophrenia and bipolar disorder and shared by first-degree relatives of such patients, suggesting that genetic factors influence connectivity patterns across psychiatric disorders. In this panel, we will present data from neuroimaging studies assessing brain connectivity in psychotic disorders, and discuss early studies seeking to identify the genetic underpinnings of connectivity-related phenotypes. Miklos Argyelan (Zucker Hillside Hospital, NY) will present resting state MRI data suggesting overlap in connectivity phenotypes between schizophrenia and bipolar disorder, as well as new data from an ongoing study examining the role of antipsychotic medications on functional connectivity. Steven Potkin (University of California, Irvine), will report on a large scale study suggesting that connectivity may be related to the manifestation of key clinical phenomena associated with illness, including hallucinations. James Kennedy (University of Toronto, Canada) will review data examining the relationship of genetic variation to white matter integrity, a structural measure of brain connectivity. Finally, Anil Malhotra (Zucker Hillside Hospital, NY), will discuss the role of polyunsaturated fatty acids (PUFAs) on brain connectivity, and new evidence for a specific role of

variation in PUFA-related genes on the development of brain connectivity throughout the lifespan. Taken together, the panel will provide an overview of connectivity studies in the psychoses, as well as discuss data on the genetic contributions to this critical characteristic of CNS activity.

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

18. Individual variation in development of compulsive behaviors: The search for a common mechanism

Chair: Laura O'Dell

Presenters: Jill Becker, Laura O'Dell, Gretchen Neigh, Kelly Klump

When does a behavior become compulsive? Whether it is the transition to compulsive drug use, eating disorders, or anxiety-related behaviors these disorders can all be triggered by common factors and stress is one of the most notable. In this panel we explore why some populations are more likely to exhibit compulsive disorders than others. We examine where there are common mechanisms that modulate compulsive behaviors in different populations, such as adolescents, females, and persons with certain genetic traits. The panel includes researchers working at various levels of analysis to elucidate the factors that promote compulsive behaviors. First, Dr. Jill Becker (University of Michigan) will provide introductory comments and a discussion of brain systems believed to modulate sex differences in stimulant use and abuse. She will discuss the interactions among reproductive hormones and stress system hormones in the expression of drug taking behaviors. Dr. Laura O'Dell (University of Texas El Paso) will compare and contrast age and sex differences in brain substrates believed to modulate tobacco use. She will discuss her latest data that illustrates the unique contribution of stress to enhancing the effects of nicotine in female rats from different states of development. Dr. Gretchen Neigh (Emory University) will present data illustrating that females demonstrate increased anxiety-like and depressive-like behaviors following chronic adolescent stress; whereas, males exhibit changes in metabolism and immune function, and are sensitive to other stressors. The implications for changes in specific pathways will be discussed. Finally, Dr. Kelly Klump (Michigan State University) will discuss the role of ovarian hormones in sex differences in genetic and neurobiological risk for eating disorders. She will discuss data from human and animal models examining developmental trajectories of risk across puberty and early adulthood.

PANEL • MONDAY, 4:30–6:30 PM • STORM PEAK

19. Juvenile social isolation and risk for psychiatric disorders

Chair: Gabriel Corfas
Presenters: Gabriel Corfas, Patricio O'Donnell, J. Amiel Rosenkranz, Kazutoshi Nakazawa

There is compelling evidence that children subjected to social isolation and neglect during early life have severe defects in cognitive function and social behaviors. Furthermore, the alterations caused by isolation are, in many ways, similar to those observed in psychiatric patients, suggesting that the modifications in brain structure, chemistry and function underlying the two endophenotypes might be related. However, the mechanisms underlying the effects of social isolation have remained poorly understood. This panel will discuss recent advances in the understanding on how juvenile social isolation alters brain structure and function, inducing behavioral phenotypes relevant to psychiatric disorders in the adult based on work performed on rodent models.

Gabriel Corfas (Boston Children's Hospital) will provide introductory remarks and will present findings on how juvenile social isolation alters prefrontal cortex myelination, and how this impacts adult prefrontal cortex mediated behaviors, including social interactions and working memory. Patricio O'Donnell (Pfizer) will present data on the impact of adolescent social isolation on dopamine-modulated physiological properties in the prefrontal cortex and the enhanced deleterious effect on behavioral outcomes in a developmental rodent model of schizophrenia. Amiel Rosenkranz (Rosalind Franklin University) will review their studies on the effects of social isolation on social fear learning and amygdala neuronal physiology. Finally, Kazutoshi Nakazawa (University of Alabama at Birmingham) will discuss the links between juvenile social isolation, impairments in the antioxidant defense capacity in parvalbumin-positive interneurons, and NMDARs in schizophrenia-like phenotypes.

PANEL • MONDAY, 4:30–6:30 PM • MT. WERNER

20. Traversing the translation of target-based hypotheses in psychostimulant addiction

Chair: Amy Newman
Presenters: Kathryn Cunningham, Athina Markou, Phil Skolnick, Amy Newman

Preclinical studies have led to the identification of multiple medication targets for the treatment of substance use disorders (SUDs). The recent approval of novel medications (albeit for indications other than SUDs) and new molecular

insights on "old" drugs have led to preclinical and now clinical investigations that are based on strong theoretical rationale regarding the neurobiology of psychostimulant dependence. Kathryn Cunningham will describe studies with the selective 5-HT2CR agonist lorcaserin (Belviq), a recently approved anti-obesity medication. Lorcaserin and investigatory, selective 5-HT2CR agonists do not exhibit abuse liability, but are potent and efficacious inhibitors of psychostimulant self-administration and reinstatement in animal models. Athina Markou will present preclinical data on metabotropic glutamate receptor 2 (mGluR2) positive allosteric modulators (PAMs) that block both the reinforcing effects of nicotine and cocaine, as well as cue-induced reinstatement of nicotine and cocaine seeking, without affecting food motivated behaviors. Some mGluR2 PAMS have reached the clinic for other indications and are slated for testing in a smoking cessation trial. Phil Skolnick will discuss preclinical studies that led to the development of TV-1380, a bioengineered butyrlcholinesterase (BuChR) that hydrolyzes cocaine >1,000-fold more rapidly than wild type BuChR. TV-1380 is currently in a Phase II trial in cocaine-dependent subjects. Amy Newman will discuss Armodafinil, a unique inhibitor of the dopamine transporter, currently prescribed for treatment of sleep disorders. The lack of abuse liability of Armodafinil and its promising effects in preclinical models of psychostimulant abuse has prompted further investigation. Thus, this panel will highlight translational approaches to the treatment of SUDs using both novel molecules and medications originally developed and approved for other indications to translate hypotheses on addiction to the clinic.

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

21. NMDA-receptor signaling in plasticity and death

Chair: Karl Ulrich Bayer
Presenters: Steve Traynelis, Haruhiko Bito, Ulli Bayer, Suzanne Zukin

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, NMDAR stimulation mediates neuronal cell death under ischemic conditions, such as stroke. This panel will present advances in our understanding of how the different patterns of NMDAR stimulation are linked to distinct downstream signaling that leads to these three opposing outcomes. Steve Traynelis (Emory) will introduce the NMDAR and will show how context-dependent NMDAR antagonists can circumvent obstacles in

neuroprotection. Haruhiko Bito (University of Tokyo) will show how distinct NMDAR input patterns can control the balance between two major Ca2+-activated plasticity mediators, the protein kinase CaMKII and the protein phosphatase calcineurin. Ulli Bayer (University of Colorado Denver) will show that "autonomous" CaMKII mediates not only LTP, but also NMDAR-dependent LTD and neuronal cell death. Suzanne Zukin (Albert Einstein) will show how epigenetic mechanisms regulate NMDAR mechanisms in plasticity and neuronal cell death.

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

22. Aggregate prone proteins in neurodegenerative disorders: Uncovering new mechanisms and discovering novel therapeutics

Chair: Warren Hirst
Presenters: Warren Hirst, Anurag Tandon, Ai Yamamoto, X. William Yang

Protein misfolding and aggregation is a pathological hallmark of many neurodegenerative disorders and is hypothesized to underlie the pathophysiology of these diseases. These processes are affected by a variety of factors including molecular chaperones, clearance pathways (ubiquitin proteasome and autophagy-lysosomal system), mutations, post-translational modification, seeding and spreading, energy deficits and protein damage. As we increase our knowledge of these mechanisms, new approaches offer themselves for therapeutic intervention—which will be presented in this panel.

Warren Hirst (Pfizer) will present on the effects of tau and α-synuclein on autophagy flux *in vitro* and *in vivo*, and will describe new cellular assays used to identify novel molecules that stimulate autophagy. Ai Yamamoto (Columbia University) has identified a key player in the selective autophagic degradation of protein aggregates known as Alfy, and have been using it to determine the toxic role of aggregates, both in the context of disease onset and propagation, as well as disease reversal in Huntington's disease models. Anurag Tandon (University of Toronto) will present the effects of phosphorylation of a key residue on α-synuclein, serine-129, on the folding, membrane binding and cellular uptake of this protein. William Yang (UCLA) will describe the role of N17 domain in Htt aggregation and Huntington's disease pathogenesis, describing the various mouse models that they have generated. Overall, this panel will provide new mechanistic insights into the pathophysiological behavior of key proteins in neurodegenerative disorders and shed light on how targeting such mechanisms may provide future therapies for these debilitating diseases.

PANEL • MONDAY, 4:30–6:30 PM • SUNSET

23. Evolvability of behavior: Genes, development, and neural circuits

Chair: Paul Katz

Presenters: Hillery Metz, Barbara Finlay, Bruce Carlson, Paul Katz

The organization and development of the nervous system affects behavioral "evolvability" by constraining it to potential evolutionary paths and by providing opportunities for natural selection to act upon. Given that even closely-related animals with similar brains can exhibit highly divergent behaviors, the question arises as to what features in the nervous system permit such evolutionary divergence. Conversely, there are many examples of behaviors arising independently in several species. This is not coincidental; it is indicative of neural and genetic traits that can be repeatedly exploited by natural selection to produce the behavior. The question of behavioral evolvability is not just academically interesting; it has implications for understanding how to apply the results of research on one species to another species. In this panel, Hillery Metz (Harvard University) will describe how the genetic mapping of a dramatic difference in burrow length between two species of wild mice has led to a candidate gene implicated in addiction behavior of lab mice. Barbara Finlay (Cornell University) will provide an evo-devo approach to brain organization, showing that differences in the size and structure of the brain result from simple changes in patterns of development. Bruce Carlson (Washington University) will discuss how different sensory coding strategies in weakly electric fish have led to increased divergence of social behavior. Paul Katz (Georgia State University) will show that in sea slugs, behaviors, which appear very similar, can actually have different neural bases.

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

24. When ski helmets aren't enough: Emerging therapies for TBI and post-traumatic epilepsy

Chair: Edward Hall

Presenters: Bret Smith, Amy Brooks-Kayal, Ivan Soltesz, Edward Hall

Traumatic brain injury (TBI) is a major unmet medical need with an annual US incidence >1.5 million persons and a high incidence of lasting neurological deficits and sequelae including posttraumatic seizures (PTS) and posttraumatic epilepsy (PTE). TBI is highly relevant to alpine skiing and snowboarding

injuries of which 17.6% are due to TBI. While use of ski helmets has cut down the incidence by as much as 60%, they do not eliminate the risk of TBI and PTE. At present, there are no FDA-approved neuroprotective treatments that improve post-TBI neurological recovery or that prevent PTS and PTE development in contrast to the increasing armamentarium of seizure suppressing compounds (aka anti-seizure drugs), which are not disease-modifying and can have negative effects on cognitive and sensorimotor recovery in TBI patients. This panel will discuss three newer approaches to the treatment of TBI that should attenuate PTE. Following a brief introduction to the epidemiology of TBI, PTS and PTE by organizer Ed Hall, Bret Smith (U. Kentucky) will present elegant studies on the pathophysiology of PTE development in mice subjected to controlled cortical impact TBI that leads to reorganization of circuits in the cortex and hippocampus such that GABAA receptor (R)-mediated inhibition is decreased while recurrent excitatory circuits are increased. Amy Brooks-Kayal (U. Colorado) will then discuss her recent work on the involvement of the JAK/STAT pathway in the TBI-induced down-regulation of GABAA R-dependent synaptic inhibition and the utility of JAK/STAT inhibitors for prevention of PTE development. Next, Ivan Soltesz (U. California-Irvine) will discuss the therapeutic potential of optogenetics for treatment of PTE. Finally, Ed Hall (U. Kentucky) will discuss the role of free radical-induced lipid peroxidation in post-traumatic brain damage including PTE development and protective efficacy of newer brain-penetrable antioxidant compounds.

BRAIN TALK TOWN MEETING • 6:45–8:00 PM • STORM PEAK

Attendance is open to all.

Drug Use in Teens

John Mendelson, *California Pacific Medical Center Research Institute* **(Moderator),** *Loren Parsons, The Scripps Research Institute, Kyle J. Frantz, Georgia State University, Thomas J. Crowley, University of Colorado, Denver*

Experts in adolescence and addiction will discuss drug use in teenagers. Although many teenagers are exposed to potentially addictive drugs, most don't suffer serious complications. Panel members will discuss risk factors for addiction, worrisome signs and symptoms and describe how the adolescent brain differs from the adult brain.

PANEL • MONDAY, 8:30–10:00 PM • STORM PEAK

25. Genetic and non-genetic contributions to abusive rodent alcohol drinking

Chair: John Crabbe
Presenters: John Crabbe, Steve Boehm, Paula Hoffman, Sarah Leibowitz

Abusive alcohol drinking often starts with binges. As chronic drinking and dependence develop, many dysfunctional neuroadaptations lead to neurotoxicity and cycles of withdrawal and relapse drinking. Rodent genetic animal models have addressed specific stages of these cycles. This panel will consider recent data on genetic and non-genetic contributions to binge, chronic and relapse drinking. John Crabbe (OHSU) will discuss studies with HDID mice, selectively bred for binge-like drinking. They show escalating, relapse-like drinking during withdrawal. However, their escalation is the same as that of control mice and is therefore not genetically linked. Transcriptional networks differ between HDIDs and controls both in which genes participate and in the nature of interconnections. Steve Boehm (IUPUI) will discuss the behavioral correlates of repeated binge-like ethanol drinking in C57BL/6J mice, including locomotor activity, cognitive changes, and anxiety-like behavior. He will also describe how the addition of caffeine to the alcohol solution affects binge-like ethanol intake, as well as associated behaviors. Paula Hoffman (UC Denver SOM) has studied the Alcohol Deprivation Effect (ADE) in the HXB/BXH panel of genetically recombinant inbred rats. After chronic preference drinking, alcohol is withheld, and the ADE is defined by enhanced drinking when it is returned. Heritability measures, QTL analysis, microarray and RNA-Seq data are integrated to assess genetic and non-genetic contributions to individual differences in the ADE. Finally, Sarah Leibowitz (Rockefeller) will discuss characteristics of Long-Evans rats drinking 20% alcohol with intermittent access. This pharmacologically-relevant drinking is linked with reduced anxiety and increased novelty-induced activity. With Jessica Barson, she finds that it is also related to neurochemical receptor activity in specific subregions of the thalamic PVN, innervated by the hypothalamic neuropeptide orexin.

PANEL • MONDAY, 8:30–10:00 PM • MT. WERNER

26. New vistas in post-mortem studies in schizophrenia: Implications for etiology and novel therapeutics

Chair: Larry Siever
Presenters: Amanda Law, Schahram Akbarian, Joel Kleinman, Larry Siever

This panel addresses genetic, post-mortem neurochemistry data, and new pharmacologic data that have important implications for the etiology of new treatments in schizophrenia and other neurodevelopmental disorders. Dr. Law

will present work discussing single nucleotide polymorphisms in the NRXN1 (neurexin-1) gene as significant predictors of antipsychotic response in patients with schizophrenia and its quantitative expression mapping over the lifespan which shows a distinctive developmental patterns of regulation, altered in schizophrenia. Akbarian will discuss studies of post-mortem tissue to evaluate chromatin structures such as chromosome loop formations in conjunction with transcriptional deficits and/or single nucleotide polymorphisms associated with cognitive performance, opening up new frontiers for neurobiology of cognition and treatment of schizophrenia. Kleinman will discuss trajectories of D1 and D2 receptors in hippocampus and prefrontal cortex and alternative transcripts in schizophrenia, bipolar disorder, and major depression during the course of human and animal development from the fetus to age 80, and their implications for new target treatment development for these disorders. Siever will discuss recent clinical genetic and post-mortem data implicating variability in a D1 promoter site that may influence D1 expression associated with clinical dementia rating (CDR) in a post-mortem sample of 727 subjects with schizophrenia, Alzheimer's Disease and controls and is associated with executive functional working memory in a sample of young conscripts. He will present new pharmacologic data suggesting that D1 agonists can improve working memory in the schizophrenia spectrum.

PANEL • MONDAY, 8:30–10:00 PM • TWILIGHT

27. Slices, cells, circuits, and steroids: Insights on estrogen action in the brain using ex vivo techniques

Chair: Bradley Cooke

Presenters: Bradley Cooke, John Meitzen, Deepak Srivastava, Eniko Kramár

The 'organizational activational' hypothesis has become a highly successful model of neural sexual differentiation. Although other factors contribute, gonadal hormones are the most potent mediators of sex-specific modifications in the nervous system, and great strides have been made toward understanding mechanisms. A highly effective experimental technique in the study of hormones on the brain is the *ex vivo* preparation, in which the system under study is removed from its *in vivo* context. This approach has led to important insights into how sex hormones influence intracellular signaling, synaptic architecture, and synaptic transmission. This symposium will endeavor to provide an engaging, multifaceted perspective on recent *ex vivo* approaches to understanding sex hormone actions in the brain. Dr. Cooke will describe his studies using 60-channel multielectrode arrays to study patterns of recurrent activity in estrogen-treated cultured networks. Dr. Meitzen will focus on his recent advances using acute slices of dorsal striatum and cultured hippocampal neurons in understanding mechanisms of non-classical, sex-specific estrogen action. Dr. Srivastava will review his model of estrogen-mediated synaptic

plasticity in cultured cortical neurons, and highlight approaches for studying the underlying molecular and cellular mechanisms. Finally, Dr. Krámar will discuss her work on estrogen-mediated potentiation of excitatory synaptic transmission, focusing particularly on the role of brain-derived neurotrophic factor in regulating cytoskeletal modifications. Together, these presentations by four upcoming researchers that share a common interest in *ex vivo* preparations will provide a multi-level perspective on sex steroid hormone effects on synapse, cell, and circuit-level mechanisms. We expect they will spark a lively discussion about future directions on the frontier of research about estrogen effects on the brain.

PANEL • MONDAY, 8:30–10:00 PM • RAINBOW

28. Interindividual variations in major depression pathology: Effects of age and the placebo response

Chair: Jon-Kar Zubieta
Presenters: Jon-Kar Zubieta, Sara Weisenbach, Olusola Ajilore

Major Depressive Disorder (MDD) represents a complex disease with both genetic and environmental underpinnings. In spite of its substantial prevalence and impact on the individual and society, there are numerous factors affecting its development and treatment response, including treatment resistance. This panel will focus on neurobiological mechanisms that influence the presentation and response to treatment in patients diagnosed with MDD. Specifically, positive expectations and conditioned responses appear to play a substantial role in treatment responses, and obscure the effects of active treatments. Aging processes have also been associated with poorer treatment response and outcomes. Dr. Jon-Kar Zubieta will present novel data examining mechanisms associated with treatment response to both placebo and active arms in treatment trials, and specifically the role of endogenous opioid and dopaminergic mechanisms in responses to treatment in MDD. Dr. Sara Weisenbach will present data on frontostriatal and hippocampal dysfunction in limbic and prefrontal regions among older adults with late life depression and their association with alterations in executive functioning and memory utilizing both functional neuroimaging and neuropsychological tests that were associated with course of illness in MDD. Dr. Olu Ajilore will describe how the emerging field of connectomics or brain network analysis can be applied to our understanding of geriatric depression. He will define and summarize connectomics, as well as discuss its clinical applications. Dr. Ajilore will present data on the clinical and cognitive consequences of impairment in structural and functional brain connectivity using resting-state fMRI, DTI, and graph theory in older subjects with depression.

PANEL • MONDAY, 8:30–10:00 PM • SUNSET

29. Modern brain banking for modern times

Chair: Barbara Lipska
Presenters: Barbara Lipska, Cristian Achim, Brent Harris, Piotr Kozlowski

Using postmortem brain tissue is now considered a necessity for progress in the investigation of the pathogenesis of neurological and psychiatric disorders. Neurobanking is expected to support neurobiological research using advanced quantitative technologies: microarrays, epigenetic assays, sequencing, whole-genome genotyping and copy number variant (CNV) determination, exome discovery, as well as proteomics and modern brain mapping techniques, such as CLARITY. In this panel, we will discuss challenges and practicalities in collecting and banking human brains for research across a variety of brain disorders. Barbara Lipska (NIMH) will present brain tissue collection methods from Human Brain Collection Core at NIMH with the focus on schizophrenia and other major mental illnesses, including standardized protocols that assure high sample quality, and present genome-wide expression and epigenetic data. Cristian Achim (UCSD) will present the California NeuroAIDS Tissue Network, and talk about clinical neuromedical and neuropsychological data integration in a national comprehensive database, standardized clinical and autopsy specimen collection and banking for genetic and epigenetic analysis, including neuropathologic assessment, and telepathology distribution of results. Brent Harris (Georgetown U) will discuss unique requirements of biobanking regarding Amyotropic lateral sclerosis (ALS) that affects both CNS and PNS, and poses a difficulty of collecting a variety of tissues that are used to purify TDP-43 aggregates and create nanobodies against unique aggregate forms for biomarker and possibly therapeutic approaches. Piotr Kozlowski (Touro College Research Bank) will present the evolution of brain banking: from selective brain collections to modern bio-banks, and changing trends in neuroscience. He will also discuss the activities of European (BNET) brain banking programs, the American Brain Banking Network, and the proposal for unified registry of specimens.

PANEL • MONDAY, 8:30–10:00 PM • SKYLINE

30. The role of GABAergic interneurons in Huntington's Disease

Chair: Michael Levine
Presenters: Michael Levine, Anton Reiner, Carlos Cepeda, Michelle Day

Huntington's disease (HD) is a neurodegenerative disorder characterized by motor and cognitive abnormalities. In HD, the most notable histopathological change is a massive loss of the ubiquitous striatal medium-sized spiny neurons

(MSNs) and a relative sparing of interneurons. However, genetic models of HD have shown that neuronal dysfunction precedes cell loss. Although excitotoxic mechanisms mediated by glutamate receptors have been invoked to explain degeneration of MSNs and HD symptoms, recent studies indicate that other neurotransmitter systems are involved. In this panel, we will discuss the emerging role of striatal GABAergic interneurons in HD symptoms. Michael Levine will introduce the panel and present a short description of evidence of alterations in inhibition mediated by activation of GABA-A receptors in multiple genetic mouse models of HD. Anton Reiner will talk about his recent work indicating that, contrary to traditional belief, fast-spiking interneurons are lost in HD. Carlos Cepeda will discuss recent advances obtained by optogenetic manipulation of striatal GABAergic interneurons to rescue synaptic dysfunction and Michelle Day will examine GABA receptor modulation by phosphodiesterase 10 (PDE10) inhibitors in HD. Overall, this work suggests that alterations in GABAergic interneurons and their interactions in neurotransmission play an important role in HD symptoms and also as a compensatory mechanism to prevent excessive glutamate excitation.

PANEL • TUESDAY, 7:30–9:30 AM • STORM PEAK

31. The "inflamed" dire consequences of TBI: Exploiting novel mechanisms and treatments for battling neuroinflammation

Chair: Nigel Greig
Presenters: Jonathan Godbout, Susanna Rosi, Cesar Borlongan, Nigel Greig

Traumatic brain injury (TBI) is the leading cause of neurological disability in the world. Some 1.7 million injuries occur in the US annually, and over 5 million Americans are living with serious long-term consequences. TBI often resolves within the first year after injury, but 70-90% of patients continue to manifest prolonged and often permanent neurocognitive dysfunctions that can substantially impact their performance and/or quality of life. It is now recognized that TBI is a process, not an event. Emerging evidence indicates that this process can lead to chronic degenerative brain disorders. Clinically, TBI is one of the most powerful environmental risk factors for development of Alzheimer's disease and dementia, with critical changes impacting brain neurochemistry and cognition over a long time period after TBI. Neuroinflammation is purported to play a pivotal role in TBI-induced neuropathology, although its influences on the long-term consequences and underlying mechanisms of injury remain unclear. In this session Jonathan Godbout will describe key immune and behavioral consequences of TBI-induced priming of microglia in a mouse model of midline fluid percussion injury. Susanna Rosi will discuss TBI-induced peripheral macrophage infiltration into the brain and the impact of aging on the innate immune

system response after TBI. Cesar Borlongan will describe neuroinflammatory responses in a chronic TBI model as well as in a modified controlled cortical impact injury to target localized brain regions beyond the cortex, and then will highlight the novel concept of stem cell graft-paved biobridges to enable brain repair. Finally, Nigel Greig will detail cognitive impairments and gene pathway changes caused by concussive as well as blast-induced mild TBIs, and their amelioration by translatable therapeutics. Hence this panel will define mechanisms underlying TBI impairments, with a focus on neuroinflammation, and highlight new translational treatment approaches.

PANEL • TUESDAY, 7:30–9:30 AM • MT. WERNER

32. Impulsivity and psychiatric disorders: Clinical and preclinical perspectives

Chair: Nathan Holtz
Presenters: Harriet de Wit, Jack Smathells, Daniel Claassen, Nathan Holtz

Impulsivity is a multifaceted behavior expressed in a number of psychiatric and neurological disorders. Components of impulsivity include risky decision making and the discounting of large delayed rewards in favor of smaller immediate rewards (impulsive choice), as well as the inability to restrain or terminate a deleterious action (impulsive action). These traits are mediated by a number of common neurobiological structures, mainly those comprising the mesolimbic dopamine system. Expression of impulsive behaviors may predict phenotypic vulnerability to certain psychiatric disorders, and may also be mediated by substances of abuse, or other dopaminergic agents used as therapies for disorders such as Parkinson disease (PD). This panel will present findings from clinical and preclinical studies that explored the role of impulsivity in psychiatric disorders and their treatment. Harriet de Wit will discuss the relationship between impulsive behaviors and sensitivity to reward by presenting research that examined behavioral measures of impulsive action or impulsive choice and the acute euphorigenic responses to a stimulant drug, amphetamine, in healthy adults. The correlations observed suggest that there may be shared underlying processes between these apparently dissimilar measures. Jack Smethells will discuss research that investigated the relationship between age, individual differences in ethanol consumption, and risky decision-making in the rat. Daniel Claassen will discuss clinical phenotypes, as well as behavioral and imaging studies, that link the emergence of impulse control disorders to dopamine agonist use in PD. Lastly, Nathan Holtz will present a novel procedure for assessing risky decision making in the rat that employs intracranial self-stimulation as the rewarding event. Research will be discussed that has used this procedure for assessing the effects of dopamine agonists on risky decision making in an animal model of PD.

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

33. Why can't a woman be more like a man? Interactions between sex and stress and responses to stimulants and toxins

Chair: Vicky Luine
Presenters: Debra Bangasser, Cheryl Conrad, Vicky Luine, Diane Miller

Evidence continues to mount that neural and behavioral responses to acute and chronic stress are markedly different in the sexes (both experimental animals and humans). Participants will present their latest work detailing the neural mechanisms that may be responsible for expressing the sex differences, the behaviors that are differentially affected by stress in the sexes, and how stress and gender interact in response to drugs and toxins. These studies have implications for understanding the etiology and management of stress related illnesses like depression, anxiety and PTSD and for gender based treatments following combat exposures to chemicals. B angasser will describe sex differences in the receptor for the stress-related neuropeptide, corticotropin releasing factor (CRF), that renders neurons of female rats more sensitive to CRF than males and data suggesting that molecular sex differences in CRF function translate into greater anxiety-related behaviors in female rats. Conrad will discuss studies that show sex differences in how chronic stress influences spatial learning and memory and the potential underlying morphological contributors that include alterations in the hippocampal area of CA3 dendritic architecture and CA1 spine morphology. Luine will present stress-dependent sex differences in anxiety, cognition and mood in rats and how chronic treatment with alcohol, administered following a stress session, reverses some deleterious effects of stress in males but exacerbates stress effects in females. Miller will present data concerning the impact of gender and stress on the neurotoxicity of various classes of compounds illustrating there is no simple, one word answer. The impact of gender and stress on neurotoxicity depends on the neurotoxic substance, as well as the type of stressor being evaluated.

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

34. It's all in the timing…

Chair: Matthew Matell
Presenters: Patrick Simen, Marshall Hussain Shuler, Matthew Matell, Martin Wiener

A representation of time has been proposed to underlie associative learning, guide our expectations, and moderate our choices, as in delay discounting. Despite its importance to adaptive behavior, the psychological and neural mechanisms underlying temporal perception and control remain controversial.

The following questions are critical to the field: Is temporal perception carried out by local structures (e.g., sensory cortices) or is there a central amodal representation of time? Are the neural activity patterns representing time monotonic (i.e., ramps or decays) or abstract network states? Are the mechanisms used for temporal processing of short, sub-second intervals, such as those underlying rhythmic behavior, the same as those used for longer supra-second timing, such as that seen with operant schedules of behavior? What about even longer intervals, such as those used in human studies of delay discounting? This panel will provide various viewpoints on these questions. Patrick Simen (Oberlin College) will discuss the suitability of a drift diffusion model developed for decision making to provide temporal control for rhythmic and non-rhythmic intervals. Marhsall Hussain Shuler (Johns Hopkins University) will speak about temporal expectations within visual cortex and its cholinergic control. Matthew Matell (Villanova University) will discuss integration of distinct temporal memories across modalities, and what this says about how time is represented. Martin Wiener (George Mason University) will discuss how multiple, overlapping neural mechanisms are available for timing across different experimental contexts.

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

35. Spike timing-dependent plasticity in cortical learning

Chair: Alfredo Kirkwood
Presenters: Robert Froemke, Alfredo Kirkwood, Harel Shouval, Pablo Celnik

LTP and LTD can be induced in an associative manner by near coincidental pre- and post-synaptic activation. This paradigm, also known as spike-timing dependent plasticity (STDP), has emerged as an attractive model of the synaptic modifications as might naturally occur in vivo. This panel will discuss recent unpublished findings implicating STDP in a wider spectrum of crucial neural processes. One of them is the maintenance of balanced excitatory and inhibitory circuits during cortical remodeling. Robert Froemke (from NYU) will describe elementary rules by which STDP and various forms of neuromodulation are coordinated in the auditory cortex to regulate excitatory-inhibitory balance during and after the induction of specific forms of long-term synaptic plasticity. Next we will discuss STDP as a model for reward-based learning. Reinforcement learning has to solve the temporal credit assignment problem, or in other words how to associate a stimulus with a reward that is delayed in time. Alfredo Kirkwood (from JHU) will present experimental evidence that STDP paradigms can induce transient eligibility traces for potentiation and depression that can be subsequently consolidated/expressed into LTP or LTD by specific neuromodulators. Using biophysically realistic models of plasticity Harel Shouval (from UT at Houston) will show

that when the eligibility traces for LTP and LTD have different temporal profiles, reinforcement learning stabilizes naturally once the network predicts the timing of the reward. Finally, Pablo Celnik (from JHU) will discuss the induction of STDP and LTP-like processes at a system level in humans using non-invasive brain stimulation, and how these approaches uncover the role of LTP-like processes as neurophysiological mechanisms underlying motor learning retention and interference. Altogether this panel reflects our growing understanding of the role of STDP-like processes in the complexity of cortical learning.

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

36. Kv2.1 potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration

Chair: Elias Aizenman

Presenters: Michael Tamkun, D.P. Mohapatra, Niyathi Hegde Shah, Federico Sesti

Voltage-gated Kv2.1 channels mediate the majority of the delayed rectifier potassium currents in cortical and hippocampal neurons, and, as such, are key regulators of neuronal excitability. In addition, Kv2.1 channels actively participate in cellular and molecular signaling pathways that regulate the life and death of neurons. Activity and injury-mediated changes in the phosphorylation and oxidation status of these channels can dramatically affect channel trafficking and biophysical function, promoting a wide range of effects on neuronal excitability, apoptotic cell death or tolerance to subsequent lethal stimuli. This panel will discuss the diverse functional, neurotoxic, neuroprotective, and neuroregulatory roles that Kv2.1 channels play in neurons. Elias Aizenman (University of Pittsburgh) will chair the panel and give brief introductory remarks. Michael Tamkun (Colorado State University) will begin the panel by discussing how non-conducting Kv2.1 channels form stable cortical ER/plasma membrane junctions that function as both trafficking hubs and sites for localized Ca2+ homeostasis. D.P. Mohapatra (University of Iowa) will then discuss the role of distinct phospho-modifications in Kv2.1 channels in the regulation of neuronal survival-degeneration dynamics in multiple neurodegenerative pathologies. Niyathi Hegde Shah (University of Pittsburgh) will discuss the role of ischemic preconditioning-mediated changes in phosphorylation and localization status of Kv2.1 channels, and the implications of these channel alterations in the expression of neuronal tolerance. Finally, Federico Sesti (Rutgers University) will discuss the role of Kv2.1 oxidation in aging brain and the early molecular events that follow the channel's oxidation.

PANEL • TUESDAY, 4:30–6:30 PM • STORM PEAK

37. Risk factors and predictors of human drug abuse

Chair: Hugh Garavan
Presenters: Jim Bjork, Patricia Conrod, Hugh Garavan, Sharon Morein-Zamir

Understanding risk factors for drug abuse has clinical and scientific value (identifying at-risk individuals, targeting interventions, identifying etiological mechanisms). Anima models have made considerable progress in identifying pre-existing risk factors and their underlying neurobiology. We discuss emerging findings from human studies –a substantial advance in translating preclinical findings to humans while also enabling us to test for risk factors (social, personality, neurobiological) that may be particular to humans. Dr. Bjork (NIDA) will discuss children with externalizing behaviors (eg conduct disorder) who are at risk for substance abuse and frequently show behavioral sensitivity to reward contingencies in decision tasks. Similar to alcoholics, fMRI data will show that not only do these teens show elevated mesolimbic reward responses, but so too do healthy teens showing risk behaviors. Dr. Conrod (Montreal) focuses on sensation seeking and impulsivity, two facets of disinhibition implicated through cognitive and neural mechanisms in substance misuse. Longitudinal, family and high-risk studies reveal that these two facets and their neural correlates dissociate at different stages in the development of addiction and have bidirectional relationships with substance misuse vulnerability. Dr. Garavan (Vermont) reports longitudinal findings in 800 adolescents showing a profile of personality, family history, life events and neurobiological functions (esp. PFC functions) predicting binge drinking two years later. Dr. Morein-Zamir (Cambridge) will show that stimulant users and their unaffected siblings share behavioral difficulties in response inhibition. However, while users show hypoactivation of relevant brain regions, the siblings show hyperactivation, an observation that might reveal resilience mechanisms and sheds light on how pre-existing genetic and environment vulnerabilities likely interact with the effects of drug-use on behavior and the brain.

PANEL • TUESDAY, 4:30–6:30 PM • MT. WERNER

38. Addressing cognition impairment in schizophrenia: Taking aim on emerging intracellular and receptor-based targets

Chair: Gretchen Snyder
Presenters: Christopher Shaffer, Sven Akkerman, Sean Smith, James Bibb

Cognitive impairment is a core feature of psychiatric diseases such as schizophrenia. While current antipsychotic medications—typically dopamine D2 antagonists—improve positive symptoms of the disease, such as acute

hallucinations and delusions, they fail to substantially alleviate negative features, such as social isolation and cognition. Often these drugs further compromise poor cognitive function in psychiatric patients. Novel intracellular signaling targets, such as phosphodiesterase (PDE) enzymes and innovative glutamate receptor strategies (i.e., allosteric receptor modulators, protein-protein interactions) have emerged as promising approaches for improving cognition in psychiatric disease. This panel will highlight exploratory preclinical projects and innovative small molecule drug development programs targeting intracellular enzymes and allosteric regulators as approaches for addressing cognition dysfunction in psychiatric diseases. Chris Shaffer (Pfizer) will summarize the preclinical and early clinical data of a novel AMPA receptor positive allosteric modulator for attenuating cognitive impairments in schizophrenia. Sven Akkerman (Maastricht) will introduce the role of PDEs in regulating object memory performance. He will discuss the design of behavioral assays used to test candidate therapeutics for cognitive improvement, focusing on an unexpected interaction between inhibitors of the cGMP-selective PDE5 and environmental enrichment in enhancing cognitive performance. Sean Smith (Merck) will present evidence for inhibitors of the striatal-enriched PDE10A as having both antipsychotic activity and beneficial effects in paradigms modeling cognitive deficits in psychosis. Finally, James Bibb (UT Southwest) will discuss the potential for protein-protein interaction targets for cognition-enhancing treatments by describing small interacting peptides (siP) that modulate Cdk5 phosphorylation of NMDA receptors to result in improved cognition in mice.

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

39. Mitochondrial ion channels and transporters in the regulation of synaptic plasticity and neuronal survival

Chair: Yuriy Usachev

Presenters: Yuriy Usachev, Gavriel David, Nickolai Brustovetsky, Elizabeth Jonas

Mitochondria supply neurons with ATP, and regulate Ca2+ signaling and generation of reactive oxygen species (ROS). All of these functions depend on highly coordinated transport of ions across the mitochondrial membranes. For example, H+ extrusion from the matrix establishes a H+ electrochemical gradient across the inner mitochondrial membrane to drive ATP production from ADP, and Ca2+ transport into and out of mitochondria regulates cytosolic Ca2+ signaling, ATP synthesis and neuronal survival. Despite significant progress in our understanding of these processes, many questions about the molecular organization, regulation and functions of mitochondrial ion channels and transporters in neurons remain to be answered. This panel will discuss essential aspects of Ca2+ and H+ transport by neuronal mitochondria.

Dr. Usachev (University of Iowa) will start the session by introducing the physiological and molecular properties of mitochondrial Ca2+ transport in neurons, focusing on the roles of two isoforms of the mitochondrial Ca2+ uniporter/channel, MCU (ccdc109a) and MCUb (ccdc109b), in mediating mitochondrial Ca2+ uptake in peripheral and central neurons. He will then discuss how the Na+/Ca2+/Li+ exchanger (NCLX) contributes to Ca2+ release from neuronal mitochondria. Dr. David (University of Miami) will describe how Ca2+ uptake and release by presynaptic mitochondria control synaptic transmission and short-term plasticity at the mammalian neuromuscular junction. Dr. Brustovetsky (Indiana University) will talk about the roles of mitochondria, NMDA receptors, Na+/Ca2+ exchanger and collapsin response mediator protein 2 (CRMP2) in glutamate-induced Ca2+ dysregulation and excitotoxicity in central neurons. Dr. Jonas (Yale University) will close the session by describing recent evidence for an interaction between Bcl-xL and the F1Fo ATP synthase c-subunit leak channel, and discuss the potential role of this interaction in H+ transport, ATP synthesis and neurite extension.

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

40. BDNF modulation of neural circuits and behavior: New insights and translational implications

Chair: Vinay Parikh

Presenters: Alexei Morozov, Maribel Rios, Jacqueline McGinty, Vinay Parikh

Brain-derived neurotrophic factor (BDNF) is the most widely expressed neurotrophin in the central nervous system. By virtue of its critical role in neuronal survival and differentiation, activity-dependent forms of synaptic plasticity, and learning and memory, BDNF signaling is a vital component of normal brain function. Although this trophic protein is widely implicated in a multitude of neuropsychiatric disorders, it remains unclear how disruption in BDNF signaling would produce aberrant behavioral states. This requires understanding of BDNF function at the neural circuit level. This panel will feature presentations on emerging studies exploring how BDNF signaling in discrete brain circuits modulates specific behaviors, and discuss the implications of data for understanding the neurobiology of psychiatric disorders. Dr. Alexei Morozov (Virginia Tech) will review data from recent studies exploring the impact of conditional deletion of BDNF in the hippocampal CA3 region on aggression, social dominance and empathy-like behaviors. Dr. Maribel Rios (Tufts University) will integrate evidence from studies delineating the role of hypothalamic BDNF in the homeostatic control of food intake and mesolimbic BDNF in hedonic impact of natural rewards. She will also discuss how these findings would translate into our understanding of the

pathophysiology of obesity disorders. Dr. Jacqueline McGinty (Med Univ SC) will highlight the role of BDNF signaling in averting cocaine abstinence-induced neuroadaptations. Specifically, she will talk about synaptic mechanisms underlying the ability of an intra-prefrontal cortical BDNF infusion to suppress cocaine-seeking behavior. Finally, Dr. Vinay Parikh (Temple University) will present recent results from studies that determine the contribution of striatal BDNF in the regulation of flexible decision-making and implications of these findings for nicotine addiction and its comorbidity with schizophrenia.

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

41. The central role of parvalbumin interneurons in critical period plasticity

Chair: Aaron McGee

Presenters: Aaron McGee, Hirofumi Morishita, Elizabeth Quinlan, Joshua Trachtenberg

The closure of developmental critical periods consolidates brain circuitry instructed by experience, but also limits plasticity that could compensate for maladaptations in brain function induced earlier in life by abnormal experience. Ocular dominance is a premier model of this experience-dependent plasticity. During the critical period, occluding vision by one eye degrades the representation of this eye in primary visual cortex. While the cumulative changes to cortical circuitry resulting from monocular deprivation are not yet known, several lines of evidence implicate parvalbumin-positive fast-spiking inhibitory neurons (PV neurons) as key regulators of critical period plasticity. This panel will discuss the how several genes that govern the initiation and cessation of the critical period operate through PV neurons, as well as describe recent findings that identify microcircuit changes required for competitive plasticity specific to the critical period. First, Aaron McGee will provide introductory comments and briefly describe how deleting the nogo-66 receptor gene (NgR1) in PV neurons is sufficient to maintain developmental ocular dominance plasticity in the adult. Next, Hirofumi Morishita will discuss mechanisms of plasticity unmasked by the removal of Lynx1, an endogenous inhibitor of nicotinic acetylcholine receptors that is highly expressed in PV neurons. Then Elizabeth Quinlan will describe the obligate role for neuronal activity-related pentraxin (NARP) in recruiting excitatory drive onto PV neurons and gating ocular dominance plasticity. Last, Joshua Trachtenberg will discuss how local PV circuit reorganization is an early and essential step in ocular dominance plasticity and how reducing PV-specific inhibition with pharmaco-genetics restores plasticity after the critical period.

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

42. Neuronal excitability in function and dysfunction

Chair: Jerry Yin
Presenters: Jerry Yin, John Disterhoft, Edi Barkai, Susan Tsunoda

Synaptic plasticity has been the most widely studied cellular mechanism that contributes to learning and memory formation. However, there has been a steady stream of research across all different organisms that correlate a second cellular mechanism, changes in intrinsic excitability, with memory formation and homeostasis. In this session, we will explore excitability and how it can contribute to neuronal function and dysfunction using fly and rodent models. Jerry Yin will describe experiments using a transgenic reporter for the well-characterized CREB (dCREB2 in flies) transcription factor. Memory dependent effects on reporter activity differ in directionality in different regions of the brain, as well as at different time points after training. John Disterhoft will discuss new data showing that both increases and decreases in excitability occur in different regions of the hippocampus during the aging process, and that these affect different AHP currents. Edi Barkai will show that persistent changes in cortical and hippocampal excitability after behavioral training can contribute to enhanced function of related circuits in a second behavior. Susan Tsunoda will discuss the role intrinsic changes play in homeostatic responses to global changes in activity, as well as in disease-related phenotypes associated with the overexpression of beta amyloid peptides in fly neurons. Collectively these talks will illustrate regional and bi-directional differences in excitability (or its correlate) during neuronal function and dysfunction in both model systems.

PANEL • WEDNESDAY, 7:30–9:30 AM • STORM PEAK

43. Functionally characterizing the transcriptional landscape of the developing human brain

Chair: Thomas Hyde
Presenters: Andrew Jaffe, James Knowles, Ed Lein, Brady Maher

The transcriptional landscape of the developing human brain is beginning to emerge from massive RNA sequencing (RNAseq) efforts, leveraging billions of data points across large cohorts of human brains to identify precise spatial and temporal changes in gene expression. Here we present a spectrum of scientific research motivated by RNAseq data in human brain, moving from raw sequencing data to functional genomics and its application to an in vivo biological system. Dr. Andrew Jaffe (Lieber Institute for Brain Development) will introduce RNAseq data, and describe annotation-free statistical methods

and computational software for identifying differentially expressed regions across human brain development in the dorsolateral prefrontal cortex (DLPFC). Dr. James Knowles (University of Southern California) will characterize RNAseq-based gene expression patterns across the entire brain through the BrainSpan project, including evidence for ~125,000 novel splice junctions across the developing and aging human brain. He will transition from characterization to functional interrogation via analyzing single-cell transcriptomes of human brain tissue. Dr. Ed Lein (Allen Institute for Brain Science) will continue with functional genomics, describing results from analyses of detailed spatiotemporal transcriptional profiling of the developing human and non-human primate neocortex. More specifically, selective analysis of neural progenitor and postmitotic cell populations reveals transcriptional signatures of cell type, age, areal and laminar patterning that are enriched for genes associated with neurodevelopmental disorders and human lineage-specific genomic features. Lastly, Dr. Brady Maher (Lieber Institute for Brain Development) will describe utilization of human RNAseq data to develop cell and animal models of illness risk, presenting data about in utero manipulation of transcription factor 4 (TCF4), a pleitropic gene associated with schizophrenia and autism spectrum disorder.

PANEL • WEDNESDAY, 7:30–9:30 AM • MT. WERNER

44. Neural circuitry underlying feeding

Chair: Paul Phillips
Presenters: Matthew Carter, Luis de Lecea, Yexica Aponte, Michael J. Krashes

Feeding is one of the most important adaptive behaviors across species. However, the neural circuitry that responds to the signaling of hunger and satiety to promote or suppress feeding, respectively, have not yet been resolved. This panel will describe experiments that use state-of-the-art genetic manipulations to address this question. Matthew Carter (Williams College) will speak about the role of neurons in the parabrachial nucleus in the control of feeding and conditioned taste aversion. Luis de Lecea (Stanford University) will link norepinephrine and the parabrachial nucleus with aversion to food. Yexica Aponte (National Institute on Drug Abuse) will describe experiments to measure and manipulate genetically-defined cell types during behavior to identify key elements of the feeding-reward circuits. Finally, Michael Krashes (National Institute of Diabetes and Digestive and Kidney Diseases) will describe specific projections to AGRP neurons of the arcuate nucleus that regulate their activity and subsequently control feeding.

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

45. Targeting cyclic nucleotide phosphodiesterases for the treatment of Huntington's disease

Chair: Anthony West

Presenters: Christopher Schmidt, Anthony West, Hai Lin, Nicholas Brandon

Several members of the cyclic nucleotide phosphodiesterase (PDE) superfamily are highly expressed in motor centers in the cortex and basal ganglia and are likely to play key roles in the modulation of motor behavior via their governance over cAMP and cGMP metabolism. In support of this, the facilitation of cyclic nucleotide signaling following down-regulation of PDE function can lead to alterations in motor behavior and motivational and cognitive functions. A growing number of studies support the utility of subtype-selective inhibitors targeting PDE2A, PDE9A, and PDE10A for the treatment of neurological disorders such as Huntington's disease (HD) and related pathologies. This panel will provide an overview of recent work examining the impact of pharmacological and genetic disruption of PDE function on neural processing in fronto-subcortical circuits in wild-type animals and models of HD and related disorders. Chris Schmidt will discuss studies comparing the effects of selective inhibitors of PDE2A, PDE9A and PDE10A on striatal cyclic nucleotide signaling in two HD models, R6/2 and Q175 Tg mice. Tony West will present recent findings from studies examining the impact of selective PDE9A and PDE10A inhibitors on cortically-evoked firing recorded in the striatum of aged (8-10 months old) wild-type and full-length BAC transgenic HD rats (BACHD). Hai Lin will present recent data evaluating the effectiveness of MP-10, a PDE10A inhibitor, in reversing the altered firing rates of neurons recorded in the globus pallidus and subthalamic nucleus in BACHD rats. Nick Brandon will describe the identification of a novel non-synonymous mutation in PDE10A2 (Y107C), within a two-generation pedigree, which associates with a distinctive non-progressive/static chorea. He will also describe the generation of a transgenic knock-in mouse with this mutation which exhibits gait abnormalities and discuss additional efforts aimed at understanding the mechanism(s) underlying these effects.

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

46. AMPA receptor regulation at postsynaptic sites

Chair: Johannes Hell

Presenters: Johannes Hell, Susumu Tomita, Jose Esteban, Terunaga Nakagawa

Glutamate is the main neurotransmitter in the brain. Postsynaptic AMPAR content determines synaptic strength, which is very stable under physiological conditions. Formation of memory is thought to be mediated by a durable

change in postsynaptic AMPAR strength. At the same time, dysregulation of postsynaptic strength underlies many mental and neurological disorders. This panel will explore mechanisms that regulate postsynaptic AMPAR content. After a brief introduction by the chair (Johannes Hell, UC Davis), he will talk about regulation of postsynaptic AMPARs by beta 2 adrenergic signaling. Susumu Tomita (Yale University) will speak about the role of auxiliary AMPAR subunits in postsynaptic AMPAR function. Jose Esteban (CSIC, Spain) will discuss the molecular machinery that controls exocytosis and endocytosis of AMPAR at the postsynaptic membrane during synaptic plasticity. Terunaga Nakagawa (Vanderbilt University) will close by providing Structural and functional insights into glutamate receptors obtained by single particle electron microscopy.

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

47. The role of CK1 and its regulation in multiple CNS disease states

Chair: Marc Flajolet

Presenters: Louis Ptacek, Paul Vezina, Camron Bryant, Cristina M. Cruciat

CK1 (Csnk1) is a ser/thr kinase that has been extensively characterized from a biochemical perspective. While a large number of earlier studies have been carried in vitro using non-brain substrates, more and more attention is given to the role of CK1 in the brain. Among the eight CK1 isoforms, the delta and epsilon isoforms seem to be the most expressed in a multitude of brain regions. Recently, the development of CK1 animal models, targeting several isoforms, combined to human genetic studies, have revived the interest for CK1 in the context of several disease states related to circadian rhythms, familial migraine, psychostimulant reward and addiction, and neurodevelopmental psychiatric disorders such as ADHD. Considering the number and the importance of some of the pathways dependent upon CK1, it is not surprising that CK1 plays a significant regulatory role in complex disorders. Here we will present some of latest studies involving CK1 or its regulation. First, Marc Flajolet (Rockefeller University) will provide introductory comments. Louis J Ptacek (University of California) will introduce and summarize recent discoveries highlighting the importance of CK1 isoforms in the circadian rhythm regulation, as well as the involvement of CK1 in different medical conditions such as familial migraine. Paul Vezina (University of Chicago) will present data on the role of CK1 isoforms for the generation of psychostimulant-induced behaviors. He will summarize in vivo pharmacological, biochemical and behavioral experiments leading to the regulation of AMPA receptor phosphorylation. Camron D. Bryant (Boston University) will present recent findings regarding the characterization of Csnk1e knockout mice in opioid and psychostimulant

reward, analgesia, and the motivational-affective components of drug withdrawal. Finally, Cristina M Cruciat (Heidelberg) will present her recent work on an important regulatory step involving the post-translational regulation of CK1 by Wnt signaling.

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

48. Developing treatments for spinal cord injury

Chair: James Fawcett
Presenters: Roman Giger, Herbert Geller, James Fawcett, John Steeves

Now that the first generation of treatments for Spinal Cord Injury (SCI) has reached clinical trials, the challenge is to develop more effective interventions. Current treatments have their greatest effect through enhancement of CNS plasticity, and less effect on axon regeneration. The panel will present three novel approaches to the enhancement of CNS axon regeneration, and discuss the level of preclinical evidence for efficacy sufficient to proceed to clinical development. Roman Giger (University of Michigan) will review recent experiments on the Nogo receptor family, which plays a central part in transmitting inhibitory influences to axons and dendrites, and can act as receptors to several types of growth inhibitory molecules. Herb Geller (NIH) will discuss the LAR family genes, which can be receptors for inhibitory chondroitin sulphate proteoglycans and also Heparan sulphate proteoglyans. He will review evidence for their involvement in blocking axon regeneration. James Fawcett (University of Cambridge) will present recent data on the loss of intrinsic regenerative ability in CNS neurons with maturation. He will show that transport of key growth-related molecules into axons becomes restricted, leading to axons that are missing vital components and therefore grow poorly. He will suggest methods to restore growth ability. John Steeves (ICORD, UBC) will discuss the process of translating experimental evidence towards clinical application with reference to SCI. He will outline the level of experimental proof of efficacy that is needed for successful translation.

PANEL • WEDNESDAY, 4:30–6:30 PM • STORM PEAK

49. Clinical application of stem cell technologies for CNS disease

Chair: Hans Keirstead
Presenters: Monica Siegenthaler, Aileen Anderson, Matt Blurton-Jones, Brian Cummings

Millions of people are affected by diseases of the central nervous system. Stem cell technologies offer therapeutic potential to these diseases in which the inherent ability for repair is limited. Although diseases of the central nervous

system include congenital, cancerous, and degenerative conditions, stem cell technologies have largely focused on limiting damage of and/or replacing tissue in degenerative diseases. In this panel, we will present various stem cell-based technologies for CNS disease. Dr. Siegenthaler (California Stem Cell Inc) will present a cancer stem cell-based immune therapy that yielded 72% survival at 2 years in phase II clinical trial in late stage melanoma patients and will discuss the application of this technology to glioblastoma multiforme. Dr. Anderson (University of California at Irvine) will present her recent data concerning the transplantation of clinically relevant fetal derived human neural populations derived from stem cells into cervically injured rodents. Dr. Blurton-Jones (University of California at Irvine) will discuss the therapeutic strategy of using neural stem cells for Alzheimer's Disease and how this strategy can be applied to treat related neurological diseases. Dr. Cummings (University of California at Irvine) will present his recent data concerning the transplantation of xenofree hES derived neural populations derived from stem cells into a rodent model of traumatic brain injury. Together these presentations will demonstrate an array of stem cell based therapies with clinical application that have over-reaching potential for several other conditions affecting the CNS.

PANEL • WEDNESDAY, 4:30–6:30 PM • MT. WERNER

50. Clinical effectiveness and mediating factors of modafinil in substance dependence and sleep disorders

Chair: Peter Morgan
Presenters: Gianluigi Tanda, Jed Black, Thomas Newton, Peter Morgan, Charles O'Brien

Modafinil is a mild stimulant approved for use in narcolepsy and other sleep disorders. An inhibitor of dopamine reuptake, modafinil has been explored as a treatment for psychiatric disorders including stimulant dependence. Its substantial use in research has increased understanding of its clinical properties and the factors behind those properties. This panel will present clinical and pre-clinical data on the use of modafinil in sleep disorders and stimulant dependence to highlight the potential of this agent, while considering potential drawbacks. Dr. Tanda will review the neurobiology of modafinil and present pre-clinical data relevant to its use in humans. Most human research experience with modafinil comes from trials in sleep disorders. Dr. Black will present results from such trials examining the effectiveness of modafinil and discussing implications for its use in psychiatric conditions. Substantial work with modafinil has also been done in stimulant dependence showing pro-cognitive effects, reversal of physiological changes associated with chronic use, and effects on the subjective and reinforcing effects of cocaine and methamphetamine. Dr. Newton will present results from laboratory studies of modafinil in chronic

stimulant users, highlighting its effect on the subjective and reinforcing effects of stimulants. Dr. Morgan will present preliminary data from a relapse prevention study in cocaine users, designed to highlight possible effects of modafinil on abstinence-related physiological changes, and showing that changes in sleep architecture predict clinical outcome, and may, in part, mediate modafinil's clinical effectiveness. Dr. O'Brien will present data from a recently completed study that confirms the positive clinical result of modafinil in heavy, chronic cocaine users, and will review this and other clinical and laboratory trials of modafinil. The panel will consider the implications of these and other findings for the present and future use of modafinil.

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

51. Molecular regulation of excitatory synapses

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

This panel will describe recently discovered mechanisms at glutamatergic synapses that control neurotransmission, synaptic plasticity, and behavior. Roche will show that CaMKII phosphorylates the intracellular domain of the postsynaptic adhesion molecule neuroligin-1 (NL-1), but not NL-3. This CaMKII site is phosphorylated in response to synaptic activity, promotes trafficking of NL-1, and regulates synapse number. Furthermore, this phosphorylation is regulated by experience demonstrating interplay between CaMKII and NL-1. Nicoll will discuss experiments using molecular replacement to test the AMPA receptor subunit rules proposed to underlie long term potentiation (LTP). In short, LTP persists in the absence of the C-tails of GluA1 and GluA2; in fact, normal LTP occurs when exogenously expressed kainate receptors replace AMPA receptors. These results suggest that LTP is associated with promiscuous reorganization of the PSD. Bredt will discuss experiments assessing potential roles for a recently described collection of AMPA receptor associated proteins identified by proteomics. High throughput biochemical and functional studies show that some of these proteins profoundly regulate AMPA receptor channels in recombinant cells and neurons. This expands the complement of transmembrane proteins that functionally control neuronal AMPA receptors. Maricq will show the central importance of UNC-116, the homolog of vertebrate kinesin-1 heavy chain (KIF5) in C. elegans, for both delivery and removal of synaptic AMPARs. UNC-116/KIF5 motors provide a rapid-response mechanism for the regulation of the number of AMPARs at synapses, and synaptic function can be restored by transient rescue of motor function in adult kinesin mutants. Studies to identify molecules that regulate kinesin-mediated delivery of AMPARs, and their selective stoppage and insertion at synapses are on-going.

52. New functions for new neuropeptides: From feeding/body weight regulation to drug abuse to chaperone function in neurodegenerative disease

Chair: Lloyd Fricker

Presenters: Lloyd Fricker, Lakshmi Devi, Dan Morgan, Iris Lindberg

Neuropeptides constitute the largest and most diverse class of cell-cell signaling molecules in brain, with over one hundred known neuropeptides. Despite many decades of work on neuropeptides, little is known about the peptides that are derived from proSAAS, one of the most abundant neuropeptide precursors in the brain. ProSAAS-derived peptides have been identified in numerous peptidomic studies on brain and other neuroendocrine tissues from humans and other mammals. These peptides are frequently found in studies examining disease biomarker studies in humans where they have been associated with Pick's disease, Alzheimer's disease, and other dementias. All of the proSAAS-derived peptides, including SAAS, PEN, and LEN, have been detected in multiple-sized forms (a hallmark of neuropeptides), and are broadly distributed throughout the brain with highest levels in the hypothalamus. Very recently, great progress has been made towards the elucidation of functions for specific peptides in this family. Lloyd Fricker, whose lab discovered many of the proSAAS peptides, will introduce the field, providing an overview of proSAAS and its peptides. Lakshmi Devi will present recent work that identifies the orphan receptor GPR171 as the big-LEN receptor and will discuss the role of this receptor in the regulation of feeding and body weight. Dan Morgan will describe studies on proSAAS knock-out mice, which show reduced body weight, elevated anxiety, and blunted sensitization to chronically administered cocaine. Lastly, Iris Lindberg will present work showing that larger proSAAS-derived peptides function as anti-aggregant chaperones for amyloid-beta peptide and other fibrillation-prone pathogenic peptides. Collectively, these data highlight the multiple and diverse functions of proSAAS-derived peptides in normal brain function as well as in CNS disease pathologies.

53. Isolation no more: Cross-modal and multisensory influences on cortical function

Chair: Hey-Kyoung Lee
Presenters: Matthew Banks, Sarah Pallas, Hey-Kyoung Lee, Patrick Kanold

Sensory experience is critical for normal development of cortical circuits and alters cortical synapses even later in life, thereby impacting cortical function. Traditionally such changes have been studied in cortical areas processing the affected sensory modality. However, experience dependent changes are often not only restricted to the deprived sensory cortical area, but can also manifest across other primary sensory cortices. Thus, even primary sensory cortices are modulated by information arising from the other senses, which may provide the basis for multisensory integration as well as cross-modal sensory compensation in the case of losing a sensory modality. This panel will cover recent findings related to cross-modal and multisensory interactions and plasticity at the level of primary sensory cortices. Matthew Banks (Univ Wisconsin-Madison) will present data that multimodal integration in auditory cortex is an important example of predictive coding, in which observed and expected sensory information is compared via cortical integration of thalamocortical and cortico-cortical inputs. Sarah Pallas (Georgia State Univ) will talk about how damage-induced re-routing of retinal axons to auditory thalamus in neonates allows auditory cortex to respond to both visual and auditory stimuli, but with compromised adult auditory function. Hey-Kyoung Lee (Johns Hopkins Univ) will discuss how losing vision potentiates the feedforward circuit of thalamocortical inputs to primary auditory cortex, which suggests a novel way to induce plasticity in the adult brain. Patrick Kanold (Univ Maryland College Park) will talk about how vision loss alters and enhances sound processing in the primary auditory cortex, which may be the basis for heightened auditory abilities in blind. Thus, this panel will cover how primary sensory cortices respond to and alter their circuitry in tune with the other senses, which highlights the global influences of each sensory system on brain function.

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

54. Neuroscience is looking for a few good brains: Funding neuroscience research and training in difficult times

Chair: Kyle Frantz
Presenters: Kathie Olsen, Elliott Albers, Kyle Frantz,

Federal budgets are tight. Endowment values remain low. Yet the mysteries of neuroscience and costs of neurological disorders sustain the attention of various stakeholders around the world. This panel will provide practical insight on the challenges and opportunities for funding neuroscience in difficult times. Dr. Olsen will provide an inside-the-beltway perspective from someone outside the government. She will consider both short-term and long-term US budget outlooks and their effects on the federal research agencies that support neuroscience and related areas, such as NIH, NSF, and DOD. Included will be impacts due to sequestration and spending caps put in place by the Budget Control Act. On the bright side, she will also highlight the new BRAIN Initiative launched in April 2013, including a historical perspective, lessons learned from the "Decade of the Brain", and the program components that may come together to yield new funds for sustained support in neuroscience. Dr. Albers will explore program and center grants to fund big science even when individual awards are down. Considering the different expectations of NIH, NSF, and private foundations, he will discuss how investigators must balance their own and their institution's missions with the vision of the agency. Opportunities for faculty development, training programs, and community engagement will be included. Dr. Frantz will address investments in a diverse cadre of future neuroscientists, with emphasis on ways to enhance education and training grants. Requirements for real broader impacts, integrated themes and strategies, solid program assessment and evaluation, and opportunities to collect and report on education research data will be discussed. Mechanisms for institutionalization of effective education and training initiatives will close the session. Together these presentations will generate new ideas among attendees for funding future brain research.

PANEL • THURSDAY, 7:30–9:30 AM • STORM PEAK

55. Novel treatments for drug and alcohol dependence

Chair: Thomas Newton
Presenters: Christopher Rodgman, Colin Haile, Thomas Newton, Steven Brimijoin

Several medications show promise as treatments for drug and alcohol use disorders. Topiramate has proved effective for the treatment of both alcohol and cocaine abuse, but has many side effects that limit its utility, specifically

somnolence, dizziness, and cognitive dysfunction. Bupropion has proved effective for the treatment of methamphetamine dependence, but only in lighter users. Disulfiram is effective for both alcohol and cocaine dependence but treatment adherence is poor and so the medication is not generally effective. We will present new data characterizing novel treatments for drug and alcohol dependence. Dr. Christopher Rodgman will present new data on how treatment with carisbamate, a medication that acts like topiramate, modifies the effects of alcohol in human volunteers. Dr. Colin Haile will present data on how treatment with penicillamine modifies to locomotor effects of cocaine in rats. Penicillamine acts like disulfiram to inhibit dopamine beta hydroxylase, thus attenuating cocaine's effects. Dr. Thomas Newton will present data showing how a new triple uptake inhibitor being developed as an antidepressant inhibits locomotor activation produced by methamphetamine in rodents. This medication acts like bupropion to block the effects of methamphetamine, but it is much more potent. Finally, Dr. Steven Brimijoin will present data from rodents and monkeys showing how transfer of a gene coding for a very active cocaine hydrolase enzyme enhances the metabolism of cocaine, thus attenuating cocaine's effects.

PANEL • THURSDAY, 7:30–9:30 AM • MT. WERNER

56. Location, location, location: Approaches to determining the function of dopamine and dopamine receptors in particular brain regions and cell types

Chair: Kim Neve
Presenters: Lauren Dobbs, Kim Neve, Martin Darvas, John Williams

For decades techniques such as microdialysis and intracerebral injections of dopamine receptor agonists, antagonists, or neurotoxins have been used to relate specific dopamine-mediated processes and behaviors to particular brain regions. Recently, a number of approaches have been developed that provide greatly enhanced specificity in terms of receptor subtype, brain region, and even particular neurons and types of neurons. In this panel, speakers will describe results obtained using four different approaches. Lauren Dobbs will present data on the role of striatal D2 receptors in cocaine reward and locomotor stimulation, obtained using a Cre-loxP approach to achieve selective loss of striatal D2 receptor in indirect pathway medium spiny neurons. Kim Neve uses a strategy in which virus-mediated D2 receptor expression on a D2-KO background is used to restore D2 receptor function in specific brain regions. He will describe his results comparing the alternatively spliced forms of the D2 receptor, D2S and D2L, in several brain regions, relating expression in these brain regions to specific types of behavior. Martin Darvas will describe a strategy in which virus-mediated Cre recombinase expression on a conditional

TH-KO background produces regionally selective loss of dopamine synthesis and will compare this strategy to 6-hydroxydopamine-induced ablation of dopaminergic neurons to identify motor and cognitive deficits related to loss of dopamine synthesis vs. loss of dopamine neurons. John Williams uses caged dopamine and Flag-D2 receptor over-expressing mice to evaluate the localization of functional D2 receptors on midbrain dopamine neurons.

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

57. Adaptive timing: Coordinating temporal precision across the synapse

Chair: George Spirou

Presenters: Paul Manis, Samuel Young, George Spirou, Leonard Kaczmarek

The auditory system must track sounds of interest against a dynamic background of fluctuating loudness and changing acoustic spectra. These environmental challenges place exceptional demands on the first few synapses along the auditory pathway, which must preserve temporal fidelity against these dynamic backgrounds to localize sounds and support other aspects of binaural hearing. The calyx of Held (CH), perhaps the largest nerve terminal in the mammalian brain, is embedded in this circuitry that defines the first location for massive binaural convergence. The experimental accessibility of the CH provides a window into synaptic and other cellular mechanisms that preserve temporal fidelity. Pre and postsynaptic functional and structural adaptive elements that support temporal fidelity will be presented and discussed. First, George Spirou (West Virginia University) will provide introductory remarks. Paul Manis (University of North Carolina, Chapel Hill) will present a compartmental, realistic biophysical model of the CH that describes neurotransmitter release at multiple (hundreds) of synaptic sites within a single calyx. Sam Young (Max Planck Florida Institute) will present roles for active zone and synaptic vesicle proteins to support a large dynamic range for rates of vesicle fusion. George Spirou will present ultrastructural substrates for rapid vesicle fusion and recovery using multi-axis, high-resolution, large volume electron tomography. Leonard Kaczmarek (Yale University) will describe adaptive features of potassium channels that are linked to protein synthesis machinery and that tune pre and postsynaptic neurons for temporal fidelity across a broad range of firing rates.

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

58. Neuroactive steroid therapeutics—translational advances on the slopes

Chair: A Leslie Morrow
Presenters: Roberta Brinton, Wenbin Deng, Christine Marx, A Leslie Morrow

Neuroactive steroids, including pregnenolone, progesterone and their GABAergic metabolites have novel pleotropic actions in the CNS. New evidence suggests that elevation of this class of steroids has promising therapeutic potential for treatment of several neurological and psychiatric disorders including Alzheimer's disease, multiple sclerosis, schizophrenia and alcoholism. This panel will address new data in both preclinical and clinical studies that supports these therapies and begins to address the mechanisms involved. Roberta Brinton of USC will present new evidence for regenerative properties of neurosteroids in animal models of Alzheimer's disease. Wenbin Deng of UC Davis will show evidence that agonists of the mitochondrial transporter that promote steroidogenesis exhibit anti-inflammatory effects in animal models of multiple sclerosis. Christine Marx of Duke will present new data on clinical efficacy for treatment of schizophrenia. Leslie Morrow of UNC Chapel Hill will present evidence that increasing steroidogenesis by viral vector-mediated gene delivery can reduce excessive drinking and ethanol reinforcement in an animal model of alcoholism. Each presenter will address the pleotropic mechanisms involved in these diverse therapeutic applications that support further development of neuroactive steroids for CNS disease.

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

59. Impulsivity: What is the underlying circuitry?

Chair: Steven Potkin
Presenters: Mark Geyer, Ross Baker, Steven Potkin, Mark Hamner

Impulsivity is a very common behavioral characteristic that cuts across traditional DSM diagnoses including schizophrenia, bipolar disorder, and PTSD. Impulsivity contributes to suicidality, substance abuse, and violence. Ventral striatal and medial prefrontal cortex dopamine release are implicated in impulsivity (Ohmura, 2012).

A proposed impulsivity circuit will be presented: prefrontal cortex, hippocampal & amygdala excitatory input (Glu) to the striatum, with modulatory input from midbrain DA neurons. The striatum inhibits (GABA) the ventral pallidum (VP) which in turns modulates the thalamus. Thalamic excitatory inputs (Glu) to the prefrontal cortex complete the loop. The right ventrolateral prefrontal cortex is key in regulating impulsivity and response

inhibition. Iowa Gambling Task performance, a medial frontal gyral function, is decreased in both schizophrenia and bipolar patients (Powers, 2013). Impulsive suicide attempts are associated with decreased frontal and temporal cortical volume in schizophrenia, schizoaffective, and bipolar subjects (Giakoumatos, 2013). Lower frontal lobe fractional anisotropy connections are associated with suicidality in bipolar subjects (Mahon, 2012). Anterior cingulate volume is negatively correlated with Barratt Impulsivity Scale scores in schizophrenia and ultra-high risk subjects. Severity of PTSD symptoms, in particular hyperarousal, negatively correlates with anterior cingulate volume. Impulsivity in PTSD is negatively correlated with hippocampal volume (Thomaes, 2010).

The speakers will discuss impulsivity as a pharmacological target; cross-species paradigms assessing impulsivity and its underlying circuitry and pharmacological modification; measures of impulsivity and imaging in schizophrenia, bipolar disorder, and PTSD, consistent with response inhibition impairment; and its modification with pharmacology.

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

60. The habenula and beyond: New questions, circuits, and roles in motivated behavior

Chair: Thomas Jhou

Presenters: Thomas Jhou, Carlos Mejias-Aponte, Eric Turner, Alice Stamatakis

In recent years the habenula and related circuitry have emerged as a powerful modulator of dopamine neurons and of motivated behavior. Seminal studies from Hikosaka's group found that some lateral habenula neurons encode negative reward prediction errors, a pattern inverse to those of dopamine neurons. This panel will explore recent new findings that explore the interaction of habenula neurons with its afferents and efferents, yielding considerable new insights into anatomical, behavioral, and physiological roles of these neurons and their relationship to other motivational circuits. First, Marisela Morales (National Institute on Drug Abuse) will provide introductory remarks. Thomas Jhou (Medical University of South Carolina) will discuss the relation of the habenula to the aversive effects of abused drugs, with implications for opponent process models of drug-seeking. Carlos Mejias-Aponte (National Institute on Drug Abuse) will discuss afferents from the ventral tegmental area cotransmitting glutamate and GABA modulating lateral habenula neurons favoring inhibition during phasic activation of VTA fibers. Eric Turner (Seattle Children's Research Institute) will discuss genetic and optogenetic studies of the reward functions of the dorsal medial habenula. Alice Stamatakis (University of North Carolina) will discuss a unique population of VTA dopaminergic neurons that release GABA in the lateral habenula to promote reward.

PANEL • THURSDAY, 4:30–6:30 PM • STORM PEAK

61. Navigating the tree line run of drug development over the next decade

Chair: David Devilbiss
Presenters: Daniel Hutcheson, Carrie Jones, Steven Leiser, Paul McCracken

The landscape of neuropsychiatric drug development is changing. Many pharmaceutical companies have determined that the risks associated with drug development for central nervous system (CNS) disorders are too great. A lack of understanding of the neurobiological mechanisms of psychiatric diseases, paucity of innovations in target identification, and lack of preclinical models with high clinical validity and predictive value are cited as among the challenges that still face development of CNS therapeutics. However to address these challenges, pharmaceutical companies are navigating this experts only terrain with pioneering approaches to CNS drug development. New drug discovery centers at academic institutions are focusing on early-stage therapeutic development to bring treatments into clinical trials. Additionally, translatable preclinical models with high predictive value are being applied throughout the drug discovery process. This panel discussion will be opened by Daniel Hutcheson (Pfizer - Chief Operating Officer) detailing how a major pharmaceutical company is rethinking its approach to address the challenges of CNS drug development. Carrie Jones (Vanderbilt - Center for Neuroscience Drug Discovery) will present how a center for drug development in an academic setting is tackling drug development with allosteric modulators. Steve Leiser (Lundbeck - BioAnalysis & Physiology) will present data on the use of EEG as a drug development strategy with a high translatable validity. Paul McCracken (Eisai - Director of Imaging Biomarkers and Personalized Medicine) will conclude with data on the use of imaging as an critical translational methodology for CNS drug development.

PANEL • THURSDAY, 4:30–6:30 PM • MT. WERNER

62. Corticostriatal plasticity and reward-related learning

Chair: Jacqueline McGinty
Presenters: Donna Calu, Susan Marie Ferguson, Alexxai V Kravitz, Colleen Hanlon

The prefrontal cortex (PFC) regulates emotional and cognitive processing through its connectivity with the dorsal and ventral striatum. In this panel, four young investigators will discuss developments in technology during the past decade that have provided precise approaches to determining the impact of manipulating corticostriatal functioning on reward-related learning. Donna Calu will discuss evidence that light delivery to the dorsal medial PFC disrupts

endogenous neural activity of halorhodopsin (eNpHR3.0)-expressing neurons that play a critical role in stress-induced reinstatement of food seeking in a female rat relapse model. Susan Ferguson will present her recent work using DREADD (Designer Receptors Exclusively Activated by Designer Drugs) receptors to better understand the role of the direct and indirect striatal pathways, as well as cortical projections to striatum, in behaviors associated with drug addiction and decision-making. Lex Kravitz will discuss evidence that direct pathway striatal neurons facilitate reinforcement whereas indirect pathway striatal neurons promote punishment. However, rather than opposing one another equally, differences in the kinetics and strength of these effects may shed light onto different plasticity mechanisms that affect each pathway during learning about positive and negative outcomes. Colleen Hanlon will discuss current studies in human cocaine users that utilize non-invasive brain stimulation in the magnetic resonance scanner to probe corticostriatal connectivity. Her results suggest that external activation of the medial PFC is associated with a greater response in the striatum of cocaine users than in non-drug using subjects and that this enhancement may be related to drug use and relapse history. Jacqueline McGinty will facilitate the discussion of how these different approaches illuminate corticostriatal plasticity underlying reward-related learning.

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

63. Methods to explore the brain: Peptides, light and toxins

Chair: Stewart Clark
Presenters: Leslie Sombers, Ream Al-Hasani, Stewart Clark, Ines Ibanez-Tallon

Neuropeptides have powerful and long-lasting effects on brain function. They modulate almost every neuronal circuit in the brain by direct action or by altering the response to classical transmitters (glutamate). Although neuropeptides are often expressed by clusters of neurons that project diffusely throughout the nervous system, they are in low abundance (relative to classical neurotransmitters). Therefore, it has been difficult to assess where and when neuropeptides are released. Leslie Sombers (North Carolina State University) will discuss an advance in voltammetry that is able to detect endogenous opioids in real-time. Complementary to this technique, is the optogenetic manipulation of neuropeptide systems. Ream Al-Hasani (Bruchas Lab, Washington University , St. Louis) will describe recent developments in using optogenetics in understanding opioid neuropeptides in the control of reward and aversive behaviors.

Bioactive peptides comprise a diverse group of neuromodulators. Some are highly conserved throughout evolution and others have evolved to bind targets within other species (toxins). Generally peptides have high affinity and

selectivity for their targets. These attributes can be technically exploited. Two methods will be discussed: 1) ablation of Urotensin II receptor expressing cells from the hindbrain (Stewart Clark, University at Buffalo), and 2) inducible and selective inhibition of exocytosis by use of tethered venom toxins (Ines Ibanez-Tallon, Rockefeller University). The first uses the microinjection of recombinant protein fusions of diphtheria toxin with neuropeptides. Therefore, it does not require genetic manipulation, and thus can be easily transferred to a variety of organisms (e.g. rats, invertebrates). The second exploits floxed inducible transcription systems within CRE expressing animals to deliver calcium channel blocking toxins to specific neuronal populations. This technique allows for the temporal "silencing" of presynaptic terminals.

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

64. Seizures, autism, neuronal injury and the plasticity of the immature brain: from bench to bedside

Chair: Claude Wasterlain

Presenters: Angus Wilfong, F. Edward Dudek, Jeffrey Ekstrand, Anne Anderson

It has been 40 years since the publication of the first experimental study of the effect of seizures on brain development, and the issue is as controversial as ever. Does the association of seizures with neuronal injury point to a causal relationship, or are seizures and neuronal injury independent effects of the same cause? When a mutation causes seizures, autism and cognitive deficits, do the seizures play a role in the development of associated pathologies? Does the loss of language and intellect in a child with status epilepticus during slow wave sleep have anything to do with the asymptomatic EEG seizures? This controversy has produced more heat than light, and there is even disagreement on the most basic facts in animal models. However, it has also improved our understanding of seizures and cerebral plasticity, and its basic molecular biology is seeing therapeutic applications.

Claude Wasterlain (UCLA) will lead the discussion. Angus Wilfong (Baylor College of Medicine) will review the clinical evidence associating early life seizures with other brain pathologies. He will describe the effects of the surgical treatment of epilepsy on a child's autistic behavior, and studies targeting the mtor pathway in tuberous sclerosis. Ed Dudek (University of Utah) will review the basic science of seizure-associated neuronal injury in animal models, and will illustrate it by showing the role of seizures in hypoxia-induced neuronal death. Jeff Ekstrand (Utah) will describe widespread extra-hippocampal neuronal injury after status epilepticus in rat pups. Anne Anderson (Baylor) will discuss pten KO mice and outline the role of the mTOR pathway in seizures, and its therapeutic implications.

This will be a highly interactive session. Presentations will be succinct, experimental data will be used to illustrate concepts and generate discussion. Bring your own ideas and show us the other side of the coin.

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

65. 45 years of motor control: Accounts of where we were and where we are

Chair: Andrew Schwartz

Presenters: Lawrence Young, Jim Bloedel, Ed Keller, Andrew Schwartz

A group of senior WCBR veterans will review 'historical' changes in concepts and principles related to four different areas of systems motor control that have taken place since the beginning of these meetings. Lawrence Young will recount how the field of human spatial orientation was expanded by the opportunity to test in weightlessness and on centrifuges. In 40 years we have moved away from the simple interpretation of otolith signals as measurement of the direction of the vertical. The ability of the nervous system to use semicircular canal, tactile and visual cues to help separate gravity from linear acceleration is a remarkable example of sensory-motor adaptation. Jim Bloedel will discuss the progressive changes in the concepts of cerebellar function during the past fifty years. This discussion will focus on the transition from concepts based on electrophysiological data in acute preparations to those based on the relationship between single and multi-electrode recordings and the motor behavior of intact animals. Findings related to the cerebellum's role in goal-directed movements, reflex regulation, as well as motor learning will be addressed. Keller will describe progress in understanding the neurophysiology of the oculomotor system. Substantial progress began with the introduction of methods to accurately measure eye movements. This allowed investigators to understand the mechanics of the orbital tissues. Next came the ability to record motoneurons in the brainstem in the alert behaving monkey. Understanding of the activity of motorneurons allowed quantitative studies of premotor centers that project to ocular motoneurons. More recent advances have carried these approaches to the level of cortical structures where motor function melds with cognitive studies. At each level of neural investigation quantitative modeling studies have provided solid theoretical foundations for the neurophysiological and anatomic studies. Andy Schwartz will discuss how concepts of motor cortical function have evolved from "upper motorneurons" to populations encoding complex aspects of behavior. The utility of these more recent functional principles will be demonstrated with brain-controlled prosthetics based on population decoding algorithms used to restore movement to paralyzed individuals.

66. COMT: From fantasy to fact

Chair: Elizabeth Tunbridge
Presenters: Amanda Law, Elizabeth Tunbridge, Daniel Weinberger

The catechol-O-methyltransferase (COMT) enzyme regulates dopaminergic transmission, particularly in the prefrontal cortex. Its gene contains a common polymorphism (Val158Met), which directly alters enzyme activity. Relative reductions in COMT activity (mediated either as the result of the low activity Met158 allele of COMT, or COMT inhibition) are generally beneficial for the performance of certain cognitive tasks, especially tests of working memory. COMT is one of the best-studied genes in psychiatric research and remains an attractive therapeutic target for treating cognitive dysfunction. However, it is increasingly clear that links between COMT and phenotypes relevant to psychiatry are modulated by a number of other factors, both genetic and environmental, and that COMT influences cognitive domains beyond working memory and executive function. This symposium will investigate some of these complexities and will examine the therapeutic potential of COMT inhibitors for psychiatric disorders. Following a brief overview of the 'classic' story, linking the COMT Val158Met polymorphism, prefrontal dopamine and executive function, Amanda Law (University of Colorado, School of Medicine) will demonstrate that multiple loci within the COMT gene modulate its function. Elizabeth Tunbridge (University of Oxford) will demonstrate that the effect of COMT inhibition on brain activation and behaviour depends on Val158Met genotype, and will discuss COMT's relevance for reward processing. Daniel Weinberger (Lieber Institute for Brain Development) will present data showing the effects of COMT inhibition in various clinical groups, as well as demonstrating interactions between COMT and other genetic factors and the environment. Together, these presentations will provide an up to date overview of the impact of COMT on brain function, and its therapeutic potential for psychiatric disorders.

Poster Abstracts

SUNDAY, JANUARY 26, 2014

P1 • Grouping central serotonin neurons by their networks

Kathryn Commons, Yueping Guo*

A current hypothesis is that serotonin neurons are organized into functional subgroups and as a consequence, malfunction of particular subgroups could yield different neuropsychiatric disorders. However, meaningful functional subgroups remain poorly defined, even though many groups of serotonin neurons have unique cytoarchitecture. In order to be functionally distinct, neurons must be differently connected to extrinsic brain regions. In this study we sought to define subregions of the largest group of serotonin neurons, those located within the dorsal raphe nucleus (DRN), by differential afferent input using the Allen Brain Connectively Atlas (Website: ©2012 Allen Institute for Brain Science. Allen Mouse Brain Connectivity Atlas [Internet]. Available from: http://connectivity.brain-map.org/). Projection patterns were aligned with reference images of serotonin neurons, and the density of axons in different areas was measured using NIH's Image J software. Principal component analysis and unsupervised hierarchical clustering were used. Two major subdivisions of the DRN were found. Specifically, there were major differences in afferent input to the rostral two thirds of the DRN in comparison to the caudal one third, or B6 portion. The rostral two thirds of the DRN received preferential innervation from the hypothalamus and preoptic areas. The caudal third of the DRN received selective innervation from anterior cingulate cortex, medial septum, mammillary nuclei and lateral habenula. Taken together with know patterns of forebrain projections, these data suggest the DRN can be divided into two groups with coherent projection sources and targets. This distinct network connectivity in turn underlies their role in behavior.

P2 • Aberrant organization of presynaptic active zones 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 describe here the structure and

organization of presynaptic terminals at the larval neuromuscular junction in flies engineered to express wild type or mutant (R521C) human FUS in motor neurons. Standard confocal imaging reveals no obvious differences in bouton size or number between wild type FUS and R521-FUS-expressing flies, but we did not explore this further because of the limitations in resolution of confocal microscopy. Instead, we imaged the presynaptic active zone marker bruchpilot using super-high resolution stimulated emission depletion (STED) microscopy. Consistent with prior work, STED imaging of bruchpilot in wild type flies reveals that it is localized in structures thought to be individual active zones, many of which are doughnut shaped. Transgenic flies expressing R521C-FUS appear to have normal numbers of bruchpilot positive active zones, but there is a 50% reduction in the number of active zones with doughnut holes. To determine quantitatively whether active zones in R521C-FUS flies are misshapen compared to those in wild type FUS flies, we examined the relationship between the size of the doughnut hole and overall active zone area. While the areas of individual active zones are similar in wild type FUS and R521C-FUS-expressing flies, the size of the bruchpilot active zone is less well correlated with the size of the doughnut hole in the R521C-FUS flies. The data suggest that aberrantly organized and misshapen presynaptic active zones may contribute to the profound defects in synaptic transmission observed in ALS.

P3 • Defects in synaptic transmission precede motor neuron degeneration in Drosophila models of amyotrophic lateral sclerosis

Mohammad Shahidullah, Irwin Levitan*

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease that leads invariably to fatal paralysis. A hallmark of ALS is malfunction and disruption of the neuromuscular junction, with eventual denervation and muscular atrophy, but the locus and site of initiation of this neuromuscular dysfunction remain unclear. Among the genes associated with both familial and sporadic forms of ALS is one that encodes the DNA/RNA binding protein Fused in Sarcoma (FUS). There now exist two Drosophila models of FUS-related ALS (called, collectively, FUS-ALS flies). In one, human FUS with ALS-causing mutations is expressed in fly motor neurons, and in the other the gene cabeza (caz - the fly homolog of FUS) is ablated. We show here, using both current clamp and voltage clamp recordings from larval motor neuron cell bodies, that motor neurons in FUS-ALS flies fire normal action potentials, and the voltage-dependent inward and outward currents in the cell bodies are indistinguishable in wild type and FUS-ALS motor neurons. Furthermore, extracellular recording from motor neuron axons demonstrates that spontaneous action potentials propagate normally along the axon, from the cell body, in FUS-ALS larvae. In marked contrast, glutamatergic synaptic

transmission at the larval neuromuscular junction is profoundly impaired in FUS-ALS larvae. The amplitude of excitatory synaptic currents, evoked in the postsynaptic muscle cell by stimulation of presynaptic motor axons, is decreased by more than 80% compared with wild type larvae. In addition, the frequency of spontaneous miniature synaptic currents is decreased dramatically in FUS-ALS larvae, suggestive of a presynaptic locus for the early defect in synaptic transmission. The results are consistent with the idea that defects in neurotransmitter release from motor neuron presynaptic terminals precede, and may contribute to, the later motor neuron degeneration that is characteristic of ALS.

P4 • Prolonged inhibition of RhoA by HSV-mediated gene transfer of C3 transferase enhances corticospinal tract regeneration after spinal cord injury

David Fink, Rachana Murthy, Marina Mata*

In spinal cord injury (SCI) activation of RhoA in axons by molecules expressed by astroglial cells inhibits axonal extension. C3 transferase (C3t) is an enzyme isolated from clostridia that inhibits RhoA by ADP-ribosylation. We tested a non-replicating herpes simplex virus (HSV)-based vector expressing C3t (vC3t) injected into motor cortex 1 hr after injury in the C6 dorsal hemisection model of SCI. The size and characteristics of the injury were determined by GFAP immunofluorescence microscopy, completeness of the lesion confirmed by retrograde tracing with fluorogold, and axonal regeneration assessed by BDA labeling. At 4 months after injury, 66% of rats with C6 hemisection and injected with vC3t into motor cortex showed regeneration of CST axons into the mid-thoracic cord; these axons were located in the normal site of the CST. The remaining 33% of animals with C6 SCI injected with vC3t had large cavities that blocked regeneration of CST axons in the proper location, but BDA positive axons were observed in aberrant locations in the lateral and ventral white matter or sprouting into the gray matter. Only 10% of rats with C6 SCI treated with control vector had any BDA positive fibers below the injury site. These data indicate that prolonged inactivation of RhoA in motor neurons by delivery of C3 transferase to the motor cortex provides significant regenerative capacity of the CST axons after cervical SCI. In injuries that result in large cavities, C3t gene transfer will need to be combined with another treatment to provide a substrate for axonal regeneration across the cavity.

P5 • LTD requires "autonomous" CaMKII and involves phosphorylation of S567 on the AMPA Receptor GluA1 subunit

Steven Coultrap, Ronald Freund, Jennifer Sanderson, Heather O'Leary, Katherine Roche, Mark Dell'Acqua, K. Ulrich Bayer*

Long-term potentiation (LTP) and depression (LTD) are two opposing forms of Ca2+-dependent synaptic plasticity thought to underlie learning, memory, and cognition. The Ca2+/calmodulin(CaM)-dependent protein kinase II (CaMKII) and its "autonomous" (Ca2+-independent) activity generated by T286-autophosphorylation have been tightly linked to LTP induction. Here, we demonstrate that NMDA receptor-dependent LTD also requires CaMKII and its autonomous activity. Like LTP, LTD induced T286-phosphorylation and was blocked by CaMKII inhibition, CaMKIIα knockout, or T286A mutation. Thus, opposing forms of plasticity share "autonomous" CaMKII as principle upstream mediator. However, the CaMKII-mediated downstream effect on the AMPA-type glutamate receptor (AMPAR) subunit GluA1 differed: While LTP promotes phosphorylation at S831 to increase channel conductance, LTD instead promoted phosphorylation at S567, a site that reduces synaptic localization and thereby current. In vitro, maximal phosphorylation by "autonomous" CaMKII required additional Ca2+/CaM-stimulation for S831, as expected for traditional substrates, but not for S567. These and other results show that S567 represents a novel substrate-class for which phosphorylation by CaMKII is favored under LTD conditions. Thus, the Ca2+-independent activity of CaMKII resulting from T286 autophosphorylation is an important mediator of both NMDA receptor-dependent LTP and LTD, and strong further Ca2+ stimulation in LTP versus weak stimulation in LTD is involved controlling the differential phosphorylation of downstream targets that results in potentiation versus depression of synaptic strength.

P6 • Measuring absolute concentrations of neurotransmitters in vivo with fast-scan controlled-adsorption voltammetry

Christopher Atcherley, Kevin Wood, Kate Parent, Parastoo Hashemi, Michael Heien*

Fast scan cyclic voltammetry with carbon-fiber microelectrodes is an excellent scheme for the detection of rapid changes in catecholamine concentrations in vivo. Due to the rapid scan rates, a large background is generated and must be subtracted to detect small concentration changes in vivo. This requirement limits this technique to measuring fast (phasic) changes. By taking advantage of the adsorptive properties of biogenic amines, such as dopamine and serotonin,

a new detection scheme, fast-scan controlled adsorption voltammetry (FSCAV) was developed to enable measuring slow(tonic) changes in the absolute concentration. By altering the waveform application frequency the time allowed for adsorption to occur is altered. A switch is then used to interrupt waveform application and apply a constant potential to maximize adsorption of biogenic amines at carbon-fiber microelectrodes. After 10s the waveform is reapplied and the resulting cyclic voltammogram is measured, enabling the measurements of absolute concentrations. Using FSCAV, the tonic concentration of dopamine in the nucleus accumbens core is measured to be 210 ± 25 nM, and 5- HT was measured to be 20 nM in the substantia nigra. The measured signals were verified pharmacologically and by electrical stimulation. Additionally, the selectivity of FSCAV for biogenic amines over metabolites and interferences is investigated.

P7 • Recruitment of serotonergic responses in cardiac vagal neurons during hypoxia and hypercapnia

Peter Byrne, Letitia Weigand, David Mendelowitz*

Parasympathetic activity to the heart increases following exposure to hypoxia and hypercapnia (H/H). Parasympathetic cardiac vagal neurons (CVNs), located in the nucleus ambiguus (NA), dominate the control of heart rate. The recruitment of excitatory 5-HT receptor-mediated responses in CVNs plays a role in the post-H/H responses; however the mechanisms underlying this recruitment remain unclear. As a first step toward understanding how H/H leads to increased 5-HT signaling in rat CVNs we examined the responses of these neurons to 5-HT in in vitro brain slices before, during, and for 20 minutes after H/H (15 min; 6% O2-9% CO2). Recording of excitatory post-synaptic currents evoked by photoactivation of caged 5-HT (100 μM for 10 ms every 30 s) revealed an inward 5-HT receptor-mediated current that increased in magnitude during H/H. In CVNs exposed to H/H this inward current increased from a mean of -8 ± 1.3 pA during normoxia (95% O2-5% CO2) to -40 ± 1.4 pA during H/H, and -75 ± 0.4 pA 20 minutes post-H/H (n=7). Pretreatment with ondansetron (100 μM), a competitive 5-HT3 receptor antagonist partially blocked the recruitment of 5-HT responses (peak amplitude during H/H of -20 ± 0.9 pA, and -40 ± 1.2 pA 20 minutes post-H/H), a respective reduction of 50% and 47% compared to responses in the absence of ondansetron.(n=3). These preliminary data suggest that 5-HT3 receptor-mediated responses are recruited during H/H and persist post-H/H, possibly due to increases in 5-HT receptor trafficking to the postsynaptic membrane in CVNs during H/H.

P8 • A primate specific and brain enriched miRNA, is involved in major depression and antidepressant treatment

Gustavo Turecki

Major depressive disorder (MDD) is a prevalent mood disorder that associates with differential prefrontal brain expression patterns. Several lines of evidence demonstrate that genes are regulated through the activity of microRNAs (miRNAs), which act as fine-tuners and on-off switches in gene expression patterns. Here we report on complementary studies using postmortem human brain samples, cellular assays and samples from clinical trials of depressed patients, and show that miR-1202, a miRNA specific to primates and enriched in the human brain, is differentially expressed in the prefrontal cortex of depressed individuals. MiR-1202 regulates the expression of the Metabotropic Glutamate Receptor 4 (GRM4) gene and responds to antidepressant treatment. These results suggest that miR-1202 is associated with the pathophysiology of depression and is a potential target for novel antidepressant treatments.

P9 • Genome-wide analysis of MeCP2-mediated transcriptional regulation in the brain

Harrison Gabel, Benyam Kinde, Daniel Ebert, Michael Greenberg*

Rett Syndrome (RTT) is neurodevelopmental disorder caused by mutations in the methyl-DNA binding protein MeCP2. While many activities have been assigned to MeCP2, it is unclear which proposed functions contribute to RTT when disrupted. Recent studies indicate that a common RTT MeCP2 missense mutation, arginine 306 to cysteine (R306C), specifically disrupts an association of MeCP2 with the NCoR transcriptional corepressor complex. Thus, a critical function of MeCP2 that is lost in RTT may be to recruit NCoR and repress transcription. We have found that neuronal-activity induced phosphorylation at threonine 308 on MeCP2 blocks NCoR from binding MeCP2, relieving transcriptional repression and facilitating activity-dependent gene induction. To better understand the function of the MeCP2-NCoR interaction we have generated MeCP2 knock-in mice carrying either the R306C or a threonine 308 to alanine (T308A) missense mutation: The R306C mutation disrupts the MeCP2-NCoR interaction, while the T308A mutation specifically inhibits the phosphorylation of T308 in response to neuronal stimulation. Candidate-based analysis of neuronal gene expression in MeCP2 T308A knock-in mice indicates that several activity-induced genes have blunted induction in response to neuronal stimulation. Notably, some of these genes are known to promote inhibitory synapse formation on excitatory neurons, suggesting that the MeCP2-NCoR interaction may help to modulate excitatory-inhibitory balance in the brain. We are now performing a systematic analysis of gene

expression and NCoR genomic binding in R306C and T308A mutant mice using RNA-Seq and ChIP-seq technologies. By understanding what genes have altered expression, and determining where on the genome NCoR binding is disrupted in these mutants we hope to build a model of dynamic MeCP2-NCoR-dependent gene regulation in the brain.

P10 • Fast-scan cyclic voltammetry; A new screening tool for anti-depressants

Parastoo Hashemi, Kevin Wood, Frederik Nijout, Michael Reed, Janet Best*

Depression, a neurological disease, debilitates the lives of millions of Americans every year. Anti-depressants are some of the most commonly prescribed medications in the USA, however these medications are variable in therapeutic outcome and have low efficacy rates. Because the in-vivo neurochemical mechanisms of anti-depressants are poorly understood, it is difficult to design them to be more therapeutically effective. Moreover, anti-depressant screening is primarily based on behavioral tests in rodents and there are inconsistencies between these tests and clinical outcome. The most common anti-depressants, selective-serotonin reuptake inhibitors (SSRIs), target the brain's serotonin system. Fast scan cyclic voltammetry (FSCV) at carbon fiber microelectrodes is a powerful tool for studying in vivo serotonin dynamics. With FSCV, we have previously identified important in vivo serotoninergic mechanisms. We also assessed the effects of systemic administration of SSRIs and found that after a single dose of SSRI, the serotonin signal was changeable within 2 hours, indicating short-term synaptic regulatory mechanisms . In this work, we find that serotonin measurements over 2 hours following SSRI administration have different profiles unique to each different anti-depressant. We create 3-dimensional mathematical models, based on Michaelis-Menten Kinetics, that describe each antidepressant profile. By training the model, we show that it can be used to positively correlate antidepressant efficacy to clinical outcome. We hence present the first voltammetric neurochemical screening method for antidepressant efficacy.

P11 • A proposed neuronal circuitry underlying reward prediction signaling by dopamine neurons

Tibor Koos

The midbrain dopaminergic system provides reward prediction error (RPE) signals that are believed to be important for the modification of synaptic and cellular properties that underlie adaptive behavioral change during reinforcement mediated learning. Elucidating how the dopaminergic (DAergic) RPE signals lead to adaptive behavioral change has been of great

interest but this line of investigation is significantly complicated by the limited understanding of the organization of cortical-basal ganglia circuits and the precise behavior function of this system. In contrast, understanding how dopaminergic RPE signals regulate the synaptic and circuit modifications that underlie the acquisition of RPE signals themselves may be more easily addressed because learned changes in dopaminergic firing offer a direct and functionally interpretable measure of circuit modification that occurs during learning. This avenue of exploration rests critically on understanding the neuronal circuitry responsible for controlling the RPE signals of DA neurons. Here, using plausible assumptions about the properties of this learning mechanism we propose a circuit model and learning rules that may account for the development of RPE signals in DA neurons during conditioning.

P12 • NMDA receptors in primary afferents are potentiated by BDNF released by microglia during the induction of neuropathic pain

Juan Carlos Marvizon, Wenling Chen, James MacRoberts*

We previously found that BDNF induces the activating phosphorylation of the NR2B subunit of NMDA receptors in primary afferents, increasing NMDA-induced substance P release measured as neurokinin 1 receptor (NK1R) internalization. Since spinal cord microglia release BDNF during the onset of neuropathic pain, we hypothesized that these NMDA receptors become potentiated after nerve injury. To confirm this, we gave rats chronic constriction injury (CCI) of the sciatic nerve and intrathecal NMDA at various times thereafter. Mechanical allodynia (hind paw withdrawal to von Frey hairs) developed during the first two days after CCI. Ipsilaterally to CCI there was a marked increase in NMDA-induced NK1R internalization that peaked 6 hr after CCI and lasted 3 days. Contralaterally, NK1R internalization increased in days 2 and 3. Intrathecal saline after CCI or intrathecal NMDA after sham surgery resulted in negligible NK1R internalization. To investigate the signals involved, CCI rats were given microglia inhibitors (minocycline, fluorocitrate or propentofylline), the BDNF scavenger trkB-Fc, the trkB antagonist ANA-12, the Src family kinase inhibitor PP2 or saline; all of which inhibited NMDA-induced NK1R internalization. We also determined whether activating microglia with lipopolysaccharide (LPS) increases NMDA-induced NK1R internalization. LPS induced microglia activation, measured with the microglia marker Iba-1 in the dorsal horn. NMDA-induced NK1R internalization increased after LPS, peaking at 6 hr and disappearing by 24 hr. This increase in NMDA-induced NK1R internalization LPS was decreased by trkB receptor antagonist ANA-12, the BDNF scavenger trkB-Fc or the Src family kinase inhibitor PP2. Therefore, NMDA receptors in primary afferent terminals are

potentiated during the induction of neuropathic pain as the result of BDNF release from microglia, activation of trkB receptors and phosphorylation of the NR2B subunit by a Src family kinase.

P13 • Hypothermia increases synaptic inhibition with effects on GABA-A receptor kinetic properties and drug interactions

David Naylor

Hypothermia has been beneficial in the treatment of severe neurological injuries that include hypoxic ischemic injury/stroke, traumatic brain injury, and status epilepticus. Here we explore hypothermia actions on synaptic inhibition using visualized whole-cell patch-clamp in hippocampal slices. We find that lowering temperature from 34 deg C to 21–26 deg C has dramatic effects on miniature IPSCs with an increase in the decay-time (11.7 +/– 4.0 to 21.2 +/– 6.4 ms; p<.05), Area-Under-the-Curve (-705 +/– 85 to –1170 +/– 331 pA ms; p<.05), and 10-90% rise-time (.36 +/– .05 to .54 +/– .14 ms; p<.05). A peak amplitude change from –61.9 +/– 13.2 to -56.0 +/– 10.2 pA at lower temperatures was not significant. Hypothermia also has effects on the effectiveness of pharmacological agents such as barbiturates with phenobarbital (200uM) having a modest 41% and 27% increase in the decay-time and AUC, respectively, during hypothermia, but a strongly significant 180% and 165% increase in decay-time and AUC under more normothermic conditions. A decrease in miniature IPSC frequency from 3.4 +/– 1.0 to 1.6 +/– .4 Hz suggests presynaptic actions of hypothermia as well. Preliminary results using a 7-state GABA-A receptor kinetic computational model suggests that hypothermia has effects on kinetic parameters including a prolongation of open state duration. Because barbiturates also prolong GABA-A receptor open-state duration, the reduced effectiveness of phenobarbital with hypothermia may represent an occlusive interaction between the two types of therapy. In conclusion, hypothermia has direct effects on GABA-A receptor kinetics that may be important at extrasynaptic sites and tonic inhibition as well. The enhancement of inhibition with hypothermia may be an important therapeutic mechanism. Computational optimization of a combination of non-pharmacological with pharmacological therapies should improve the effect and outcome of treatment, while minimizing untoward effects with re-warming.

P14 • Directly testing the functional roles of resting state networks

Stephen LaConte, Giuseppe Pagnoni, Jonathan Lisinski, Anders Eklund, Cameron Craddock*

Over the last several years, we have developed a real-time fMRI system that is based on predictive models from a class of multivariate techniques (e.g. support vector machines (SVMs), neural networks, and linear discriminant analysis) that determine the relationship between the image data and the corresponding sensory/behavioral conditions (brain states). In our implementation, this intensive computational modeling can be done during and immediately after a training run (when the MR scanner is idle and setup and instructions are occurring for the testing feedback run). Once a model is trained, it can be used to decode new images in a computationally efficient manner (LaConte et al., 2007; LaConte, 2011). Although direct, real-time access to the DMN and other resting state networks for scientific investigation has been previously impossible, our latest technological development in this area has been the ability to track resting state networks in both offline and real-time fMRI settings. We are actively pursuing this capability as a tool for neurofeedback to study the mechanism of default mode network (DMN) regulation and its role in psychiatric and neurological disorders (Craddock et al., 2011; Craddock et al., 2012; Eklund et al., 2013). In this talk we present our methodology as well as discuss our latest results and ideas from ongoing neurofeedback experiments and a set of experiments that aim to directly test the roles of resting-state networks with real-time fMRI.

P15 • Causal inference in multisensory speech perception

Michael Beauchamp, John Magnotti, Weiji Ma*

During speech perception, humans integrate auditory information from the voice with visual information from the face. This multisensory integration increases perceptual accuracy only if the two cues originate from a common cause, a requirement largely ignored by current quantitative models of speech perception. The temporal relationship between two cues provides strong evidence about the causal relationship between auditory and visual speech events. We developed a generative model of multisensory speech perception that uses asynchrony to accomplish the critical step of determining whether the auditory and visual information arise from a common cause. In the model, observers integrate the auditory and visual cues according to the likelihood that these cues have the same underlying cause, giving them weight proportional to their reliability. The model makes specific predictions about how temporal information should be used to determine the likelihood that two speech events originated from a single talker. We tested these predictions with data

from thirty-seven participants that performed a synchrony judgment task using audiovisual speech stimuli that had varying asynchrony, visual cue intelligibility, and visual cue reliability. We compared the causal inference model with a popular alternative approach for assessing synchrony perception, Gaussian curve fitting. The causal inference model provided a better fit to the behavioral data with fewer free parameters than the Gaussian method across four conditions and two experiments. The causal inference model achieves this better fit by adding constraints derived from a principled analysis of how an optimal observer should solve the causal inference problem using the asynchrony and reliability of the cues. Because the causal inference model is derived from a principled understanding of the task, model parameters are directly interpretable in terms of stimulus and subject properties.

P16 • Evidence for neuroinflammation in the NS-PTEN KO mouse model of cortical dysplasia with epilepsy

Amy Brewster, Lena Nguyen, Anne Anderson*

Cortical dysplasia (CD) is characterized by malformation of the cortex and epilepsy. At the molecular level, CD is associated with hyperactivation of the mammalian target of rapamycin (mTOR) pathway and with inflammation and gliosis (micro- and astrogliosis). While aberrant mTOR signaling and neuroinflammation are associated with recurrent seizures, the link with epilepsy is unclear. In this study, we evaluated neuroinflammation in a mouse model of CD characterized by epilepsy and constitutively active mTOR pathway due to a neuronal subset-specific knockout of the PTEN gene (NS-PTEN KO). We used western blotting and immunohistochemistry to examine the protein levels and distribution of markers of microglia (IBA1, CD11b), astrocytes (GFAP), neurons (NeuN), and mTOR pathway activation (phosphorylated ribosomal S6 protein)(p-S6) in the hippocampi of adult NS-PTEN KO and WT mice. We found that the staining for IBA1, CD11b, GFAP and p-S6 appeared stronger in hippocampi from KO compared WT mice. In KOs, IBA1- and CD11b-stained microglia appeared amoeboid and hypertrophied compared to WTs. As expected, intense p-S6 staining was evident in cells lacking PTEN within the granule cell layer dentate gyrus of the KOs. p-S6 staining co-localized with NeuN in both WT and KO groups. However, only in KOs was p-S6 staining co-localized with scattered CD11b-stained microglia within CA1 and CA3 hippocampal areas. Our findings suggest increased activation of micro- and astroglia in the hippocampus of NS-PTEN KO mice, and hyperativation of the mTOR pathway in reactive microglia, suggesting a role for mTOR hyperactivity in the inflammatory process associated with CD. Future studies will evaluate if immunosuppressant treatments have seizure-attenuating effects in this model of CD.

P17 • Towards a possible animal model for late chronotypes

Sheng Zhou, Jonathan Qiao, Tiecheng Liu, Jimo Borjigin*

Biological rhythms are described as chronotypes, commonly associated with sleep-wake cycles controlled by the pineal gland. Despite offering insights into personalized medicine, chronotypes are not well understood due to a lack of precise animal models and standard measurement techniques. Present experimental procedures approaches in chronotype experiments are limited as they only take into account variations in chronotypes among different animal strains. Here, we conduct a long-term rat-based melatonin cycle study controlling for facility, company, strainal, and temporal variation toward the development of an animal model for 'late' chronotype. Data collection was performed on outbred Sprague Dawley, Wistar, Long Evans, and CD rats over the course of eight years. Pineal microdialysis was used to collect samples of melatonin, a hormone whose phasic secretion may be utilized as a key chronotype marker. The relative concentrations of melatonin throughout the day were then determined using high performance liquid chromatography (HPLC). Of particular interest, rats of the same strain but from different companies or facilities displayed statistically significant temporal differences in their melatonin cycles. Through controlling for the aforementioned differences, we see the Sprague Dawley rat as a potential animal model for late chronotype due to its consistency. Such a longitudinal, quantitative characterization of chronotypes will facilitate more exact approaches toward biological rhythm research.

P18 • Brainstem stimulation augments information integration in the cerebral cortex of desflurane-anesthetized rats

Anthony Hudetz, Siveshigan Pillay, Jeannette Vizuete, Xiping Liu, Gabor Juhasz*

Anesthetic agents may suppress consciousness by reducing the number of available brain states and consequently information integration. Neuromodulatory brainstem and subcortical circuits exert precise control of the cortical state, arousal and attention. Here we test the hypothesis that electrical stimulation of the nucleus Pontis Oralis (PnO) can increase information integration in cortical neuronal networks of the rat in vivo. Extracellular unit activity and local field potentials were recorded in freely moving animals from parietal association (PtA) and secondary visual (V2) cortices via chronically implanted microwire arrays at three levels of anesthesia produced by desflurane: light sedation (3.5%), unconsciousness (4.5%), and moderately deep anesthesia (6.0%). Information integration was characterized by integration (multiinformation) and interaction entropy, estimated from the statistical distribution of coincident spike patterns. PnO stimulation elicited

electrocortical activation as indicated by the reductions in δ- and θ-band powers at the intermediate level of anesthesia. PnO stimulation augmented integration and interaction entropy; these changes were most consistent in the PtA at all desflurane concentrations. Visual stimulation of the contralateral retina, after PnO stimulation, with discrete light flashes elicited an additional increase in interaction entropy relative to Post-PnO at 3.5, and 4.5% desflurane in V2. The results suggest that PnO may modulate spontaneous ongoing and sensory stimulus-related cortical information integration under anesthesia. Supported by NIH/NIGMS R01-GM056398.

P19 • Roles of the unique α4:α4 agonist binding site in the (α4)(β2)2-nicotinic acetylcholine receptor isoform in a form of positive allosteric modulation and in desensitization of functional responses

Ronald Lukas, J Brek Eaton, Harrison Stratton, Yongchang Chang, John Cooper, Jon Lindstrom, Paul Whiteaker*

Realization is new that nicotinic acetylcholine receptors (nAChR) composed as pentamers of α4 (a4) and β2 (b2) subunits can exist as two structural isoforms that also happen to have ~100-fold different sensitivities to acetylcholine (ACh) and nicotine. This has potentially enormous implications, because high-sensitivity (HS) (a4)2(b2)3-nAChR would be expected to respond not just to synaptically-released ACh, which achieves concentrations of 0.1-1 mM, but also to interstitial ACh presumably active in "volume" neurotransmission and to pharmacological nicotine, both of which are estimated to be present at ~100 nM. By contrast, low-sensitivity (LS) (a4)3(b2)2-nAChR would be expected to respond only to synaptic ACh. We have used pharmacological and mutagenesis approaches to characterize these a4b2-nAChR isoforms created from either loose subunits or as concatenated pentamers. From findings, we conclude that low concentration agonist binding at a4:b2 subunit interfaces activates and selectively desensitizes the HS response, which also is ~20% of the 5-fold higher overall response to ACh of LS a4b2-nAChR. We also conclude that the unique a4:a4 interface found only in LS a4b2-nAChR is an LS "agonist" binding site, occupation of which positively allosterically modulates receptor function. Collectively, these studies establish roles for a4:b2 interfaces in receptor activation at low agonist concentrations, but also for the a4:a4 interface in amplifcation of responses in the presence of agonists at higher concentrations, such as acheived for ACh at cholinergic synapses. This work also indicates that HS vs. LS a4b2-nAChR activity can be differentially manipulated using interface-specific ligands, opening up novel therapeutic avenues for treatment of nicotine dependence and psychiatric disorders that likely underlie nicotine dependence.

P20 • Mathematical and voltammetric evidence for dual-transport of serotonin *in vivo*

Kevin Wood, Frederik Nijout, Mike Reed, Janet Best, Parastoo Hashemi*

Serotonin neurotransmission is important to study to improve treatments for neuropsychiatric disorders such as depression. Given fast scan cyclic voltammetry's ability for providing real-time kinetics of neurotransmission; it is well suited for studying antidepressant effects on serotonin. Electrical stimulation of the mouse medial forebrain bundle provokes terminal serotonin release in the substantia nigra pars reticulata, which is detectable voltammetrically. We find three distinct responses to the same stimulus. We characterize these responses as fast, slow, and hyrbrid based on serotonin's clearance. Michaelis-Menten modeling and pharmacology reveal an important inhibitory role for autoreceptors and support two independent serotonin reuptake mechanisms. Fast responses follow low affinity, high efficiency clearance while slow responses follow a high affinity, low efficiency reuptake. Hybrid responses have characteristics of both response kinetics. Importantly we show that fast, slow, and hyrbrid serotonin responses are differently affected by acute administration of a common antidepressant. Such information enhances our understanding of the chemical heterogeneity of complex *in vivo* serotonin responses to antidepressants.

P21 • Activity of locus coeruleus norepinephrine neurons during behavioral response inhibition

Matthew Riedy, Gary Aston-Jones*

Response inhibition is a central element in the executive control of behavior. Humans suffering from attention deficit hyperactivity disorder (ADHD) and other cognitive pathology show impaired performance on clinical measures of behavioral response inhibition. Importantly, impairment is recovered in humans by treatment with the selective norepinephrine (NE) reuptake inhibitor Atomoxetine. As locus coeruleus (LC) is a primary source of NE in the brain, and the only source for cortex, these data identify an important role for LC-mediated modulation of behavioral response inhibition. To analyze the activity of LC-NE neurons during behavioral response inhibition, we trained rats to perform a modified reaction time task. Rats were reinforced with aqueous sucrose or punished with a lights-off timeout to train cue-contingent rapid release (<650 msec) of an operant lever. Rats were biased towards short (0.5 sec) vs. long (1.5 sec) pre-cue lever holds by controlling trial-delivery ratio (65:35 / short:long). Rats were required to inhibit their pre-potent short trial response on less frequent long trials. Upon reaching training criterion (<15% premature releases; >70% correct trials) rats were

implanted with drivable microwire tetrodes in LC. Rats then had single-unit, multi-unit, and local field potential recordings (LFP) collected from LC as well as simultaneous orbitofrontal cortex (OFC) LFP, electroencephalogram (EEG), and electromyogram (EMG) recordings across several sessions. Prior results revealed a greater phasic response of LC single units on correct vs. incorrect response inhibition trials. We predict a phasic response of LC neurons associated with successful inhibition of pre-potent short responses on correct long trials. These ongoing studies promise to reveal properties of LC function important for behavioral response inhibition and the associated cognitive functions.

P22 • Chronic intermittent hypoxia/hypercapnia diminishes excitatory glutamatergic, but does not alter inhibitory neurotransmission to cardiac vagal neurons in the dorsal motor nucleus

Ned Cauley, David Mendelowitz, Jhansi Dyavanapalli, Olga Dergacheva*

Individuals with Obstructive Sleep Apnea (OSA) have an increased risk of developing cardiovascular diseases such as hypertension, arrhythmias, myocardial ischemia, stroke, and sudden death. These adverse cardiovascular events are caused, in part, by an imbalance in the autonomic nervous system, including diminished cardioprotective parasympathetic activity to the heart. Parasympathetic cardioinhibitory vagal neurons (CVNs) are located in both the nucleus ambiguus and dorsal motor nucleus (DMNX). To identify likely alterations in function of CVNs with OSA we examined changes in the synaptic pathways to CVNs in the DMNX after 4 weeks of exposure to chronic intermittent hypoxia/hypercapnia (CIH/H). There was a significant decrease in both the frequency and amplitude of glutamatergic excitatory postsynaptic currents (EPSCs) to CVNs in rats exposed to CIH/H as compared to control animals. There were no significant changes in the inhibitory neurotransmission to CVNs upon comparing IPSCs in CIH/H exposed rats and control animals. The significant decrease in excitatory neurotransmission to CVNs of CIH/H animals would result in less parasympathetic activity and a subsequent increase in heart rate and risk of adverse cardiovascular events with chronic perturbations that occur in OSA.

P23 • PDE5 inhibition does not improve object memory performance in rats after environmental enrichment

Sven Akkerman, Jos Prickaerts, Anne kristin Bruder, Kevin Wolfs, Harry W.M. Steinbusch, Tim van Mierlo, Arjan Blokland*

Drug effects are usually evaluated in animals that are housed under maximally standardized conditions. However, it is assumed that rats raised in an enriched environment (EE) may be more comparable to the human situation as compared to rats raised under maximally standardized laboratory conditions. Therefore the validity of the use of standard housed animals in drug research could be questioned. In the present study we examined the cognition enhancing effects of vardenafil, a PDE5 inhibitor, in three different groups of male Wistar rats in an object recognition task (ORT). We used rats that were solitarily (SOL) or socially (SOC) housed under standard conditions, and socially housed rats in an EE. EE animals, but not SOL and SOC animals, were able to remember object information after 24 h. An interval of 48 h was needed to make EE rats forget the object information. Treatment with vardenafil improved object memory in SOL and SOC animals but not in EE rats. In EE animals the dorsal hippocampus was heavier compared to the other groups. However, no differences were observed in the amount of cells the DG, CA3 and CA1 of the dorsal hippocampus. Neither were their any differences in pre- and postsynaptic density. No changes in PDE5 mRNA- or protein expression levels were observed. P-CREB was increased in EE rats only whereas beta-catenin was not affected, suggesting that the MAP kinase signaling pathway becomes more activated after EE and the Akt pathway is not affected. The lack of a memory enhancement in the EE rats by the PDE5 inhibitor vardefanil cannot be explained by changes in hippocampal morphology or PDE5 levels. A possible explanation could be that vardenafil treatment results in overstimulation of the MAP kinase signaling pathway in the hippocampus of EE rats. Because PDE5 inhibition was never shown to improve human memory performance, the present data may suggest that EE animals could be a more valid animal model for testing cognition enhancing drugs.

P24 • Discovery and characterization of a G protein-biased agonist that inhibits β-arrestin recruitment to the D2 dopamine receptor

David Sibley, R. Benjamin Free, Lani Chun, Jingbo Xiao*

A high-throughput screening campaign was conducted to interrogate a 380,000+ small molecule library for novel D2 dopamine receptor modulators using a calcium mobilization assay. Active agonist compounds from the

primary screen were examined for orthogonal D2 dopamine receptor signaling activities including cAMP modulation and β-arrestin recruitment. While the majority of the confirmed hits activated all signaling pathways tested, several compounds showed a diminished ability to stimulate β-arrestin recruitment. One such compound (MLS1547) is a highly efficacious agonist at D2 dopamine receptor-mediated G protein-linked signaling, but does not recruit β-arrestin, as demonstrated using two different assays. The compound does, however, antagonize dopamine-stimulated β-arrestin recruitment to the D2 receptor. Radioligand binding assays suggest that this compound binds to the orthosteric site of the D2 receptor with a Ki of ~1 μM. In an effort to investigate this chemical scaffold further, ~24 close structural analogs of MLS1547 were studied and characterized with respect to their ability to inhibit cAMP accumulation or stimulate β-arrestin recruitment by the D2 receptor. A number of compounds were similar to MLS1547 in that they exhibited agonist activity for inhibiting cAMP accumulation, yet they were unable to stimulate β-arrestin recruitment (i.e., they were highly biased). In contrast, other compounds were either unbiased or displayed various degrees of partial G protein signaling bias. This information provided the basis to use pharmacophore modeling and molecular docking analyses to build a preliminary structure activity relationship to predict the functionally-selective properties of this series of compounds. In summary, we have identified and characterized the first G protein-biased agonist of the D2 dopamine receptor and identified structural features that may contribute to its biased signaling properties.

P25 • Hippocampal network disruptions after diffuse brain injury in swine

John Wolf, Alexandra Ulyanova, Kevin Browne, Paul Koch, Michael Grovola, Victoria Johnson, D.Kacy Cullen*

Functional and circuit level activity changes in the hippocampus induced by mild traumatic brain injury (mTBI) were studied using a swine model of closed-head rotational acceleration. In order to replicate the range of forces experienced by the brain during mTBI, we utilized coronal rotational accelerations (200-300 rads/sec) that induce little or no loss of consciousness (< 5 min) or subdural hemorrhage, yet exhibit axonal pathology. We utilized in vivo electrophysiological recordings to investigate the changes in hippocampal function in sham versus injured animals using high-density recording arrays and simultaneous afferent stimulation. Multi-electrode electrophysiological recordings (linear, 32-channels) were performed in the dorsal hippocampus. The time point of 7 days post injury was used in order to compare the results to our previous in vitro slice recordings. Concentric bipolar stimulation was performed in Schaffer collaterals, perforant path, and the entorhinal cortex,

using either paired-pulse or theta-burst paradigms. Input-output curves were generated and paired-pulse paradigms were utilized to examine changes in neurotransmitter release probabilities from injured versus sham animals. Changes in baseline network activity were visualized pre and post theta-burst stimulation to examine changes in hippocampal excitability underlying post-traumatic epileptogenesis. Current source density analysis was utilized to examine changes in synaptic inputs post injury to hippocampal layers. Changes in the oscillatory activity in the injured animals suggest a hyper-excitable network compared to sham recordings. The results of this electrophysiological analysis of hippocampal excitability in vivo are similar to previously reported slice results in vitro. These data indicate that mild traumatic brain injury in swine leads to dysfunction in various aspects of hippocampal circuitry post-injury, potentially underlying epileptogenesis and/or cognitive dysfunction.

P26 • Mitochondrial DNA: An early biomarker of preclinical Alzheimer's disease

Ramon Trullas, Petar Podlesniy, Joana Figueiro-Silva, Albert Llado*

There is a large amount of previous evidence indicating that mitochondrial function is altered in Alzheimer's disease (AD). However, previous work could not provide indication on whether mitochondrial dysfunction is an early event or a result of the disease process. Using quantitative PCR techniques, we measured circulating cell free mitochondrial DNA (mtDNA) in cerebrospinal fluid (CSF) from study participants classified according to their concentrations of Aβ1-42, t-tau and p-tau in CSF and by the presence or absence of dementia, in: asymptomatic subjects at risk of AD, symptomatic patients diagnosed with sporadic AD, pre-symptomatic subjects carrying pathogenic PSEN1 mutations and patients diagnosed with Fronto-temporal Lobar Degeneration (FTLD). In addition, we measured mtDNA copy number in cultured cortical neurons from mutant Amyloid Precursor Protein/Presenilin1 (APP/PS1) transgenic mice. We found that asymptomatic patients at risk of AD, and symptomatic AD patients, but not FTLD patients, exhibit a significant decrease in circulating cell free mtDNA in the CSF. In addition, pre-symptomatic subjects carrying pathogenic PSEN1 gene mutations show low mtDNA content in CSF before the appearance of AD related biomarkers in CSF. Furthermore, cultured cortical neurons from APP/PS1 transgenic mice exhibit less mtDNA copies per cell before the appearance of altered synaptic markers. These findings indicate that low content of mtDNA in CSF may be a novel biomarker for the early detection of preclinical AD and support the hypothesis that mtDNA depletion is a characteristic pathophysiological factor of neurodegeneration in AD. Support: CIBERNED & SAF2011-23550, CSD2010-00045, FIS 11/00234, 12/00013, 11-03035

P27 • Super-physiological pharmacology by mGlu4 receptor positive allosteric modulators

Robbin Brodbeck, Elena Dale, Michael D. Collins, Noel J. Boyle, Hong Zhang, Lia K. Isaac, Megan H. Schmidt, Christina Chimento, Huailing Zhong, Francine C. Acher, Dario Doller, Xinyan Huang*

Modulation of biological targets by allosteric ligands is a key area of research, in particular with respect to G-protein coupled receptor (GPCR) function. This is an attractive strategy when facing unfavorable chemical space or compromised selectivity at the orthosteric binding site. The metabotropic glutamate (mGlu) receptors are prone to positive (PAMs) and negative (NAMs) allosteric modulation. From a drug design perspective, PAMs present unique challenges, in contrast with NAMs, which follow more "traditional" pathways. Allosteric ligands can activate the receptor directly (allosteric agonists) or can modulate the activity of the receptor in the presence of the endogenous ligand glutamate ("pure" PAMs). Because of the complex nature of allosteric phenomena, the detection and quantification of these effects are challenging. In our mGlu4 PAM project, we have deviated from a traditional EC_{50}/E_{max} and glutamate fold-shift driven approach. Instead, we applied an "Operational Model" analysis to experimental datasets from different *in vitro* functional assays. This approach allowed the characterization of chemically diverse PAM based on the allosteric parameters a, b, pK_B and T_B. In this study, we report results on mGlu4 PAM tool compounds ADX88178, VU0361737 and Lu AF21934 using a calcium-flux assay, a dynamic mass redistribution (DMR)- based Epic Label-Free assay, *in vitro* binding of [$^3H_2$]-LSP4-2022 (a novel mGlu4 orthosteric radioligand), and brain slice electrophysiology. These data support the existence of super-physiological levels of receptor function driven by these allosteric ligands.

P28 • Circadian regulation of visual function: control of contrast sensitivity by a dopamine → NPAS2 → cyclic AMP signaling pathway in retinal ganglion cells

Michael Iuvone, Christopher Hwang*

The mammalian retina contains circadian clocks that regulate visual functions on a daily basis, optimizing high resolution vision during the daytime and low resolution high-sensitivity vision at night. Optimal contrast detection requires retinal dopamine, and daytime contrast detection is reduced in mice with a conditional knockout of the tyrosine hydroxylase (TH) gene in the retina. Circadian oscillators are composed of negative and positive transcription-translation feedback loops involving a conserved set of core clock proteins. CLOCK and NPAS2 are homologous circadian clock proteins with overlapping roles in the feedback loops. Either protein can dimerize with BMAL1 to drive

the negative feedback loop of the oscillator and clock output. The relative contributions of CLOCK and NPAS2 to retinal circadian oscillators have not been previously explored. This study examined the localization and role of NPAS2 in the circadian rhythm of contrast sensitivity function (CSF). NPAS2 was localized to a subset of retinal ganglion cells (RGCs). Targeted deletion of the genes encoding TH, dopamine D4 receptors (D4Rs), NPAS2, or the type 1 adenylyl cyclase (AC1) elicited nearly identical disruptions of the circadian rhythm of CSF; daytime contrast sensitivity was reduced with no effect on the nighttime response. In wild type mice, transcripts encoding D4Rs, NPAS2, and AC1 were all rhythmically expressed. In D4R knockout mice, NPAS2 and AC1 transcript rhythms were abolished in RGCs and photoreceptors. In NPAS2 knockout mice, AC1 transcript rhythms were also abolished in RGCs but not in photoreceptors, suggesting that NPAS2/BMAL1 heterodimers activate the circadian E-box in the AC1 promoter in ganglion cells. The results indicate that circadian control of contrast detection involves a signaling pathway in RGCs in which dopamine regulates the rhythmic expression of NPAS2, which in turn regulates rhythmic AC1 and cAMP levels.

P29 • mTOR pathway hyperactivity in a mouse model of cortical dysplasia with epilepsy is associated with alterations in the Kv1.1 potassium channel

Anne Anderson, Lena Nguyen, Amy Brewster*

Hyperactivity of the mammalian target of rapamycin (mTOR) pathway is associated with epilepsy in human and animal models of cortical dysplasia. Inhibition of the mTOR pathway attenuates epileptiform activity, suggesting a role for the mTOR pathway in the regulation of neuronal excitability. However, the underlying molecular mechanisms are unknown. There is emerging evidence for mTOR-dependent regulation of protein translation and surface expression of various potassium channels including Kv1.1, which is mainly localized in the axon initial segment (AIS) where it plays a critical role in repolarization. Aberrant levels of Kv1.1 have been linked to neuronal hyperexcitability and epilepsy. We evaluated whether excessive mTOR signaling due to loss of PTEN, a negative regulator of the pathway, contributes to alterations in Kv1.1. We measured protein levels and the distribution of Kv1.1 in hippocampus of 6 week-old neuronal subset-specific conditional PTEN knockout (NS-PTEN KO) and wildtype (WT) mice and in PTENfloxed/floxed primary hippocampal neuronal cultures transduced with RFP-Cre lentivirus to delete PTEN. In parallel, we evaluated the effects of rapamycin vs. vehicle treatment on Kv1.1 alterations. We found a significant increase in Kv1.1 in the hippocampus of NS-PTEN KO compared to WT mice. Rapamycin restored Kv1.1 to WT levels ($p<0.05$). There was an increase in Kv1.1 in

somatic regions of dentate granule cells in the hippocampus of NS-PTEN KO compared to WT brains and increased somatic staining for Kv1.1 coupled with weak staining in the AIS in cultured hippocampal neurons lacking PTEN compared to the control (non-transduced) neurons. Excessive mTOR signaling in hippocampal neurons is associated with increased protein levels and mislocalization of Kv1.1 to the soma. These data suggest Kv1.1 remodeling may be one candidate mechanism that contributes to neuronal hyperexcitability and epilepsy in the NS-PTEN KO mice.

P30 • Augmented inhibition from WIN55,P212-2 sensitive interneurons diminishes CA1 output after traumatic brain injury

Akiva Cohen, Brian Johnson, Chris Palmer, Elliot Bourgeois, Brendan Putnam, Jaclynn Elkind*

The neurological impairments associated with traumatic brain injury include learning and memory deficits and increased susceptibility to seizures. The hippocampus is critically involved in both of these phenomena and one of the brain structures most susceptible to damage by traumatic brain injury. To examine the spatiotemporal pattern of evoked excitatory and inhibitory responses in the CA1 region after lateral fluid percussion injury, we used a combination of voltage sensitive dye, field potential and patch clamp recording in mouse hippocampal brain slices. When the Schaffer collaterals were stimulated in slices from injured mice we found increased hyperpolarization in stratum oriens, and a decrease in the percentage of pyramidal neurons firing stimulus-evoked action potentials. Increased hyperpolarization in stratum oriens persisted when glutamatergic transmission was blocked. However, we found no changes in stratum oriens responses when the alveus was stimulated to directly activate stratum oriens. These results suggest that the increased stratum oriens hyperpolarization evoked by stratum radiatum stimulation was mediated by interneurons that have cell bodies and/or axons in stratum radiatum, and form synapses in stratum oriens. Cholecystokinin positive basket cells in CA1 have an anatomy consistent with these results and 100 nM WIN55,212-2, which selectively blocks GABA release from cholecystokinin positive basket cells, restored CA1 output in slices from injured animals. These findings support the hypothesis that increased GABA release from cholecystokinin positive basket cells contributes to the reduced CA1 output following traumatic brain injury.

P31 • Photoactivation of fibers originating from parvocellular neurons in the paraventricular nucleus of the hypothalamus releases oxytocin in the brainstem

Heather Jameson, Ramon Pinol, David Mendelowitz*

In addition to the classic effects of the hormone oxytocin (OXT) on uterine contraction and milk ejection, recent work has suggested oxytocin 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 suggesting this excitatory pathway is facilitated by endogenous OXT release from these synaptic terminals. In order to further test this hypothesis and additionally elucidate the conditions required for OXT release from PVN fibers, we dispersed within the brainstem Chinese Hamster Ovary (CHO) cells highly sensitive to oxytocin. 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 preliminary data shows photoactivation of ChR2 containing PVN fibers elicits a large increase in intracellular calcium in specific populations of OXT sensitive CHO cells. Only those CHO cells near the PVN fibers and synaptic endings and in close proximity to CVNs had increases in intracellular calcium upon photoactivation of PVN fibers. This work supports and extends the hypothesis that excitation of parvocellular PVN fibers releases OXT at their brainstem CVN targets.

P32 • GAT1 expression in human brain: alternate transcripts, expression in development, and potential relationships to brain function and schizophrenia

Michelle Mighdoll, Gianluca Ursini, Andrew Jaffe, Ran Tao, Barbara Lipska, Daniel Weinberger, Joel Kleinman, Thomas Hyde*

Abnormal GABA-mediated neurotransmission is one of the consistent postmortem findings in schizophrenia. In the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia, postmortem studies have consistently revealed alterations in GABA signaling (Lewis et al., 2005).

The GABA signaling system undergoes profound and well-characterized developmental changes. Accordingly, we undertook a series of experiments to investigate developmental changes in GABA signaling in normal human brain in order to relate them to schizophrenia, as this disorder is thought to have neurodevelopmental origins. Alternative splicing is known to affect more than half of all genes, and has been proposed as a primary drive of the evolution of phenotypic complexity (Lander et al., 2001; Johnson et al., 2003). Using RNA-seq, we potentially have identified 10 novel GAT1 transcripts, and we identified an association of expression of some of the novel GAT1 splice variants and schizophrenia. We have also identified two novel intragenic GAT3-GAT1 splice variants that may regulate the expression levels of GAT1, as we confirmed the relationship between GAT1 and GAT3 by their similar lifetime expression patterns. To investigate the developmental expression profile of the full-length GAT1 and GAT3 transcripts, and of the novel GAT1 splice variants, we assessed mRNA expression levels from the prefrontal cortex of both non-psychiatric controls and patients with schizophrenia; we also assessed exon level expression of GAT1 and GAT3 exons in the DLPFC from RNAseq data. Both GAT1 and GAT3 prefrontal mRNA expression levels are high during fetal development and peak during childhood, with a decline in adulthood. Both showed increased prefrontal expression in patients with schizophrenia as compared to controls. We also found that a SNP located between exons 1 and 2 on GAT1, rs1710880, was significantly associated with GAT1 expression (carriers of the minor allele had increased GAT1 expression).

P33 • Dopaminergic resetting of circadian food anticipatory activity rhythms in the rat

Ralph Mistlberger, Andrea Smit, Mateusz Michalik, Danica Patton*

Daily rhythms of behaviour and physiology are jointly controlled by a master pacemaker in the hypothalamic suprachiasmatic nuclei that mediates synchrony to daily light-dark cycles, and by food-entrainable circadian oscillators (FEOs) that mediate synchrony of food anticipatory activity (FAA) to daily feeding schedules. The location of FEOs responsible for circadian FAA, and the pathways that entrain these FEOs are currently under investigation. Circadian rhythms of clock gene expression in the dorsal striatum are reset by dopamine receptor 2 (D2) agonists (Hood et al, 2010). To examine a role for D2 signalling in the timing of FAA, rats were fed 3h/day in the light period (ZT6-9) until stable FAA emerged. Rats then received the D2 agonist quinpirole (1 mg/kg IP) alone or after pretreatment with the dopamine synthesis inhibitor AMPT. By comparison with saline injections, quinpirole at ZT11 or ZT4 induced a small but significant phase delay of FAA onset. Delay shifts were larger in rats pretreated with AMPT. RTPCR was used to measure effects of

quinpirole on clock gene expression (per1, bmal1, re-erba) at 4 time points in a potential site of action, the dorsal striatum. Quinpirole altered clock gene expression compared to saline, consistent with a role for dorsal striatal clocks in food anticipatory rhythms. No significant phase shifts were observed in response to the D1 agonist SKF81297. These results suggest that FEOs driving food anticipatory activity rhythms in rats can be reset by dopamine signalling at D2 receptors, most likely in the dorsal striatum.

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P34 • Neuroticism scores predict the impact of acute tryptophan depletion in subgenual cortex

Olaf B. Paulson, Bettina Hornbøll, Julian Macoveanu, James B. Rowe, Rebecca Elliott, Olaf B. Paulson, Gitte Moos Knudsen, Hartwig R. Siebner*

Introduction: The serotonergic neurotransmitter system is involved in the modulation of emotions. Recent pharmacological studies have demonstrated serotonin's (5-HT) role in processing emotional facial expressions. Here we tested whether individual differences in neuroticism scores predict the effect of reduced 5-HT signaling on brain activity while processing facial expressions.

Methods: Twenty-two participants (8 females, mean age 31.5 ± 6.2 years) were studied with whole-brain fMRI at 3 T while viewing facial expressions. The task included male and female faces showing either neutral, angry or fearful expressions in alternating blocks. Participants were asked to determine the gender of each presented face. The study included two sessions with identical fMRI and task protocols, differing only by a 5-HT challenge. In a counterbalanced order, participants underwent an fMRI session with acute tryptophan depletion (ATD) to lower central 5-HT and a control session without 5-HT manipulation. Statistical analyses of task and intervention related changes in the blood-oxygen level dependent (BOLD) signal were performed in SPM5 with significance set at $p<0.05$ corrected for multiple comparisons.

Results: ATD did not alter significantly the group mean neural response to angry or fearful expressions. However, relative to the control session, after ATD the neural responses in subgenual cortex correlated positively with increased neuroticism scores. This correlation was only significant for viewing fear expressions.

Conclusion: Our results suggest that manipulations of central 5-HT levels with ATD have a higher impact on individuals with high neuroticism scores, in terms of orbitofrontal processing of fear stimuli. Our results point to a crucial role of serotonergic neurotransmission in the orbitofrontal regions in emotional processing of human faces.

P35 • Up-regulation of mGlu5 receptors in brain—A new common feature of antidepressant drugs action

Andrzej Pilc, Palucha Agnieszka, Gabriel Nowak, Krzysztof Wedzony*

Metabotropic glutamate 5 (mGlu5) receptors are functionally connected with NMDA receptors. The antidepressant activity of the NMDA receptor antagonist ketamine both in the preclinical and in the clinical studies as well as the antidepressant-like activity of mGlu5 receptor negative allosteric modulators (NAMs) led us to investigate if prolonged administration of different antidepressant drugs as well as mGlu5 receptor NAM - MTEP causes changes in the mGlu5 receptor binding and protein expression as well as expression of Homer proteins in the rat brain. We also aimed to investigate whether mGlu5 receptor antagonist induce activation of mTOR signaling in the prefrontal cortex (PFC) in rats. The results clearly show that a prolonged treatment with antidepressants of different mechanisms of action such as escitalopram, reboxetine, milnacipran, moclobemide and imipramine as well as with MTEP led to a significant increases in the [3H] MPEP binding in homogenates of the hippocampus and/or cerebral cortex. The increase in mGlu5 receptor protein expression was also observed, though it was not always parallel to the increase in binding. The expression of Homer proteins was not influenced by antidepressant drugs. Moreover MTEP induced a rapid, but not sustained antidepressant-like effect, which was not related to the activation of mTOR cascade. In summary, the up-regulation of mGlu5 receptors seems to be a general feature of the action of several antidepressant drugs and of MTEP, but the antidepressant-like activity of MTEP does not depend on the activation of mTOR signaling. Supported by Demeter grant.

P36 • *In vivo* and *in vitro* zebrafish models for CNS axonal regeneration after injury

Jeffery Plunkett, Alexis Tapanes-Castillo, Fran Shabazz, Katerina Vajn, Martin Oudega*

Axon regeneration in the injured mammalian spinal cord is thwarted by inhibitory molecules, such as chondroitin sulfate proteoglycans (CSPGs) expressed at the injury site. Strikingly, in the adult zebrafish (Danio rerio) some brainstem neurons are able to grow their axon beyond a spinal cord injury, despite the presence of CSPGs. Based on these findings, we developed an overall working hypothesis that the ability to grow an axon over CSPGs is intrinsic to a subpopulation of zebrafish brainstem neurons, and it entails the expression of a distinct set of genes. To investigate the axonal growth response of zebrafish brainstem neurons to CSPGs, we developed a primary neuronal culture system using adult brainstem cells from wild-type zebrafish. We characterized our cultures molecularly and morphologically, and investigated

how growth-inhibiting molecules interact to regulate axon outgrowth in vitro. Our recent studies have focused on the zebrafish CSPG neurocan, and the prospective zebrafish CSPG receptor, receptor-type protein tyrosine phosphatase sigma a (ptprsa). Our in vivo work demonstrates the expression of neurocan and ptprsa pre- and post CNS injury and suggests that gene expression may not be governed by injury. We are also studying the role of neural progenitor/stem cells in brainstem axon regeneration by examining the expression of nestin, an intermediate filament protein and putative stem cell marker, in vivo pre- and post-injury and in vitro. Together our work aims to generate data that may serve as a foundation for the development of tailored strategies to promote axon regeneration across injury sites in the spinal cord. Funded by U.S. Dept. of Defense W81XWH-11-1-0645 to JAP.

P37 • Synaptic protein changes in the posterior cingulate in the progression of Alzheimer's disease

Stephen Scheff, Mubeen Ansari, Milos Ikonomovic, Elliott Mufson*

Functional imaging studies have identified the posterior cingulate cortex (PPC) (BA23) as an area affected early in the progression of Alzheimer's disease (AD). Prior research from our laboratory demonstrated significant synaptic loss in both the hippocampus and inferior temporal cortex in individuals with mild cognitive impairment (MCI). We have also shown a loss of synapses in the PPC in AD. Since the PPC has direct connectivity with the medial temporal lobe, we tested whether or not synaptic change occurs in this region early in the disease progression. We quantified changes in several key synaptic proteins using short postmortem (PMI) cases from the ADC at the University of Kentucky and Rush Medical Center. Clinical diagnosis was based upon neuropsychological testing within 12 months prior to death resulting in subjects categorized as no cognitive impairment (NCI), MCI, and AD. All groups were age and PMI matched. In addition, samples were analyzed for changes in soluble Abeta1-42 and [3H]PiB binding. Both the AD and MCI cohorts showed a significant decline in both pre and post synaptic proteins compared to the NCI group. AD and MCI groups were significantly different from each other. The changes in synaptic proteins significantly correlated with the subject's Mini Mental State Examination (MMSE). Although levels of soluble Abeta 1-42 were significantly increased in both AD and MCI, there did not appear to be any significant association with the different synaptic proteins. In contrast, [3H]PiB binding showed a very strong association with both pre and post synaptic changes. This is the first study to evaluate changes in both pre and post synaptic proteins in this paralimbic association region as a function of disease progression, which may signal a region involved early in the disease process. Supported by NIH grants AG27219, AG028383, AG14449, AG042475

P38 • Optogenetic assessment of heterosynaptic suppression of inputs in the ventral striatum

Julie Brooks, Gwendolyn Calhoon, Patricio O'Donnell*

The ability of the ventral striatum (VS) to influence goal-directed behavior rests on complex afferent interactions within this region. However, the neuronal mechanisms governing information integration remain unclear. Medium spiny neurons (MSNs) serve as a site of convergence for excitatory input from brain regions involved in goal-directed behavior, including the prefrontal cortex (PFC) and hippocampus (HP). Our laboratory previously demonstrated that during periods of high frequency PFC activation, baseline coherence between VS and HP activity can be lost in favor of PFC-VS synchrony. We speculate that PFC-driven disruption of VS-HP synchronization involves local heterosynaptic suppression of inputs. This assertion is based on in vivo electrophysiological recordings from anesthetized rats demonstrating that robust PFC stimulation leads to a reduction in ongoing HP-evoked responses in MSNs. Furthermore, heterosynaptic suppression is believed to involve an inhibitory mediator, as this effect is partially reduced following administration of a GABAA receptor antagonist. As the reduction is not complete, it is likely other mechanisms contribute to the suppression. Here we further explored the synaptic mechanisms involved in PFC-evoked heterosynaptic suppression of MSN responses to competing synaptic inputs. Whole-cell recordings were performed from rats receiving hippocampal injections of a viral vector expressing channelrhodopsin 2 under the CamKinase II promoter. Input interactions between electrical stimulation of PFC fibers and optical stimulation of HP inputs were tested in VS MSNs. Optogenetically evoked HP responses were attenuated at a short latency following burst-like electrical stimulation of corticostriatal fiber tracts, but not at a longer latency, similar to in vivo observations. These findings further substantiate the assertion that shifts in VS neuronal activity may involve local suppression of competing afferent inputs converging on the same MSN.

P39 • A general theory of intertemporal decision-making and time perception

Vijay Mohan K Namboodiri, Stefan Mihalas, Tanya Marton, Marshall Hussain Shuler*

The question of how animals and humans make decisions about future events has been a major line of study in fields as diverse as economics, ecology, psychology, clinical behavior and neuroscience for the past eighty years. Experiments from these fields have established some fundamental phenomena such as hyperbolic discounting. In addition, a wide variety of behaviors

including "anomalous" behaviors have been observed. Our present work aims to provide a single unified conceptual framework for explaining this diversity of observations. In order to achieve this goal, we develop a computationally simple algorithm resulting from a constrained optimization of reward rates that could be used by animals to make such choices. Based on this algorithm, we further derive an equation for the subjective representation of time by an individual. This mathematical expression for subjective time explains many fundamental observations made in behavioral studies of timing in animals and humans. Our theory provides an explanation for observations including, but not limited to, hyperbolic discounting, "magnitude" and "sign" effects, correlation between temporal discounting and time perception, "scalar timing" as well as the underproduction and increased representational errors of time intervals by impulsive individuals. It has clinical implications for the study of impulsivity as seen in behavioral and neurological disorders like Parkinson's disease, schizophrenia and addiction.

P40 • HspB1 silences translation of PDZ-RhoGEF by enhancing miR20a and miR128 expression to promote neurite extension

Marina Mata, Xiankui Sun, David Fink*

HspB1 is a small chaperone protein implicated in neuron survival and in neurite growth responses. We have previously reported that in cortical neurons, expression of HspB1 from a genomic herpes simplex virus (HSV)-based vector (vHspB1) decreased RhoA activity and RhoA-GTP protein without changing total RhoA levels, and reversed the inhibition of neurite extension induced by NogoA-Fc. HspB1 decreased PDZ-RhoGEF, a RhoA specific GEF, while other regulators of Rho activity were unchanged. We now report that HspB1 enhances the expression of microRNAs 20a, 128 and 132 in cortical neurons and that co-transfection of cells with HspB1 and specific inhibitors of miR20a or miR128 prevented the decrease in PDZ-RhoGEF. Using the 3'UTR of PDZ-RhoGEF mRNA in a luciferase reporter construct we observed that HspB1, miR20a and miR128 each inhibited luciferase activity. We conclude that HspB1 regulates RhoA activity through modulation of PDZ-RhoGEF levels achieved by translational control through enhanced expression of specific miRNAs (miR20a and miR128). Regulation of RhoA activity by translational silencing of PDZ-RhoGEF may be the mechanism by which HspB1 enhances neurite growth. These results may have important clinical implications, as mutations in HspB1 have been identified in hereditary motor neuronopathies and Charcot Marie Tooth Type 2 neuropathies.

P41 • Optogenetic stimulation of locus coeruleus noradrenergic neurons increases inhibitory neurotransmission to parasympathetic cardiac vagal neurons in the nucleus ambiguus

David Mendelowitz, Xin Wang*

Locus coeruleus (LC) neurons play an essential role in maintaining wakefulness and attention, conditions that also influence the balance of autonomic activity. Heart rate is determined predominantly by the activity of cardioinhibitory parasympathetic cardiac vagal neurons (CVNs) that originate in the brainstem nucleus ambiguus (NA). CVNs are intrinsically silent, and depend on synaptic activity to generate their firing and alter their activity. In this study we test the hypothesis that activation of LC neurons diminishes parasympathetic to the heart by altering synaptic activity to CVNs. Mice that express Cre recombinase selectively in tyrosine hydroxylase neurons were crossbred with a channelrhodopsin-2 (CHR2)/EYFP Cre-dependent mouse strain. CVNs in the NA were identified by the retrograde tracer rhodamine. Photostimulation of ChR2-expressing LC neurons elicited large depolarizations (average inward current of 150pA) that were sufficient to evoke firing in LC neurons. Photoactivation of LC neurons did not alter excitatory neurotransmission to CVNs but evoked a significant increase in inhibitory neurotransmission to CVNs. The IPSCs frequency in CVNs was facilitated by 73.7±21.8% ($p<0.01$) upon LC photoexcitation. This increase in IPSC neurotransmission was blocked by the α-1 receptor inverse agonist prazosin (3μm). The LC induced increase in inhibitory neurotransmission to CVNs in this study is a likely mechanism for the changes in heart rate that occur during awake/sleep cycles and changes in alertness.

P42 • Possible attenuation of the subjective effects of alcohol by the antiepileptic carisbamate in participants with alcohol-use disorder

Christopher Rodgman, Colin Haile, Rollin Hawkins, Daisy Thompson-Lake, James Mahoney III, Richard De La Garza, Thomas Newton*

Topiramate has been shown to reduce heavy drinking in individuals with alcohol-use disorder (AUD). Topiramate is associated with significant side effects, but carisbamate shares a similar mechanism of action to that of topiramate but with fewer side effects. To determine if carisbamate may be a potential pharmacotherapy for AUD we conducted a preliminary inpatient, double-blind, placebo-controlled within-subjects human laboratory safety interaction study assessing carisbamate in combination with alcohol. For phase

1, participants (N=5) with AUD were admitted to our research facility and randomly administered carisbamate (300 mg, BID) or placebo for 4 days. On day 4, participants then received 16 % alcohol (0.8 g/kg) or 1 % alcohol placebo during two 4 hour sessions (AM and PM). Cardiovascular measures (heart rate, HR; systolic, SBP; and diastolic blood pressure, DBP), breathe alcohol content (BAC) and subjective ratings (Alcohol Urge Questionnaire, AUQ; Biphasic Alcohol Effects Scale, BAES; Drug effects questionnaire, DEQ; and Positive and Negative Affect Schedule, PANAS) were taken at regular intervals throughout the test sessions and was repeated following a two week wash-out period when participants returned for phase 2 of the study. Because the study is ongoing and blinded we are reporting treatments as drug A and drug B. Results showed that within session alcohol administration was associated with significant increases in BAC, and SBP following alcohol but not placebo (p's<0.05). Further, trends for treatment main effects following treatment with drug B (compared to drug A) were found for "HIGH" ($p=0.06$) , "LIKE" ($p=0.15$) and "Want more" ($p=0.067$), a measure of craving following alcohol. Adverse events did not significantly differ between treatments ($p>0.05$). Drug B tended to decrease the subjective effects of alcohol. Neither treatment was associated with significant adverse events.

P43 • Circadian adaptation improves sleep, vigilance, and heart rate variability of night shift workers

Diane B. Boivin, Philippe Boudreau, Guy Dumont*

Introduction: Individuals vary greatly in their capacity to tolerate shift work. The results of two field studies are presented to address this issue and illustrate the role of circadian factors in individuals' tolerance to shift work.

Methods: Experiment 1: 15 night nurses (mean±SD: 41.8±7.9 years) were studied during 2 weeks on a permanent night schedule. Ten nurses were exposed to bright white light at night, goggles in the morning, and regular daytime sleep (intervention group). Their sleep was recorded at home by Nightcap or polysomnography (PSG). Circadian phase was assessed at the start and end of study by constant routines and plasma melatonin and cortisol rhythms (1x/h).

Experiment 2: 15 police officers on patrol (mean±SD: 30.1±5.2 years) working rotating shifts were studied 48 h in the lab before and after 7 consecutive night shifts. During visits 1 and 2, two 8-h sleep periods were scheduled either at night or in the day, respectively. Sleep, psychomotor performance, mood, alertness, HR, and saliva samples (1x/h) were collected in the laboratory. Mixed effect models were used for analyses.

Results: Experiment 1: Following night shifts, intervention nurses had longer diurnal sleep duration (Mann-Whitney, p=0.05) and greater circadian phase delay (t-test, p=0.04) than control nurses. Experiment 2: In 7 officers, salivary melatonin peaked during daytime sleep at visit 2. They had faster reaction times ($p \leq 0.045$), greater alertness ($p \leq 0.01$) and mood ($p \leq 0.01$) than the other officers. The LF:HF ratio was significantly lower in these adapted officers compared to the others (p=0.02). Total sleep time and efficiency were reduced during visit 2 compared to visit 1 the non-adapted group only ($p \leq 0.02$).

Conclusions: Physiological and behavioral tolerance to night work is significantly affected by an individual's degree of circadian adaptation to shift work. Research supported by the CIHR and IRSST.

P44 • Neuroprotective effects of the natural compounds resveratrol and piceid

Jane Cavanaugh, Sneha Potdar, Erika Allen, Mayur Parmar*

Natural dietary supplements are being hailed as age defying and may, in some cases, present a sustainable medical solution for people around the world. Within the next few decades the aged population in the U.S. will be greater than ever before, increasing the demand for cost-effective medicine for the elderly. One of the major health problems in the elderly are motor deficits, caused, in part, by a loss of dopaminergic neurons. Oxidative stress is known to play a part in this neuronal loss. Resveratrol, a natural compound found in grapes and wild blueberries, has antioxidant, anticancer, and anti-inflammatory properties. Our lab has shown that resveratrol protects dopaminergic-like cells (SH-SY5Y) against oxidative stress. However, resveratrol has low bioavailability, making it important to find alternative compounds with similar properties. Piceid (RV8), an analog of resveratrol, is more lipophilic and has greater bioavailability than resveratrol. Similar to resveratrol, RV8 protects SH-SY5Y cells against oxidative stress produced by exposure to dopamine. Interestingly, RV8 activates the MAP kinases ERK1/2 and 5. Following inhibition of the ERK1/2 or ERK5 pathways, the neuroprotection afforded by RV8 is lost. In order to test if apoptotic pathways are also involved in RV8 mediated neuroprotection, we examined the expression of Bcl-2, an anti-apoptotic protein, following dopamine +/– piceid exposure. Cells exposed to dopamine alone showed reduced Bcl-2 levels. RV8 pretreatment inhibited this dopamine-induced loss of Bcl-2. Overall, these findings suggest that the neuroprotective effects of RV8 are mediated via the activation of ERK1/2, ERK5, and anti-apoptotic proteins.

SPECIAL POSTER SESSION— HIGHEST RANKING POSTERS

P45 • Long-term effects of estradiol on network-level activity in dissociated rat hippocampus

Alexander Calhoun, Remus Osan, Steve M. Potter, Bradley Cooke*

Sexual differentiation in the brain is largely mediated by gonadal hormones. In rats, estrogen exposure during development masculinizes in the brain, producing a wide range of morphological changes that translate into male-typical behavior in adulthood. There is also growing evidence that estrogens are involved in learning and memory. In hippocampal neurons, estradiol produces a rapid increase in spine density and a general increase in excitatory network tone. We are investigating how estradiol influences the recurrent activity patterns of hippocampal neurons in vitro, the long-term effects of pre-exposure to estradiol ("masculinization"), and whether pre-exposure alters the effect of future estradiol exposure. To examine these effects on populations of neurons, we grow sex-specific, dissociated cultures of rat hippocampal neurons on 60-channel multielectrode arrays (MEAs). These MEA cultures allow us to record patterns of firing activity from dozens of individual neurons continuously for several days and provide easy optical access for microscopy. Examining the spatiotemporal patterns of the highly synchronized, population-wide bursts of activity that arise in vitro, and how they change over time, gives insight into the network-level effects of neural plasticity. Cultured neurons from male embryos are "masculinized" with estradiol during the first week in vitro, and male and female cultures are allowed to grow for 2-3 weeks before additional estradiol exposure. Ongoing experiments are testing the hypothesis that early differentiation of synaptic connectivity with estradiol leads to a permanent alteration in the diversity of recurring activity patterns. Preliminary results indicate that estradiol changes the burst rate and the action potential rate within bursts. We are now using cluster analysis and principal components analysis to identify recurring activity patterns within bursts.

P46 • Developmental antioxidant treatment prevents abnormalities in a rat model of schizophrenia

Gwendolyn Calhoon, Hugo Tejeda, Jan Harry Cabungal, Danielle Counotte, Eastman Lewis, Michel Cuenod, Kim Do, Patricio O'Donnell*

Schizophrenia (SZ) is a complex neurodevelopmental disorder with an equally complex etiology, including genetic and environmental factors. For this reason, identifying a final common pathway accounting for the neurophysiological abnormalities associated with the disorder is critical for developing successful treatment strategies. Oxidative stress disrupting the development of cortical excitation-inhibition balance has been proposed as one such common mechanism in SZ. We evaluated whether antioxidant treatment during development reverses cellular and neurophysiological abnormalities in the neonatal ventral hippocampal lesion (NVHL) model of SZ. Using stereological cell counting, we found that the NVHL produced oxidative stress in PV-interneurons during development, leading to reduced cortical PV expression in adulthood. Juvenile and adolescent treatment with the antioxidant N-acetyl cysteine prevented the reduction of prefrontal parvalbumin interneurons, and rescued two well established neurophysiological deficits associated with the NVHL, measured in anesthetized rats and in vitro. These findings suggest that oxidative stress during presymptomatic stages can confer vulnerability for abnormal adult brain function in a developmentally compromised brain, and highlight oxidative damage as a mechanism in the etiology of SZ.

P47 • Genetic dissection of cerebellar circuitry in cognitive, social, and affective behavior

Erik Carlson, Julia Licholai, Karn Dhillon, Larry Zweifel*

The cerebellum is reciprocally connected with limbic system structures including the prefrontal cortex, striatum, ventral tegmental area, amygdala, and hippocampus. Virtually nothing is known about how specific neuronal populations within discrete cerebellar nuclei influence behavior. We propose that a specific deep cerebellar nucleus (the major output of the cerebellum), the dentate nucleus of cerebellum (DNC), is essential for cerebellar-dependent regulation of cognitive functions, social functions and affective state. To test this, we used the virally delivered Designer Receptor Exclusively Activated by a Designer Drug (DREADD) receptor, hM4Di, to reversibly inhibit specific populations of D1 receptor-expressing neurons in DNC during performance of specific behaviors. We found that in the presence of clozapine-N-oxide, which activates the DREADD Receptor and causes inhibition of neuronal activity, Drd1aCre/+;DNC-hM4Di mice (Drd1aCre/+ mice bilaterally injected with

AAV-FLEX-hM4Di-YFP in DNC, N = 12) or Drd1aCre/+;DNC-GFP mice (Drd1aCre/+ mice bilaterally injected with AAV-FLEX-GFP in DNC, N = 12) showed alterations in performance in specific behaviors. Drd1aCre/+;DNC-hM4Di mice had significantly poorer performance on Barnes Maze probe trial than controls ($P < 0.05$), without differences in distance traveled or in velocity of movement. Drd1aCre/+;DNC-hM4Di mice had significantly less time in the open arms on elevated plus maze than Drd1aCre/+;DNC-GFP mice ($P < 0.05$), lower prepulse inhibition of the acoustic startle reflex than Drd1aCre/+;DNC-GFP mice ($P < 0.05$), and could not discriminate between novel and familiar mice on a three-chambered social task, while Drd1aCre/+;DNC-GFP mice were able to ($P < 0.05$). No changes were seen between groups on a simple instrumental conditioning task for food reward. Our results indicate that a specific neuronal population within the DNC is required for specific cognitive, social, sensory, and affective behaviors.

P48 • Extrasynaptic NMDA receptor modulation of fast-spiking interneurons

Eastman Lewis, Patricio O'Donnell*

Disinhibited cortical circuits are central to current views of schizophrenia pathophysiology. Non-competing NMDA receptor antagonists, known to be psychotomimetic in adults, have been proposed to exert their effect primarily by blocking receptors on fast-spiking interneurons (FSI) yielding increased pyramidal cell activity. Reductions in NMDA signaling early in development, globally using pharmacological approaches or specifically in parvalbumin (PV) positive interneurons leads to behavioral and electrophysiological phenotypes resembling phenomena observed in schizophrenia. However, it has recently been demonstrated that the contribution of NMDA receptor activation to excitatory postsynaptic events is minimal in FSI compared to pyramidal cells, calling into question the role that NMDA receptors play in FSI physiology within the adult cortex. Interestingly, cortical FSI show a significant tonic NMDA current in vitro, suggesting that while synaptic events onto FSI might not have a substantial NMDA component, glutamate could modulate FSI activity via extrasynaptic NMDA receptors. We tested whether FSI express functional NMDA receptors in the adult medial prefrontal cortex (mPFC) using whole-cell recordings to measure changes in excitability in response to bath application of NMDA. We found that NMDA leads to an increase in FSI excitability accompanied by slight depolarization. Given that transporters typically keep glutamate well confined to the synaptic cleft, we tested for the presence of extrasynaptic NMDA receptors by recording evoked synaptic currents in FSI in the presence and absence of the glutamate re-uptake inhibitor TBOA. Synaptic currents acquired an enhanced NMDA component during

TBOA application suggesting the presence of extrasynaptic NMDA receptors. Our results indicate that even in the absence of a significant synaptic NMDA component, extrasynaptic NDMA receptor activation is likely to play a meaningful role in regulating adult mPFC FSI activity.

P49 • Ryanodine receptor channels mediate critical sub-cellular calcium signals during normal and optogenetically enhanced neuronal regeneration in C. elegans

Christopher Gabel, Lin Sun, James Shay, Melissa McLoed*

Regulated calcium signals play conserved instructive roles in neuronal repair, but how localized calcium stores are differentially mobilized to stimulate regeneration within native contexts is poorly understood. We have found that localized calcium release from the endoplasmic reticulum (ER) via ryanodine receptor (RyR) channels is critical in stimulating initial regeneration following traumatic cellular damage in vivo. Employing in vivo laser axotomy of single neurons in C. elegans, we find that mutation of unc-68/RyR greatly impedes both outgrowth and guidance of regeneration. Performing extended in vivo calcium imaging, we measure sub-cellular calcium signals within the immediate vicinity of the regenerating axon end that are sustained for hours following axotomy and completely eliminated within unc-68/RyR mutants. Furthermore, using a novel optogenetic approach to periodically photo-stimulate the axotomized neuron, we can enhance its regeneration. The enhanced outgrowth depends on both amplitude and temporal pattern of excitation and is blocked by disruption of UNC-68/RyR. This demonstrates the exciting potential of emerging optogenetic technology to dynamically manipulate cell physiology in the context of neuronal regeneration and links the effect to innate cellular calcium signaling. Within an established mammalian growth cone amplification of calcium gradients via RyR calcium release triggers an attractive guidance response and growth cone turning. Our current work is focused on the possible link between this molecular mechanism of axon guidance and the role of RyR signaling in initiating regenerative outgrowth. Taken as a whole, our findings define a specific localized calcium signal mediated by RyR channel activity that stimulates regenerative outgrowth and can be dynamically manipulated for beneficial neurotherapeutic effects.

P50 • Influence of M1 and M4 muscarinic acetylcholine receptor activation on sleep/wake architecture, quantitative electroencephalography and cognition

Robert Gould, Michael Nedelcovych, Ditte Dencker, Michael Wood, Shaun Stauffer, Jurgen Wess, Jeffrey Conn, Carrie Jones*

Xanomeline, an M1/M4- preferring muscarinic acetylcholine receptor (mAChR) agonist attenuated the positive symptoms and some cognitive impairments in patients with schizophrenia supporting further development of subtype selective mAChR activators for the treatment of neuropsychiatric disorders. Current antipsychotic treatments target the positive symptoms in schizophrenia largely without effects on negative or cognitive symptoms or sleep disturbances. mAChR activation is implicated in mediating cognition and sleep/wake architecture. Understanding subtype selective effects of mAChR activators is integral for development of novel treatments. In the present studies, we examined M1 and M4 mAChR activation on sleep/wake architecture and quantitative electroencephalography (qEEG), comparing effects of novel M1 and M4 positive allosteric modulators BCQA and VU0152100, respectively with effects of xanomeline. Xanomeline increased wakefulness in rats, similar to effects of acetylcholine esterase inhibitors. These effects were recapitulated in part by M1 but not M4 mAChR activation. In contrast, M4 mAChR activation delayed onset of paradoxical sleep, similar to effects of current antipsychotic medications. During wake both M1 and M4 activation induced a decrease in low frequency and an increase in high frequency power suggesting an increase in arousal. Ongoing studies using M1 and M4 selective knockout mice trained to perform visual discrimination tasks implemented on computer touchscreens demonstrate cognitive impairments similar to those seen in patients with Schizophrenia, including deficits in repeated discrimination learning suggesting increased susceptibility to interference from previously learned information. Together, these data support further development of M1 and/or M4-preferring mAChR ligands as novel treatments for sleep and cognitive disruptions in schizophrenia. MH086601, MH087965, MH093366, NS065867

P51 • Neuropeptide PACAP-induced modifications in Kv2.1 channel provides neuroprotection against cerebral ischemia/reperfusion injury

Raeesa Gupte, Lipin Loo, Andrew Shepherd, Durga Mohapatra*

Cerebral ischemic stroke followed by enhanced reperfusion leads to depolarization of neuronal resting membrane potential and excessive release of glutamate, which collectively result in a sustained increase in intrinsic excitability and neuronal death. Voltage-gated K+ (Kv) channels are critical

regulators of neuronal action potential frequency, duration and amplitude, and therefore provide homeostatic control of excitability under neuromodulatory, hyperexcitable and ischemic conditions. Dynamic modulation of the major somatodendritic Kv channel, Kv2.1 via protein phosphatase-2B (PP2B)-dependent dephosphorylation and enhanced voltage-dependent channel activation under these conditions has been shown to constitute one such homeostatic mechanism. Intracerebroventricular administration of the neuropeptide, pituitary adenylate cyclase-activating peptide 38 (PACAP38) has been shown to provide neuroprotection against ischemia/reperfusion injury; however, the underlying mechanism is not well understood. PACAP38 binds to its receptor PAC1R, and activates multiple G-protein-coupled signaling cascades, including Gαq-PLCβ-mediated activation of protein kinase C (PKC) in rodent hippocampal neurons, as per our observations. We found that PACAP38 exposure leads to dephosphorylation of Kv2.1 and voltage-dependent channel activation in hippocampal neurons. Such dephosphorylation of Kv2.1 was attenuated by the specific inhibitors of phosphatase PP2A, but not by inhibitors of PP1A or PP2B. Furthermore, PACAP38-mediated dephosphorylation was also attenuated by the specific inhibitor of PKC, which is suggestive of a novel PAC1R-PKC-PP2A signaling axis underlying Kv2.1 modulation. This dephosphorylation-mediated upregulation of Kv2.1 channel activity by PACAP38 also resulted in increased survival of hippocampal neurons against in vitro hypoxic/ischemic-reperfusion insult, thereby providing a mechanism that underlies the protective effects of PACAP38 against this mode of neuronal death.

P52 • Pharmacological and functional properties of triheteromeric GluN1/GluN2A/GluN2B NMDA receptors

Kasper Hansen, Kevin K. Ogden, Stephen F. Traynelis*

NMDA receptors (NMDARs) are essential for many processes in the CNS, but are also implicated in a range of neurological and psychiatric disorders. They are tetrameric ligand-gated ion channels comprised of two glycine-binding GluN1 and two glutamate-binding GluN2 subunits (GluN2A-D). Studies on recombinant NMDARs generally describe diheteromeric receptors assembled from GluN1 and one type of GluN2. However, at least two different GluN2 subunits have been identified in most NMDAR-expressing cells and a large proportion of native receptors are triheteromers in that they contain GluN1 and two different GluN2. In contrast to our understanding of recombinant diheteromeric NMDARs, little is known about the function of triheteromeric NMDARs. We compared properties of recombinant GluN1/GluN2A/GluN2B triheteromers with those of GluN1/GluN2A and GluN1/GluN2B diheteromers using electrophysiological recordings and a new method that

allows selective cell-surface expression of triheteromeric receptors. This comparison revealed striking differences in modulation of triheteromers by extracellular Zn2+, which binds and inhibits GluN2A, and the GluN2B-selective antagonist ifenprodil. Extracellular Zn2+ inhibited triheteromers and GluN1/GluN2A diheteromers with similar potency and efficacy, whereas potency and efficacy of ifenprodil at triheteromers was markedly reduced compared to GluN1/GluN2B diheteromers. However, the presence of extracellular Zn2+ synergistically enhanced potency and efficacy of ifenprodil at triheteromers. Furthermore, kinetic measurements revealed that the glutamate deactivation time course of GluN1/GluN2A/GluN2B triheteromers was distinct and intermediate from those of GluN1/GluN2A and GluN1/GluN2B diheteromers. These results provide quantitative evaluation of the functional and pharmacological properties of GluN1/GluN2A/GluN2B triheteromers, which are presumably the most abundant NMDARs in the adult forebrain and therefore important therapeutic targets.

P53 • Mu opioid receptors hyperpolarize respiratory-controlling Kölliker-Fuse neurons

Erica Levitt, Erica Levitt, Ana Abdala, Julian Paton, John Williams*

Respiratory depression is the primary cause of death from opioid overdose, yet little is known about the cellular mechanisms of opioids on respiratory-controlling neurons. The Kölliker-Fuse (KF) is a nucleus of the pontine pneumotaxic center that regulates respiration, especially the inspiratory/expiratory phase transition. In the in situ arterially perfused working heart-brainstem preparation of rat, injection of the mu opioid agonist DAMGO (1 mM, 120 nl) into the KF caused robust apneusis that was similar to complete silencing of the KF. In whole-cell recordings from KF neurons contained in rat brain slices, activation of mu opioid receptors hyperpolarized a majority (75%) of KF neurons. The hyperpolarizing current produced by [Met5] enkephalin (ME) was concentration-dependent, reversed at the potassium equilibrium potential and was blocked by BaCl2, characteristics of a G protein-coupled inwardly rectifying potassium (GIRK) conductance. As expected, this ME-induced hyperpolarization reduced the excitability of the neuron in response to either current injection or local application of glutamate. Unexpectedly, the partial agonist morphine produced the same amplitude current as full agonists DAMGO or ME, indicating a large receptor reserve. The presence of many spare receptors could reduce the degree of desensitization induced by prolonged application of ME. Indeed, only minimal acute desensitization of the ME-mediated GIRK current was observed. This lack of desensitization of mu opioid receptors on respiratory-controlling KF neurons correlates with the lack of tolerance to the respiratory depressant effects of opioids. Supported by DA08163 (JTW) and DA33036 (ESL).

P54 • H3.3 nucleosomal dynamics regulate synaptic development and plasticity in post-replicative neurons

Ian Maze, Wendy Wenderski, Rosemary Bagot, Henrik Molina*

Since their discovery in the late 1960's, the existence of histone variants has suggested an alternative mechanism for introducing small sequence variations into the eukaryotic epigenome, phenomena that are now known to govern fundamental aspects of chromatin structural organization, nucleosomal dynamics and transcription. Recent discoveries that mutations in specific histone variants and their associated chaperones contribute to human disease suggest an essential function for histone variant regulation during critical periods of cellular development. The variant histone H3.3 is specifically enriched at transcriptionally active genes and within gene promoters, at certain heterochromatic loci and at regulatory elements in mammalian cells. Unlike canonical H3 proteins, which require mitosis for active nucleosomal deposition, H3.3 is efficiently transcribed and incorporated into chromatin in a DNA replication-independent manner in post-mitotic neurons suggesting a potential role for H3.3 in activity-dependent nucleosomal reorganization. Here, using both embryonic and adult neurons obtained from mouse and human brain, we employ a combination of proteomic, genomic and functional analyses to demonstrate that H3.3 expression, turnover kinetics and genomic deposition are tightly regulated by alterations in neuronal activity. Specifically, our data indicate that sub-populations of H3.3 are rapidly turned over in a proteasomal-dependent manner in neuronal chromatin following periods of cellular activity, and that these dynamics are essential to transcriptional events necessary for establishing and maintaining various aspects of synaptic development and plasticity. Furthermore, direct manipulations of H3.3 nucleosomal dynamics in adult mouse hippocampus reveal an essential role for histone variant exchange during periods of learning and memory formation.

P55 • Activation of noradrenergic locus coeruleus neurons promotes anxiety- like and aversive behaviors

Jordan McCall, Ream Al-Hasani, Christopher Ford, Michael Bruchas*

The locus coeruleus (LC) and its projections are the primary source of norepinephrine for the mammalian forebrain. The LC is a target for corticotropin-releasing factor, opioid neuropeptide containing neurons, and is highly enriched with all four opioid receptor types. LC tonic firing increases during stress and this increase is thought to be controlled by opioid and CRF activity. Therefore, we hypothesized that specific modulation of LC neuronal firing could lead to anxiety-like and aversive behaviors. We used optogenetic light stimulation to specifically increase LC-NE neuronal activity. Consistent

with previous reports, we demonstrate increased LC firing rate in response to stress in vivo. We investigated the role of this increase in LC-NE activity in negative affective behaviors. We report consistent firing of LC-NE neurons following repeated 5hz light stimulation in vitro and in vivo. We examined the effect of increasing tonic LC-NE firing on anxiety- and aversion-like behaviors using both conditioned place aversion and a real-time aversion paradigm. We found that increasing tonic firing of LC-NE neurons, consistent with CRF release in the LC, induces a subsequent aversion to the stimulated context. This same stimulation is aversive in real-time, with animals choosing to avoid increased activation of these neurons. Furthermore, increased LC-NE firing results in decreased open arm time in the elevated zero maze, and time in the center of the open field test, both assays for anxiety-like behavior. We also investigated the central amygdala inputs into the LC that regulate its firing, and the LC-NE neuronal projections back to the amygdala in these behaviors. These data suggest that increasing the firing rate of LC-NE neurons is sufficient to produce negative affective behaviors including aversion and anxiety. Together these results suggest that noradrenergic locus coeruleus tone is important for anxiety and aversive behavioral states.

P56 • Characterization of a novel JNK-mediated mechanism of cannabinoid tolerance

Daniel Morgan, Brian Davis, 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 in vivo. These mice express a form of CB1 where putative G protein-coupled receptor kinase (GRK) phosphorylation sites at serine residues 426 and 430 have been mutated to non-phosphorylatable alanines (S426A/S430A). Desensitization-resistant S426A/S430A mutants exhibit an enhanced and prolonged hypothermic response to delta-9-THC, endocannabinoids, and the synthetic cannnabinoid CP 55,940. This finding suggests that the magnitude and duration of the acute response to cannabinoids is dependent on GRK/arrestin-mediated desensitization. The dose response curves for the analgesic and hypothermic effects of delta-9-THC and CP 55,940 in S426A/S430A mutant mice treated are shifted to the left relative to wild-type littermates and maximum hypothermic response to high doses of these drugs are increased for the S426A/S430A mutants. This finding indicates that the pharmacological mechanism responsible for the increased response of S426A/S430A mutant mice to delta-9-THC involves increased potency and efficacy for cannabinoid agonists. S426A/S430A mutants exhibit a significant but modest delay in tolerance to delta-9-THC and CP 55,940 suggesting that other mechanisms for cannabinoid tolerance exist in these mutants that lack the "classic" GRK/

arrestin mechanism of desensitization. Pre-treatment of wild-type mice with an inhibitor of c-Jun N-terminal kinase (JNK) causes a partial block in the development of tolerance to analgesic effects of daily 30 mg/kg delta-9-THC injections. In contrast, pre-treatment of S426A/S430A mutant mice with JNK inhibitor causes a near complete (85%) 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.

P57 • Effects of transient overexposure of Neuregulin-3 during early postnatal development on adult behaviors related to schizophrenia

Clare Paterson, Amanda Law*

Neuregulin 3 (NRG3) is a susceptibility gene implicated in several neurological and psychiatric disorders, including schizophrenia. NRG3 is a growth factor and specific ligand for ErbB4, expression of which is highest during neurodevelopment and enriched within the brain. Expression of NRG3 is elevated in the prefrontal cortex of patients with schizophrenia and associated with risk genetic variation in the gene. At present, the neurobiological functions of NRG3 are poorly understood and the mechanisms of how dysregulation of the NRG3 gene relate to the pathophysiology of illness are unknown. In this study, we synthesized the bioactive epidermal growth factor (EGF) domain of NRG3 and using in-vivo peripheral injection studies in neonatal mice, demonstrate that the NRG3 EGF domain is able to cross the blood brain barrier and is bioactive, as measured by activation of brain ErbB4 and AKT. To mimic overexpression of NRG3 during one critical neurodevelopmental window, C57BL6 male mice were injected daily from postnatal day 2-10 with vehicle (PBS/0.1% BSA) or 3mg/kg NRG3. Mice were tested in adulthood using a comprehensive battery of behavioral tasks relevant to schizophrenia. Mice developmentally exposed to NRG3 showed specific and selective deficits in social novelty and social preference as well as exhibiting an anxiety-like phenotype in the open field. Fear conditioning, temporal order object recognition and sensorimotor gating were unaffected in NRG3 developmentally exposed mice. In conclusion, our research suggests NRG3 is critical in normal brain development and function, and provide initial data as to how perturbation of NRG3 at specific developmental stages may be pathophysiologically relevant to the development of neurological deficits in brain disorders, including schizophrenia.

P58 • Non-vesicular release of dopamine by ventral tegmental area projections to the lateral habenula

David Root, Alexander Hoffman, Cameron Good, Carl Lupica, Marisela Morales*

One of many brain regions receiving tyrosine hydroxylase (TH)-expressing fibers from ventral tegmental area (VTA) neurons is the lateral habenula (LHb). While dopamine (DA) release has not been reported within LHb, recent investigations have shown that LHb neurons exhibit DA-receptor dependent electrophysiological changes in response to cocaine. We recently identified a subset of VTA neurons capable of DA synthesis, but lacking the capacity for accumulation of DA in synaptic vesicles due to the absence of vesicular monoamine transporter 2 (VMAT2). TH neurons lacking VMAT2 are found in the anteromedial VTA, proximal to the distribution of VTA neurons that project to the LHb. We report here that nearly all VTA TH-expressing neurons projecting to LHb lacked VMAT2 mRNA. Consistent with the lack of VMAT2, LHb electrical stimulation or optical stimulation of mesohabenular TH fibers expressing Channelrhodopsin2 did not produce phasic DA release, measured by fast scan cyclic voltammetry. Given that LHb DA concentrations are dependent on VTA DA neurons, we hypothesized that LHb DA is released in a vesicle- and impulse-independent manner. Whole-cell recordings from LHb neurons in brain slices under conditions that did not sustain vesicular release, application of cocaine or the dopamine transporter (DAT) inhibitor GBR12935 resulted in electrophysiological responses reflecting the activation of local DA D2 or D4 receptors. These data indicate that VTA TH-expressing neurons lacking VMAT2 project to LHb, utilize a novel non-vesicular mechanism of DA release, and the DAT plays a crucial role in regulating habenular extracellular DA levels for local activation of DA receptors. We propose that mesohabenular non-vesicular DA release plays a role in modulating psychostimulant reward and aversion

P59 • Molecular and circuit basis of impaired hippocampal-prefrontal synchrony in a mouse model of the 22q11-microdeletion

Andrew Rosen, Makoto Tamura, Jun Mukai, Mihir Topiwala, Maria Karayiorgou, Joseph Gogos, Joshua Gordon*

The 22q11.2 microdeletion confers a significant increase in the risk of developing schizophrenia. Df(16)A+/¬– mice, engineered to lack the syntenic locus, exhibit a number of schizophrenia-related phenotypes, including deficits in spatial working memory (SWM) and impaired hippocampal-prefrontal synchrony. Mice with haploinsufficiency of either Zdhhc8 (Zdhhc8+/¬–) or Dgcr8 (Dgcr8+/¬–), component genes from within this locus, also have

SWM deficits and are therefore useful tools with which to explore neural substrates of schizophrenia-related cognitive deficits. Here we demonstrate that Dgcr8 and Zdhhc8 haploinsufficiency result in a robust but selective disruption in synchrony between the ventral hippocampus (vHPC) and medial prefrontal cortex (mPFC). Furthermore, we show that the temporal specificity of the deficit differs between genes. While Dgcr8 haploinsufficiency specifically impairs pre-training (baseline) synchrony, the effects of Zdhhc8 haploinsufficiency are apparent only after task acquisition. These results suggest circumscribed functional roles for Dgcr8 and microRNAs and Zdhhc8 and palmitoylation as potential molecular mediators of long-range connectivity deficits seen in the 22q11 microdeletion model of schizophrenia predisposition. In addition, the findings suggest a central role for the vHPC-mPFC circuit in the behavioral and physiological impairments associated with the 22q11.2 microdeletion.

P60 • Imaging the ultra-structure of inositol trisphosphate receptors using super-resolution microscopy

Ian Smith, Divya Swaminathan Ian Parker*

IP3-mediated Ca2+ signals underlie a variety of biological phenomena including gene expression, electrical excitability, secretion and synaptic plasticity. These signals are built upon a hierarchical organization of inositol trisphosphate receptors (IP3Rs), which are arranged in clusters on the endoplasmic reticulum (ER). The spatial distribution of these channels is crucial in determining the patterning of intracellular Ca2+ signals. Immunostaining experiments of the IP3R show a dense distribution throughout the cell and studies utilizing GFP-tagged IP3Rs show the IP3R to be highly motile. This is in contrast to observations that local IP3-mediated Ca2+ signals arise repeatedly from a small number of fixed locations within the cell suggesting the underlying cluster of IP3R on the ER membrane are stable entities. Here we have used super-resolution imaging techniques to investigate this paradox and to explore the distribution of IP3Rs on a super-resolved (nanometer) scale.

Single-molecule imaging experiments to locate and track type 1 IP3Rs tagged with a photoswitchable fluorescent protein reveals two populations of IP3Rs. We find that ~69% of the IP3R molecules are freely motile, undergoing random walk motility, whereas the remaining molecules are essentially immotile. Of these immotile IP3Rs, a fraction are organized in clusters with the number of immotile clusters comparable to the number of functional Ca2+ release sites identified in cells. Further, the footprint of such clusters is comparable to the

super-resolved mapping of native IP3Rs via STORM. It has previously been reported that IP3Rs rapidly cluster together in response to IP3. However, no such changes in overall motility, or in clustering of immotile IP3Rs were apparent following activation of IP3/Ca2+ signaling. We conclude that stable clusters of small numbers of immotile IP3Rs underlie local Ca2+ release sites, whereas the more numerous motile IP3Rs appear functionally silent.

P61 • Central glucagon-like peptide-1 receptors play a critical role in cocaine taking and seeking in rats

Heath Schmidt, Kelsey Ige, Elizabeth Mietlicki-Baase, Leonardo Guercio, Mathieu Wimmer, Chris Pierce, Matt Hayes*

Glucagon-like peptide-1 receptor (GLP-1R) signaling in the brain is physiologically relevant for the control of food intake. Administration of the GLP-1R agonist exendin-4 directly into the ventral tegmental area (VTA) selectively reduces intake of palatable food and food self-administration maintained on a progressive ratio (PR) schedule of reinforcement. Since the reinforcing properties of both food and cocaine are mediated, in part, by the mesolimbic dopamine system, it is plausible that GLP-1R signaling in the VTA controls for appetitive behaviors that extend beyond food intake and include cocaine taking and seeking. However, the role of GLP-1R signaling in cocaine addiction is unclear. The goal of these experiments was to determine the role of VTA GLP-1R signaling in cocaine self-administration and the reinstatement of cocaine seeking, an animal model of relapse. Initially, rats were trained to press a lever for intravenous infusions of cocaine (0.25 mg). Exendin-4 (0, 0.005 and 0.05 μg) was microinjected directly into the VTA immediately prior to a cocaine self-administration session. A separate cohort of rats was trained to self-administer cocaine. After 21 days of cocaine self-administration, drug taking was extinguished by replacing cocaine with saline. Once rats had extinguished their cocaine self-administration behavior, reinstatement of cocaine seeking was elicited by an acute priming injection of cocaine (10 mg/kg, i.p.). Exendin-4 was microinjected directly into the VTA immediately prior to a reinstatement test session. Intra-VTA administration of exendin-4 dose-dependently attenuated cocaine self-administration and cocaine priming-induced reinstatement of drug seeking. This is the first study demonstrating a role for VTA GLP-1R signaling in cocaine taking and seeking. Collectively, these findings support the hypothesis that central GLP-1R signaling, in addition to regulating food intake, plays a critical role in cocaine-induced behavioral plasticity.

P62 • Locus coeruleus optoICSS: Selective noradrenergic activation's role in reinforcement

Karl Schmidt, Chelsea Koller, Elena Vazey, Caroline Bass, Ilana Witten, Karl Deisseroth, Gary Aston-Jones, David Weinshenker*

It is generally accepted that dopamine is the primary neurotransmitter of the brain's reward system. While accumulating data indicates that norepinephrine (NE) may also be important for some forms of reward and reinforcement, there are conflicting reports from the literature. For example, some groups found that electrical stimulation of the noradrenergic locus coeruleus (LC) could maintain operant behaviors, while others obtained the opposite result. Because these intracranial self-stimulation (ICSS) studies were limited by issues of electrode placement, could not discriminate between stimulation of LC cell bodies or fibers of passage, and likely resulted in collateral stimulation of non-noradrenergic cells in the area, a clear interpretation of these studies is elusive. We are taking an optogenetic approach to overcome these technical obstacles and conclusively determine how the LC fits into the brain's reward circuitry and whether noradrenergic activity can function as a reinforcer. We set out to use optogenetic techniques to selectively express channelrhodopsin (ChR2) in noradrenergic cell groups and assess the effects of their activation as a consequence of lever pressing behavior. We have tested the selective expression of ChR2 in the LC using two different viral systems: a Cre-dependent AAV-DIO in TH:Cre transgenic rats and a lentivirus driven by an LC-specific phox2b-dependent PRSx8 promoter. Because the PRSx8 had stronger expression in the LC, we have been using this system for our behavioral experiments. Preliminary results suggest that optogenetic stimulation of the LC can serve as a reinforcer to maintain lever-pressing behavior, implicating this noradrenergic nucleus as a component of the brain's reward system.

P63 • The somatodendritic K+ channel Kv2.1 regulates neuronal resilience and death in response to HIV-1 gp120

Andrew Shepherd, Lipin Loo, Durga Mohapatra*

Latent reservoirs of HIV infection within the CNS are thought to underlie a recent increase in the incidence of HIV-associated neurodegeneration and neurocognitive disorders that are collectively referred to as HAND. We have identified a critical ability of the major somatodendritic voltage-gated K+ channel, Kv2.1, to bi-directionally regulate neuronal survival and death associated with HAND. Following acute exposure of cultured rat hippocampal neurons to the HIV-1 coat glycoprotein gp120, Kv2.1 channels undergo rapid dephosphorylation, a change associated with increased delayed-rectifier K+ currents (IDR) at minimally depolarizing potentials. These changes are dependent upon chemokine co-receptors CCR5/CXCR4 as well as the

protein phosphatase 2B (calcineurin) and lead to homeostatic suppression of neuronal excitability, providing acute neuroprotection. This is evident from observations that specific inhibition of calcineurin activity or blockade of Kv2.1 function by stromatoxin-1 (ScTx-1) results in non-apoptotic neuronal death upon acute gp120 exposure. However, with more prolonged exposure to gp120 (3-24 hours), CXCR4-induced activation of p38 MAPK leads to phosphorylation of Kv2.1 at S800 and results in a sustained enhancement of IDR conductance and current density at minimal depolarizing potentials. These changes contribute to a marked and chronic elevation in K+ efflux from neurons, leading to mitochondrial dysfunction, caspase activation and, ultimately, neuronal apoptosis. Interestingly, gp120-induced neuronal death can be prevented not only by the Kv2.1 blocker ScTx-1, but also by the approved anti-Alzheimer's drug Aricept (Donepezil), a compound originally described as an acetylcholinesterase inhibitor, but has also been shown to inhibit Kv2.1 channel activity. These observations shed new light upon the mechanism of HIV-induced neuronal death and suggest the further exploration of p38 MAPK-phosphorylation of Kv2.1 as a novel potential therapeutic target.

P64 • Direct hippocampal-prefrontal input supports spatial working memory

Timothy Spellman, Joseph Gogos, Joshua Gordon*

Working memory is impaired in patients with schizophrenia, as well as in multiple rodent models of schizophrenia, and intact hippocampal (HPC) and prefrontal function has been shown to be important for normal delayed non-match to place performance (DNMTP). Pyramidal cells of intermediate and ventral Ca1 and subiculum send major projections to the medial prefrontal cortex (mPFC), but the precise role that direct input from the HPC to the mPFC plays in spatial working memory is unknown. To study this role, we applied the light-driven proton pump eArch3.0 to HPC-mPFC afferents to allow for temporally-precise and reversible control of this pathway during a T-Maze DNMTP task. We stereotactically targeted AAV5 vectors carrying eArch3.0-EYFP or mCherry under the control of a CaMKIIa promotor to the ventral and intermediate HPC, resulting in infection of 45% (+/– 13%) of neurons in vCa1. We then tested the effects of terminal inhibition in the T-Maze. All mice were trained to criteria on the task. On subsequent task sessions, HPC-PFC terminal fields were silenced during a subset of interleaved, pseudo-randomized trials in one of four task phases: Sample Phase, Choice Phase, Whole Trial, or None. In eArch3.0-injected animals but not in mCherry-injected controls, T-Maze performance was significantly impaired on trials in which terminals were silenced during the entire duration of the trial or during the Sample Phase alone but not when silenced during Choice Phase ($p = 0.002$

and p = 0.003, p = 0.35, respectively). Stereotrode recordings of multiple single PFC cells made during the task revealed that silencing decreased PFC activity during runs made to the goal arms (p = 0.01). These findings suggest a critical role for HPC-driven PFC excitation in the acquisition phase of spatial working memory.

P65 • NPCs cultured at physiologically relevant oxygen tensions have a survival advantage following transplantation

Sybil Stacpoole, Daniel Webber, Bilada Bilican, Alastair Compston, Siddharthan Chandran, Robin Franklin*

Traditionally, in vitro stem cell systems have employed oxygen tensions that are far removed from the in vivo situation. This is particularly true for the central nervous system, where oxygen (O2) levels range from 8% at the pia to 0.5% in the midbrain—whilst cells are usually cultured in a 20% O2 environment. Cell transplantation strategies therefore, typically introduce a stress challenge at the time of transplantation as the cells are switched from 20% to 3% O2 (the average in adult organs). We have modelled the oxygen stress that occurs during transplantation, demonstrating that in vitro transfer of neural precursor cells (NPCs) from a 20% to 3% O2 environment results in significant cell death, whilst maintenance at 3% O2 is protective. This survival benefit translates to the in vivo environment, where culture of neonatal rat cortical NPCs at 3% rather than 20% O2 approximately doubles survival in the immediate post-transplantation phase. Furthermore, NPC fate is affected by culture at low, physiological O2 tensions (3%), with particularly marked effects on the oligodendrocyte lineage, both in vitro and in vivo. We propose that careful consideration of physiological oxygen environments, and particularly changes in oxygen tension, has relevance for the practical approaches to cellular therapies.

P66 • Acute but not chronic effects of NMDA receptor antagonism on EEG and ERPs in awake-behaving rats

Elyse Sullivan, Patricia Timi, L. Elliot Hong, Patricio O'Donnell*

Neurophysiologic endophenotypes such as event-related potentials (ERP) in the electroencephalogram (EEG) are promising candidate biomarkers that can be non-invasively obtained in both humans and rodents and inform about cortical information processing. ERPs are altered in schizophrenia, and we decided to explore whether these EEG measures are altered in rodent models of schizophrenia. We developed a novel procedure in which we can record EEG signals in freely moving rats in a manner comparable to human EEG. We chronically affixed disk electrodes to the surface of the intact skull in several

locations so we could measure signals from multiple regions simultaneously. In addition, we unilaterally implanted electrodes into the auditory cortex, hippocampus, and medial prefrontal cortex to measure local field potentials (LFP) concurrent with surface EEG signals. We were able to elicit mismatch negativity (MMN) during oddball stimuli, entrainment to the steady-state click trains at 5-80 Hz and sensory gating to paired clicks. As NMDA receptor antagonists such as Ketamine and PCP are known to produce cognitive and behavioral symptoms similar to those seen in schizophrenia, we decided to explore whether rodent EEG measures would be affected by acute or chronic NMDA receptor antagonism. Acute NMDA receptor antagonist administration (MK801; 0.1 mg/kg, ip) resulted in increased gamma power in surface EEG channels during the paired-click paradigm.. Acute MK801 was also able to augment intertrial coherence (ITC) during click trains in our auditory steady state paradigm. Interestingly, 21-day chronic MK801 administration did not produce lasting changes in the same neurophysiological measures assessed 24 hours after the last drug injection. The data suggest that whereas acute MK801 effects on EEG and ERP measures are robust, there are no long-lasting consequences of chronic NMDA receptor antagonism on auditory ERPs.

P67 • Nav1.6 somato-dendritic localization in hippocampal neurons is via an ankyrinG-independent mechanism

Elizabeth Akin, Kristen Brown, Sanaz Sadegh, Aubrey Weigel, Jean-Baptiste Masson, Diego Krapf, Michael Tamkun*

Voltage-gated sodium (Nav) channels are responsible for the initiation of the neuronal action potential. This function is innately tied to its subcellular polarized distribution in neurons, with a high concentration of Nav protein within the axon initial segment (AIS). This localization, and thus function, is lost after traumatic brain injury. Furthermore, the number and isoform of Nav channels is altered in some forms of epilepsy. Despite the importance of this protein and its localization, little is known about the real-time dynamics of this channel on the neuronal surface. To address Nav localization and dynamics, we created a Nav1.6 construct tagged with the photoswitchable fluorophore, Dendra2, which was expressed in cultured rat hippocampal neurons. We combined single-particle tracking with photoactivated localization microscopy (spt-PALM) such that we could follow a small subset of Nav1.6-Dendra2 molecules. A steady-state density of active fluorophores was maintained via a low-power activation laser and the trajectory of each molecule was determined using an automated detection and tracking algorithm. Consistent with previous observations, this method showed that AIS Nav1.6 channels are stably anchored, presumably to AnkyrinG. In contrast, somato-dendritic Nav1.6 channels showed both diffusive behavior and periods of transient confinement within specific membrane regions, thus creating small membrane clusters. To determine if this transient confinement is due to interactions with ankyrinG, we removed the ankyrin binding motif (ABM) from Nav1.6. Despite the loss of axonal localization, this mutant channel still trafficked effectively to the surface. Surprisingly, single-particle tracking of both the full-length and mutant channels demonstrated that both channels have similar behaviors of transient confinement. This implies that the Nav1.6 somatic localization is by a novel, ankyrinG independent method.

P68 • Phosphodiesterase 4 inhibition differentially regulates GluN2B and GluA1 receptor phosphorylation *in vivo* and *in vitro*

Gretchen Snyder, Stephanie Cruz*

Dopamine D1 receptors promote cAMP production and are positively linked to the activity and expression of NMDA-type (GluN2B) and AMPA-type (Glu1A) glutamate receptors. Several classes of phosphodiesterase (PDE) enzymes that regulate cAMP availability modulate dopamine pathways

controlling glutamate receptors. PDE4 is a cAMP-selective PDE abundantly expressed in brain regions receiving dopamine innervation, including prefrontal cortex (PFC), nucleus accumbens (Nac), and striatum (STR). We studied the impact of PDE4 activity on D1 receptor-dependent phosphorylation of glutamate receptors in mouse brain. C57Bl/6 mice were treated in vivo with vehicle (saline) or the dopamine D1 agonist dihydrexidine (DHX) in the absence or presence of the PDE4 inhibitor, rolipram (ROL) then killed at 30 min by focused cranial microwave irradiation. PFC, Nac, and STR samples were immunoblotted for normalized levels of phosphorylated Y1472-GluN2B, S845-GluA1, and T202/Y204- ERK1/2. DHX treatment (1.8-18mg/kg) dose-dependently elevated the in vivo phosphorylation state of GluN2B in PFC, but not in Nac or STR. Systemic ROL (2.5mg/kg) elevated basal phosphorylation of GluA1 and further enhanced GluA1 phosphorylation by DHX (10mg/kg) in all three brain regions, whereas this treatment blocked the increases in phospho-GluN2B and phospho-ERK1/2 levels induced by DHX. Interestingly, bath incubation of mouse cortical slices with ROL did not block DHX-stimulated phosphorylation of GluN2B or ERK1/2, suggesting that systemic ROL negatively regulates cortical GluN2B via an extra-cortical site of action. As in the in vivo studies, GluN1 phosphorylation in cortical slices was increased additively by bath application of DHX and ROL. The data indicate that activation of dopamine D1 signaling pathways after systemic DHX regulates GluN2B receptors in vivo in a region-specific manner. Further, cortical GluN2B and GluA1 receptors are differentially affected by changes in PDE4 activity.

P69 • Clinical, genetic and cellular findings in Christianson Syndrome

*Eric M. Morrow,*Qing Ouyang, Matthew Pescosolido, Sofia Lizarraga*

Background: Christianson syndrome (CS) is a newly-recognized, autism-related condition caused by mutations in the X-linked Na+/H+ exchanger 6 (NHE6). CS is among the most common X-linked developmental brain disorders. NHE6 is an endosomal protein that regulates intra-endosomal pH. The gene expression of NHE6 have also been found to be decreased in autism postmortem cortex relative to control in transcriptome studies. A related protein, endosomal NHE9, has also been implicated in autism, and is upregulated in autism transcriptome studies.

Objectives: The immediate goal of our study is to understand the function of NHE6 and NHE9 in neuronal circuit development and to link this novel cellular mechanism to other previously characterized autism-related pathways.

Methods: We are taking a translational, integrated approach. Our focus has been on cellular and neurodevelopmental studies in NHE6 and NHE9 null mouse lines. We are also studying NHE6 mutant human cortical pyramidal neurons

derived from patients using iPSC technologies. Finally, we are also following families longitudinally using clinical research assessments wherein there are boys with NHE6 mutations.

Results: We find that in the absence of NHE6, intra-endosomal pH is overacidified. This overacidification is association with attenuated endosomal signaling including via the BDNF/TrkB signaling pathway. These defects in signaling are associated with impoverished neuronal arborization and synapse development in the mouse model at the morphological and electrophysiological level. In patient-derived neurons, we see similar findings, yet interestingly, we also see an associated upregulation of NHE9. This latter finding stands in parallel to our prior observations in autism transcriptome studies. Patients with CS demonstrate failures in postnatal brain growth which complement the findings in mouse related to undergrowth of neuronal arbors.

Conclusion: We report cellular abnormalities, overacidification of endosomes and abnormalities in endosomal signaling, in cellular models for CS that may be amenable to intervention with small molecules screens. Our cellular models, access to animal models and our patient registry, put us in a good position moving forward with regard to development of treatments.

P70 • Changes in gene expression in the CNS of myostatin and insulin-like growth factor 1 genetically-modified mice

Sonsoles de Lacalle, Stephen Murata, Ursula Muñoz, Inma Castilla de Cortazar*

Sarcopenia is characterized by the loss of skeletal muscle mass with gradual decline in muscle function, reduced insulin sensitivity and increased oxidative damage, and impairment in spinal motoneurons. Pathways involved in regulating muscle mass are the IGF-1-PI3K-Akt pathway, the myostatin (mstn) signalling pathway and the NFkB pathway, and typically, IGF-1 signalling cascade inhibits the mstn pathway in skeletal muscle through the common intracellular Akt signaling pathway. Whether a dysruption in the normal balanced interaction between the IGF-1 and mstn pathways could affect the nervous system, has not been explored directly.

Using microarray analysis we detected changes in gene expression in the CNS of animal models of mstn and IGF-1 dysfunction, to identify shared signal transduction cascades. Expression of MSTN in a mouse heterozygous for IGF-1 (IGF-1–/+), and expression of IGF-1 in the MSTN null (MSTN–/–) mice were unchanged. However, expression of IGFBP3 was significantly decreased when mstn was constitutively overexpressed (MSTN TG) mice. Several genes were downregulated in the brain when myostatin is altered. Three of these genes (ODC1, PTCH1 and RBP1) were also significantly downregulated in the CNS of IGF-1–/+ mice. Another set of genes showed significant changes in these animals, but in opposite direction: WNT2 was downregulated in

MSTN–/– (–2.34 fold) and in the MSTN TG (–3.20 fold) but upregulated in the IGF-1–/+ mice (+1.55 fold); JUN was downregulated in MSTN–/– (–1.85 fold) and upregulated in IGF-1–/+ mice (+2.34 fold), and FASN was downregulated in MSTN TG but upregulated in IGF-1–/+ mice (+1.5 fold).

Our results suggest that the interaction between IGF-1 and MSTN in skeletal muscle may also be extended to an interaction within the CNS, implying perhaps that the fine tuning between these two signaling cascades, crucial for normal muscle development and growth, could be regulated at the CNS level.

P71 • Chronic epileptic encephalopathy in adult patients with bilaterally synchronous frequent and/or prolonged subclinical epileptiform discharges

Denson Fujikawa, Eliot Licht, Rebecca Jacobsen*

We followed four patients with infrequent convulsive seizures for four to 10 years, with periodic EEGs and neuropsychological tests. All four had bursts of frontally predominant, bilaterally synchronous 1.5-3 Hz spike or polyspike and slow-wave discharges (SWDs) that initially comprised 15% to 88% but were reduced to 5% or less of total EEG time with appropriate antiepileptic drugs. Case 1 showed a 30-point improvement in his verbal WAIS-R score, and Case 3 a 21-point improvement in his performance WAIS-R score over nine and five-year periods, respectively, with normalization of frontal executive function. Cases 2 and 3 showed no improvement in frontal executive dysfunction despite being free of SWDs for nine and five years, respectively. Case 3, however, had 21% SWDs at the time of his final neuropsychological test and subsequently moved out of state, so no further follow up was possible. These patients had variable degrees of epileptic encephalopathy and subclinical SWDs. They illustrate the importance of minimizing the occurrence of SWDs with appropriate antiepileptic drugs and long-term monitoring with neuropsychological tests, because chronic cognitive deficits are potentially reversible.

P72 • Progesterone suppresses the development, but not expression, of cocaine choice under concurrent reinforcement in female rats

Tod Kippin, Kyle Ploense, Gema Olivarria, Dan Maliniak, Amanda Carr, Kerry Kerstetter*

Sex differences in cocaine dependence indicate that women relative to men exhibit a more severe addiction profile. Female rats also exhibit higher operant responding for cocaine reinforcement relative to males which is modulated by exogenous and endogenous cycles in estrogen and progesterone. We

have shown that female rats exhibit an estrogen-dependent preference for cocaine reinforcement over food reinforcement. Here, we examine the impact of progesterone on the cocaine-food choice in female rats either when progesterone is administered throughout the experiment or only once cocaine-food choice behavior has been established. Intact female Sprague-Dawley rats were trained respond (FI:20s) on different levers for food (2 x 45 mg pellets) or cocaine (1.0 mg/kg IV) and then allowed to choose between the two reinforcers under concurrent reinforcement. Throughout training and testing one group of females received daily progesterone (0.5 mg) and another received vehicle (0.1 ml of peanut oil). A third group of rats received no hormone treatments during training and initial testing but then received vehicle or progesterone prior to 5 daily test sessions. All rats readily acquired responding for food and for cocaine. Females receiving daily vehicle throughout the experiment exhibited a preference for cocaine over food whereas, females treated with daily progesterone throughout the experiment exhibited a preference for food over cocaine. Conversely, progesterone treatment during only the choice testing portion of the experiment failed to impact the preference for cocaine. These data indicate that progesterone can suppress the development of a preference for cocaine over a natural reinforcer in females but does not alter an established preference for cocaine over natural reinforcers. These findings suggest that progesterone may have a prophylactic effect on addiction development but unlikely to be useful in its clinical management. Supported by NIDA (1R01DA027525).

P73 • Bidirectional control of lateral habenula neurons by release of glutamate and GABA from ventral tegmental area inputs

Carlos Mejias-Aponte, Dave Root, Steven Zhang, Huiling Wang, Alexander Hoffman, Carl Lupica, Marisela Morales*

Ventral tegmental area (VTA) and lateral habenula (LHb) are involved in addiction and clinical depression. We show that the mesohabenular pathway from the VTA to LHb consists of a novel population of neurons capable of releasing both GABA and glutamate. Using a combination of retrograde tract tracing and in situ hybridization, we found that mesohabenular neurons co-express vesicular glutamate transporter 2 (VGluT2) mRNA and glutamic acid decarboxylase (GAD) 65/67 mRNAs, molecular markers for glutamatergic and GABAergic neurotransmission, respectively. Confocal microscopy revealed co-expression of VGluT2 and vesicular GABA transporter (VGaT) proteins within mesohabenular terminals from VTA VGluT2 neurons. Electron microscopy revealed the presence of VGluT2-protein or VGaT-protein in terminals from VTA VGluT2 neurons projecting to the LHb. Whole-cell recordings of synaptic currents in LHb neurons receiving inputs from

mesohabenular neurons expressing channelrhodopsin-2 (ChR2) under control of the VGluT2 promoter demonstrated overlapping inward AMPA receptor and outward GABAA receptor components. In-vivo single-unit recordings showed that brief activation of ChR2, expressed under control of CAMKII-, VGluT2- or VGaT-promoters in mesohabenular fibers, mostly inhibited LHb neurons. Furthermore, this mesohabenular synaptic inhibition was greatly attenuated by local blockade of GABAA receptors. Conversely, longer-duration ChR2 activation of mesohabenular axons more frequently resulted in excitation of LHb neurons. These data provide convergent evidence of a population of VTA neurons providing combined monosynaptic glutamatergic and GABAergic inputs to LHb neurons, and we suggest that excitatory or inhibitory effects on LHb neurons by the same GABAergic/glutamatergic mesohabenular axons is dependent upon the duration of mesohabenular neuron activation.

P74 • Nucleus accumbens synaptic plasticity in a genetic mouse model of bipolar mania

Puja Parekh, Michelle Sidor, Sade Spencer, Yanhua Huang, Colleen McClung*

It has been well established that the circadian molecular clock regulates monoaminergic systems that control mood, anxiety and motivated behaviors. Using a validated mouse model of bipolar mania, the ClockΔ19 mutant mouse, we investigate how a disruption in the circadian gene, Clock, leads to molecular and physiological abnormalities in mesolimbic circuitry, contributing to a manic-like phenotype. Specifically, we focus on synaptic alterations in the nucleus accumbens (NAc), an area that receives dopaminergic projections from the ventral tegmental area (VTA). Clock mutant mice display abnormalities in VTA dopaminergic activity leading to elevated extracellular dopamine in the NAc. Because the NAc is generally believed to be involved in goal directed behavior, studies from our lab have focused on the role of this region in the manic model. These studies have found deficits in phase coupling and locking of the NAc with other brain regions important for exploratory behavior in the Clock mutants, as well as altered expression of synaptic proteins and morphological changes in medium spiny neurons (MSNs), the projection cells of the NAc. Additionally, it has been hypothesized that inhibition of MSNs is necessary for increased reward and anti-anxiety behaviors, characteristics of Clock mutants. Using in vitro electrophysiological recordings, we have found a decrease in excitatory synaptic strength at NAc MSNs of mutant animals compared with wildtype littermates to indicate a disruption in glutamatergic signaling in this region. These findings point to MSN excitatory synapses as a potentially critical downstream target of dopamine dysfunction in Clock mutants and support the hypothesis of reduced excitatory synaptic strength underlying aspects of the manic phenotype.

P75 • Induction of endoplasmic reticulum-plasma membrane contacts is a non-conducting function of the Kv2.1 voltage-gated potassium channel

Philip Fox, Diego Krapf, Michael Tamkun*

The voltage-gated potassium channel Kv2.1 localizes to micron diameter clusters on the soma of hippocampal pyramidal neurons and transfected HEK 293 cells. In both cell types, Kv2.1 clusters mark sites of membrane protein trafficking, while on the neuronal soma, Kv2.1 clusters reside above sub-surface cisterns. In the hippocampus, Kv2.1 channels rapidly translocate out of clusters in response to hypoxic insult. Thus, Kv2.1 localization is a sensitive indicator of hypoxic brain trauma. Channels localized to clusters are largely unable to flux K+ suggesting Kv2.1 possesses an auxiliary, non-conducting function. We present evidence that one non-conducting function of Kv2.1 is to induce the formation of endoplasmic reticulum (ER)-plasma membrane (PM) contacts. In HEK 293 cells, the cortical ER (cER) as observed by TIRF microscopy typically consists of a meshwork of tubules. Expression of Kv2.1 induced the enlargement of cER tubules into micron diameter sheets, mirroring the clustered localization of the channel. An ultrastructural analysis using thin-section electron microscopy and immuno-gold labeling indicated that cER is brought into close apposition to the PM (<30nm) opposite dense immuno-gold labeling for Kv2.1. These data suggest that Kv2.1 functions to direct the formation of hypoxia-sensitive ER-PM contacts through interactions with unknown lipids or proteins in the ER. Since ER-PM contacts have a well-established role in Ca2+ homeostasis, these structures may link ER Ca2+ to endo- and exocytosis.

P76 • The Rocky Mountain multiple sclerosis center tissue bank provides tissue to researchers around the globe

Kristina Bliss, Rae Russell, Helen Madsen, BK Kleinschmidt-DeMasters, John Corboy*

The Rocky Mountain Multiple Sclerosis Center (RMMSC) Tissue Bank was founded in 1976. Funded in part by the National MS Society, our Tissue Bank is one of only a few MS-related tissue banks in the nation. Animal models are of limited utility in the research of multiple sclerosis. The RMMSC Tissue Bank has distributed specimens to hundreds of investigators worldwide and to date, over thirteen hundred people have consented to be donors after death. A wide range of laboratories, specializing in neuroscience and functional imaging, request tissue to enhance their studies. Tissue Bank coordinators are on-call and work to preserve tissue with pathologists around the country as well as at the

University of Colorado Hospital. We have over 450 frozen and formalin-fixed diseased and control tissues. We will present the inner workings of our tissue procurement, storage and distribution. We will highlight the value of the tissue bank within the MS community. The manner in which tissue is procured and stored is critical in ensuring the quality of the samples in research. The RMMSC Tissue Bank provides a unique bridge between those who live with MS and the scientific community. As one of the few brain banks that specialize in MS, we provide high quality tissue samples to researchers around the globe. Without this critical resource, MS research on human tissue would not be possible.

P77 • Impulsivity, perfectionism and serotonin regulation in anorexia nervosa

David Jimerson, Devon Carroll, Barbara Wolfe*

Recent behavioral and neurobiological research on eating disorders has focused on neurocognitive domains including impulsivity, compulsivity, perfectionism and cognitive rigidity. Thus, elevated impulsivity has been implicated in binge episodes characteristic of bulimia nervosa and binge eating disorder. Research on the role of impulsivity in anorexia nervosa (AN) is of current interest, given evidence for (1) a binge-eating/purging subtype of the disorder (described in DSM-5); and (2) dysregulation of CNS serotonin—a moderator of impulsivity—in patients studied at low weight and following weight restoration. The current study was designed to assess whether an intervention to decrease serotonin synthesis could attenuate symptoms of anxiety and perfectionism that commonly persist following recovery from AN. Participants included 15 medication-free, normal-weight women who previously met diagnostic criteria for AN. Baseline assessments showed elevated ratings of anxiety and perfectionism in comparison to control values. The two week intervention consisted of an ad lib diet supplemented with a tryptophan (TRP)-free mixture of branched-chain large neutral amino acids (LNAA) using a randomized, placebo-controlled, double-blind crossover design. The active phase intervention decreased the TRP/ΣLNAA ratio ($p<.01$), providing indirect evidence for decreased CNS serotonin synthesis. In preliminary results, the amino acid intervention was associated with significantly increased impulsivity ratings, while ratings of anxiety and perfectionism were not significantly altered. These results extend previous evidence for an association between reduced serotonin function and increased impulsivity. Dieting, which indirectly decreases CNS serotonin function, has been identified as a risk factor for AN. Results of this study suggest that increased impulsivity associated with diet-induced alterations in serotonin function may contribute to onset or post-treatment relapse in AN.

P78 • BDNF modulation of parasympathetic cardiac vagal neurons located in the nucleus ambiguus

Ryan Bateman, Ruiqian Wan, Mark P. Mattson, David Mendelowitz*

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that has been shown to have many roles in neural plasticity, development and neuronal network function. Furthermore various activities such as exercise and fasting, both of which increase parasympathetic activity, augment BDNF expression. Since BDNF signaling has also been implicated in the regulation and control of heart rate, in this study we examined the role of BDNF in modulating neurotransmission to cardiac vagal neurons (CVNs) in the nucleus ambiguus which generate parasympathetic activity to the heart. Whole-cell patch clamp electrophysiology was used to study neurotransmission to CVNs in wild type BDNF+/+ as well as heterozygous BDNF+/– mice. Our results indicate glutamatergic excitatory postsynaptic currents (EPSCs) to CVNs were significantly increased in wild type mice as compared to heterozygous BDNF mice. Additionally, GABAergic inhibitory postsynaptic currents (IPSCs) were significantly diminished in wild type mice as compared to heterozygous BDNF mice. Together, these results suggest BDNF enhances parasympathetic activity to the heart by increasing excitatory and decreasing inhibitory neurotransmission to CVNs, which would result in a subsequent decrease in heart rate. These results provide a functional basis for understanding how BDNF production can alter autonomic activity and in particular the parasympathetic regulation of heart rate.

P79 • Antagonism of lipopolysaccharide activation of nodose ganglion neurons by CP 55,940

Gaylen Edwards, Juliane Johnston, Kimberly Freeman*

Endocannabinoids have been suggested to modulate gastrointestinal afferent activity initiated lipopolysaccharide (LPS) (Neurogastroenterol.Motil. 24:956, 2012). Moreover, endocannabinoid receptors are located on cell bodies of vagal afferent nerves in the nodose ganglia (Am. J. Physiol 263: G63, 2010). Thus, an interaction between signaling pathways involving LPS and endocannabinoids has been suggested. The purpose of these studies is to explore the effect of pretreatment with a cannabinoid agonist, CP 55,940, on nodose neuron activation by LPS in vitro. To determine the effect of CP 55,940 and LPS on neuron activation, rats were anesthetized and nodose ganglia were extirpated. The neurons were dissociated and plated. The cells were treated with media, CP 55,940, LPS, CP 55,940 followed by LPS, or AM 251, a CB1 receptor

antagonist, and CP 55,940 followed by LPS. Immunocytochemistry was performed to stain the cells for cFos as a measure of cell activation. Neurons were identified using neurofilament immunoreactivity. The neurons on each treated coverslip were counted using fluorescence imaging, and the number of neurons that were cFos positive was counted in order to calculate the percentage of activated neurons per coverslip. Pretreatment with CP 55,940 decreased the percentage of neurons expressing cFos-immunreactivity in response to LPS. This observation suggests that endocannabinoids inhibit LPS activation of nodose ganglion neurons. (Supported by Office of the VP for Research and Dept of Physiol and Pharmacol, Univ of Georgia).

P80 • Effects of spinal cord injury on firing properties of identified neurons in the mouse spinal cord

Ronald Harris-Warrick

Spinal cord injury (SCI) results in a loss of descending drive from the brain to the spinal Central Pattern Generator (CPG) networks that organize and drive locomotion. As a consequence, we propose that the spinal neurons and their synaptic connections undergo slow plastic changes that can lead to dysfunction and retard locomotor recovery. Bennett and coworkers have shown that rat sacral motoneurons become hyperexcitable and fire prolonged plateau potentials after SCI, due in part to changes in intrinsic current expression. We have examined the excitability and serotonin responsiveness of synaptically isolated motoneurons (MNs) and V2a interneurons (INs) in slices of the mouse lumbar cord one month after a complete spinal transection at T8-9. V2a INs are ipsilaterally projecting excitatory INs which help maintain normal left-right hindlimb alternation at high locomotor speeds. One month after SCI, these INs do not change their intrinsic properties: their baseline activity, responses to current injection and action potential properties are unchanged. However, they become 100-1000-fold more sensitive to serotonin modulation, with threshold excitation at 10 nM serotonin rather than 1-10 μM serotonin in controls. This is associated with an increase in 5HT2C receptor expression. Lumbar motoneurons show similar SCI-induced increases in serotonin sensitivity. They have moderate increases in excitability: about half of the synaptically isolated SCI MNs are tonically active at rest, compared to 8% of control MNs, and require increased holding currents at -70 mV. However, they do not exhibit bistable responses to current steps or ramps. Sacral MNs showed the same pattern of changes. It is likely that species differences explain the different results obtained after SCI in rat and mouse spinal MNs. Supported by NIH NS17323.

P81 • Safety assessment of an intraspinal cell delivery system in yucatan mini-pigs

Tanya Wyatt, Monica Siegenthaler, Martin Marsala, Gabriel Nistor, Han S Keirstead*

A GLP study was conducted in Yucatan mini-pigs to assess the safety profile of a novel intraspinal cell delivery system. In contrast to rodents, the spinal neuroanatomy of pigs is very similar to human with respect to the total cross-sectional gray matter area, the glial index (number of glial cells/number of neurons), and the spinal blood supply. The anatomical similarities between pig and human allow for a representative assessment of safety for an intraspinal cell delivery surgical procedure. MotorGraft cells, which have previously been shown to be safe in rodents, were used to examine the safety of the delivery system. Administration of MotorGraft was performed using a 30-gauge needle built into a magnetic spinal-pulsation-cancellation system that is attached to a digital micro-injector via microtubing. To assess both acute and delayed adverse effects, animals were survived for either 7 or 21 days. During the in-life period, detailed clinical examinations and observations for mortality and morbidity were performed daily. Individual body weights were performed at least weekly. Prior to and post cellular administration, the animals were assessed for sensory and motor function. Graft cell presence, injection site pathology, cell distribution pattern, gliosis and nerve fiber degeneration were examined. Based on the interim results of this study, bilateral intraspinal cellular injections can safely be performed in the thoracic spinal cord of Yucatan mini-pigs. There were no significant clinical observations nor any residual sensory or motor function deficits following cellular delivery using the spinal-pulsation-cancellation system. Full histopathology results are currently pending. In conclusion, the surgical procedure and mechanism of intraspinal delivery are safe. The spinal cord pulsation-cancellation system has great potential for providing a safe method for intraspinal cell delivery for the treatment of spinal cord injuries and diseases.

P82 • Acute stress impairs reward and error signaling in prefrontal cortex

David M. Devilbiss and Craig W. Berridge

Stress impairs adaptive reward-driven behaviors dependent on optimal Prefrontal Cortex (PFC) function. This deficit underlies habitual behaviors associated with stress that can precipitate relapse of drug use, gambling, and other addiction-related behaviors and likely contributes to the anhedonia associated with stress-related disorders. Electrophysiological and imaging evidence connotes impaired PFC functions, including working memory and attention, are dependent on a suppression of persistent spiking activity. Yet

stress additionally impairs reward processing, including sensitivity to both rewarding and error signaling, associated with PFC dysfunction. Here we demonstrate that reward-related neuronal signaling within the medial PFC of rats performing a delayed-response task of working memory is potently suppressed by stress. Error-related signaling, found in neurons that selectively respond to trial completion as well as error-related signaling of delay-related neurons, was also robustly suppressed by stress. We demonstrate the behavioral relevance of stress-related suppression in reward and trial outcome-evaluation spiking of these neurons by demonstrating that trial success and task performance is best predicted by spiking during the reward and outcome evaluation over delay-related or other task-related activity. This provides insight into how stress may act to impair appropriate decision-making and behavioral flexibility by suppressing reward and error-related signaling.

P83 • Methadone maintenance and HIV risk in Ukraine

George Woody, Sergii Dvoriak, Andrey Karachevsky, Anna Pecoraro, Irina Trofimchenko, Sumedha Chhatre, Joseph Schumacher*

Background: Opioid dependence treatment is an important way to reduce HIV and other infectious diseases, particularly in Ukraine since HIV opioid use is one of the major modes of transmission. We studied the acceptability and impact of methadone maintenance (MM) on opioid use and HIV risk behaviors among 50 opioid-dependent individuals, 25 HIV+ and 25 HIV–. Prior to this, no MM studies had been conducted in Ukraine.

Method: Non-randomized, open pilot study of acceptability and impact of methadone maintenance therapy (MMT) on opioid use and HIV risk behaviors among 50 opioid-dependent individuals, 25 HIV+ and 25 HIV–. The Risk Assessment Battery and Addiction Severity Index measured past 30-day HIV risk and opioid use at baseline and weeks 4, 8, 12, and 20.

Results: 50 participants enrolled; 48 completed 4, 8, and 12-week follow-ups; and 47 completed 20-week follow-ups. Opioid use was compared between and within groups using negative binomial models. Log values of sex, drug, and total HIV risk scores were compared between and within groups using Proc Mixed models. Scores showed significant ($p<0.0001$) reductions in opioid use (Baseline: M=20.2, SD=12.4 days/past 30; Week 20 M=0.4; SD=1.0), drug risk (Baseline: M=3.6, SD=3.3; Week 20 M=0.40, SD= 1.5), and sex risk (Baseline: M=4.1, SD=1.9; Week 20 M=2.9, SD=1.7) over time, with no differences between HIV+ and HIV- groups. Patients were given an opportunity to taper off MM at week 12, but none did.

Conclusion: MM was well tolerated and accepted by HIV+ and HIV– patients in Ukraine, and opioid use and HIV risk significantly behaviors decreased.

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P84 • Examination of dopaminergic modulation of corticostriatal information processing in an animal model of Huntington's disease

Cameron Pollock, Thibaut Sesia, Kathy Toreson, Chuma Obineme, Patricio O'Donnell*

Huntington's disease (HD) is a progressive and fatal neurodegenerative disorder that produces marked cognitive deficits, often predating the motor symptoms characteristic of the disease. HD is characterized by severe striatal atrophy by the time of the clinical diagnosis. A progressive deterioration of dopamine D2 and D1 receptors, as well as dopamine transporter (DAT) availabilities, has been correlated with the age of onset and with deficits in planning and verbal tasks, but not with chorea and other cognitive impairments. DA agents used in clinical trials, however, appear to be most efficient in treating motor symptoms. While numerous HD models exist, a unified picture of the state and evolution of the dopaminergic system in the disease pathology is still needed. Here we assess the state of mesolimbic systems involved in the neural bases of cognitive deficits in HD using a promising new model, BACHD (Tg5; Yu-Taeger et al., 2012). This model effectively reproduces HD biomarkers such as accumulation of mutant htt protein, reduced DA receptor binding potential in aged transgenic animals, and behavioral symptoms such as progressive motor deficits. We set out to characterize the mesolimbic dopaminergic system throughout the lifespan of the BACHD model using juxtacellular recordings in the prefrontal cortex (PFC) and ventral tegmental area (VTA), and intracellular recordings in the dorsal and ventral striatum. In young animals between the ages of 3 and 6 months, we found no difference in dopaminergic neuronal activity in the VTA between wild-type (WT) and Tg5. Likewise, pyramidal neurons in the PFC did not respond differently to stimulation of VTA efferents between WT and Tg5 young animals. Striatal medium spiny neurons show no change in the ability of VTA stimulation to attenuate PFC inputs between young WT and Tg5 rats. In aged animals, there is a trend towards increased activity in the VTA in Tg5 vs WT animals.

P85 • Ablation of the inhibitor of DNA binding 4 (Id4) gene results in effects on circadian clock function

Giles Duffield, Maricela Robles-Murguia, Tim Hou, Sandy Duffield, Kathleen McDonald*

Id genes comprise a family of four genes that encode helix-loop-helix (HLH) transcriptional inhibitors. Our earlier studies have focused on the role of Id2 with the circadian system, revealing its contribution to input, output and core clock function (interaction with the bHLH clock components CLOCK and BMAL1) (Duffield et al 2009 Curr Biol 19:297-304; Hou et al 2009 JBC

284:31735-45; Ward et al 2010 JBC 285:38987-39000; Mathew et al 2013 PLoS ONE 8:e73064). Here we expand our studies to explore the potential role of Id4 within the circadian system. Our new studies examine aspects of the circadian clock and photoentrainment of Id4–/– mice, revealing that mutant mice have: a reduction in wheel-running activity; a shorter free-running period length; a reduction in the magnitude of phase delays in response to a 10 hr extension of the light phase; a reduction in the magnitude of phase delays in response to both saturating and sub-threshold light pulses; and an earlier phase angle to lights off (ZT12), and this is exacerbated when examined under a short 6:18 photoperiod. Several of these characteristics are the opposite to those exhibited by the Id2–/– mouse, suggesting either an opposing influence of the ID4 protein within the circadian system, or the absence of ID4 results in changes in expression or activity of other members of the Id gene family. To explore the molecular underpinnings of the Id4–/– phenotype we tested whether the absence of ID4 resulted in changes in Id1, Id2 and Id3 expression in the hypothalamic suprachiasmatic nucleus: qRT-PCR analysis revealed a significant elevation in Id1 expression. It is plausible that this elevation in Id1 and/or the absence of ID4 might result in changes in interactions with the bHLH canonical clock components or with targets downstream of the clock. These results reaffirm that Id genes play an important role within the circadian system, and complement our previous findings that have focused primarily on the Id2 gene.

P86 • FRET analysis of GluA2 AMPA receptors reveals structural rearrangement within the C-terminal domain during receptor activation

*Anders S. Kristensen *, L. Zachariassen, M. Katchan, D. S. Pickering, A. Plested*

AMPA receptors (AMPARs) are glutamate-gated cation channels that mediate the majority of fast excitatory neurotransmission in the central nervous system. AMPARs are formed by homo- or heterotetrameric of GluA1 to GluA4 subunits. An recent X-ray crystal structure of a full-length homomeric GluA2 AMPAR have allowed unique insights into AMPAR molecular structure and provides an improved framework for beginning to understand the structural mechanisms underlying receptor function, regulation and pharmacological modulation. In the present study, we have explored dual insertion of cyan and yellow variants (CFP and YFP, respectively) of green fluorescent protein at various positions in the GluA2 AMPA receptor subunit to enable measurement of intra-receptor conformational changes using Förster Resonance Energy Transfer (FRET) in live cells. We identify dual CFP/YFP-tagged GluA2 subunit constructs that retain function and display intra-receptor FRET. This includes a construct (GluA2-6Y-10C) containing YFP inserted in the intracellular loop between the M1 and M2 membrane-embedded segments and CFP inserted

in the C-terminal domain (CTD). GluA2-6Y-10C displays FRET with an efficiency of 0.11 while retaining wild-type receptor expression and kinetic properties. We have used GluA2-6Y-10C to study conformational changes in homomeric GluA2 receptors during receptor activation. Our results show that the FRET efficiency is dependent on functional state of GluA2-6Y-10C and hereby indicates that the intracellular CTD undergoes conformational changes during receptor signaling.

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PANELISTS

Cristian Achim*
Elias Aizenman*
Olu Ajilore*
Schahram Akbarian*
Sven Akkerman*
Elliot Albers*
Ream Al-Hasani*
Anne Anderson*
Ana Andreazza*
Yexica Aponte*
Miklos Argyelan*
Jarek Aronowski*
Rosemary Bagot*
Ross Baker
Otsuka employee-salary
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Jill Becker*
Nichole Berchtold*
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Haruhiko Bito*
James Bjork*
Jed Black*
Jim Bloedel*
Matt Blurton-Jones*
Stephen Boehm*
Stephanie Borgland*
Cesar Borlongan
SanBio, Inc. stock options, research grant, intellectual property rights

Nick Brandon
Astra-Zeneca employee-salary
David Bredt
J & J employee
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Roberta Brinton*
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Nickolai Brustovetsky*
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Lundbeck, Teva; Consulting
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Lique Coolen*
Gabriel Corfas*
John Crabbe*
Thomas Crowley
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Harriet de Wit*
Gregory del Zoppo*
Mark Dell'Acqua*
Wenbin Deng*
Lakshmi Devi*

* denotes no disclosurers

David Devilbiss
NextStep Biomarkers LLC, ownership interest/managment

Ralph DiLeone*

John Disterhoft
Naurex Pharmaceuticals, honorarial, advisory board

Lauren Dobbs*

Paula Dore-Duffy*

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Nigel Greig*

Chen Gu*

Colin Haile
MDT, Inc—salary

Edward Hall*

Mark Hamner
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Ming-Hu Han*

Colleen Hanlon*

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Warren Hirst
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Paula Hoffman*

Alex Hoffman*

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David Hutcheson
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Thomas Hyde*

Ines Ibanez-Tallon*

Andrew Jaffe*

Thomas Jhou*

Elizabeth Jonas*

Carrie Jones
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Len Kaczmarek*

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Hillery Metz*
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Servier, consulting; Intra-Cellular Therapies, Inc. and Epinomed Inc., consulting/stock options
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Susanna Rosi*

Benjamin Saunders*

Akira Sawa
Amgen, Pfizer,J & J, Sucampo, Taisho, Takeda, Astra Zeneca, AbbVie—consulting fees; Astellas, Takeda, Mitsubishi-Tanabe, Dainippon-Sumitomo, Sucampo J & J—research support

Chris Schmidt
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Federico Sesti*

Christopher Shaffer
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Kelli Sharp*

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Harel Shouval*

Monica Siegenthaler
California Stem Cells, Inc—employee

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Patrick Simen*

Phil Skolnick*

Jack Smethells*

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Sean Smith
Merck—employee, salary, stocks

Gretchen Snyder
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Deepak Srivastava*

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John Steeves
Asubio, Alseres, Neuralstem, Novartis, Exerion—consultant fees

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George Wilcox*

Angus Wilfong
Lundbeck, Cyberonics, Inc—consulting; Novartis, UCB—research funding

John Williams*

Ai Yamamoto
NeuroPhage Pharmaceuticals, research contract

William Yang*

Larry Young*

Sam Young*

Yimin Zou*

Jon-Kar Zubieta*

Suzanne Zukin*

POSTERS

Elizabeth Akin*
Sven Akkerman*
Anne Anderson*
Ryan Bateman*
Michael Beauchamp*
Kristina Bliss (Wells)*
Diane B. Boivin
Merck Canada, Servier Canad; Valeanta—paid speaker, travel support; Alpha LogikConsultants Inc—Founder; Aeroport de Montreal, Ministre de Transports du Quebec—consulting fees
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Robbin Brodbeck
Lundbeck employee-salary
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Ned Cauley*
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Sonsoles de Lacalle*
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Denson Fujikawa*
Harrison Gabel*
Christopher Gabel*
Robert Gould*
Raeesa Gupte*
Kasper Hansen*

* denotes no disclosurers

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Sybil Stacpoole*

Elyse Sullivan*

Ramon Trullas*

Gustavo Turecki*

John Wolf*

George Woody*

Tanya Wyatt
California Stem Cells employee—salary

Sheng Zhou*

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* denotes no disclosurers

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