49TH ANNUAL WCBR

JANUARY 23–28, 2016

BRECKENRIDGE, COLORADO

WINTER CONFERENCE ON BRAIN RESEARCH

WELCOME TO THE 49TH WINTER CONFERENCE ON BRAIN RESEARCH (WCBR)!

We are back in Breckenridge for the 2016 meeting with a fantastic program, including a week of strong science, collegial interactions, and productive networking. WCBR was established in 1968 in Lake Tahoe, as a conference organized by a handful of neuroscientists from the University of California, Los Angeles. Over the years, the meeting has grown to host as many as 400-500 participants annually. Long-time attendees consistently praise the high quality of science presented at WCBR, which always spans a broad range of topics, along with the highly interactive nature of the meeting, which often leads to effective collaborations. Networking is a true highlight of this meeting, with formal and informal discussions emerging at the scientific sessions, at conference breakfasts, lunches and receptions, as well as by the fireside or on the ski slopes.

We kick off the meeting with a **Welcome Reception** on Saturday evening, where you can greet long-time friends, welcome new attendees (wearing blue badges), congratulate Travel Fellows (wearing ribbons), and thank Travel Fellowship mentors (also wearing ribbons). On Sunday, we dive into science with an **Opening Breakfast** featuring our keynote speaker, **Dr. Miguel Nicolelis**, M.D., Ph.D., Professor of Neurobiology, Biomedical Engineering, and Psychology and Neuroscience at Duke University. Dr. Nicolelis has provided unique contributions to advance the field of brain-machine interface, and his presentation is entitled: "*Brain-machine interfaces: from basic science to neurological rehabilitation.*" In addition, he will lead the **Brain Talk Town Meeting** on Monday evening, aimed to be a dialogue among scientists and non-scientists. Another regular feature in our meeting is the **Outreach Program**, which supports our attendees visiting K–12 classrooms and community organizations to share their enthusiasm for scientific research and medical practice. We encourage everyone to consider volunteering in this program, as a way to give back to the communities that host our meeting.

We will also have vibrant poster sessions, with the best posters from junior investigators shown during a **Special Poster Session** and Reception on Tuesday. Awards will be given to the most meritorious posters identified by the Program Committee. Please take time to visit the **Exhibits** during all the poster sessions. On Wednesday, we offer the Smitty Stevens Memorial (NASTAR) Race for skiers and snowboarders, followed by a **Mountain Lunch**. Also on Wednesday, please be sure to attend the **Business Meeting** following

the afternoon sessions, where we will hold elections for Program Chair-elect, Facilities Chair-elect, Education Chair-elect and several board members. We will also discuss the program, budget, and future sites for the meeting. Because board members are critical for WCBR, we encourage you to nominate yourself or a colleague for open positions in clinical, cellular/molecular, or systems/behavioral neuroscience, with the only requirement being that nominees have participated in at least three meetings. We will close the week with the **Annual Banquet**, at which awards for the Best Posters and the Ski Race will be announced, while we dine and dance with lively music and atmosphere.

We are an all-volunteer organization, and this meeting is possible owing to the great effort of all those individuals serving on the Board of Directors and several committees, as well as to the generous donations of our sponsors.

We are sure you will have a great time. Enjoy the meeting!

Patricio O'Donnell, Acting Conference Chair
Paul Phillips, Conference Chair-elect

Contents

General Information

HEADQUARTERS is the Beaver Run Resort & Conference Center. All scientific activities will be held there.

WCBR INFORMATION DESK AND MESSAGE CENTER are in the Registration Area, Floor 3 Foyer, Beaver Run Resort & Conference Center.

The information desk hours are as follows:

	Morning	*Afternoon*
Saturday, January 23	8:00 am–12:00 pm	3:30 pm–7:30 pm
Sunday, January 24	6:30 am–10:00 am	3:30 pm–7:00 pm
Monday, January 25	7:00 am–10:00 am	3:30 pm–6:00 pm
Tuesday, January 26	7:00 am–10:00 am	3:30 pm–6:00 pm
Wednesday, January 27	7:00 am–10:00 am	3:30 pm–5:30 pm
Thursday, January 28	7:00 am–10:00 am	

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. In efforts to be more environmentally friendly, please return your black registration pouch to the WCBR Information Desk at the end of the meeting.

EXHIBITS AND POSTER SESSIONS are in Peak 1–4. Refreshments are provided from 3:30 pm to 4:30 pm, Sunday through Wednesday. Exhibitor setup is Sunday, January 24, 12:00 pm–3:00 pm. All exhibitors should have their materials removed by 10:00 pm on Wednesday, January 27. Poster setup details are below.

POSTER SESSION I, SUNDAY, JANUARY 24
Posters can be set up after 12:00 pm on Sunday

Posters will be available for viewing from 3:30 pm–10:00 pm on Sunday. Presenters will be at their posters from 3:30 pm–4:30 pm. Posters must be removed by 10:00 pm on Sunday.

POSTER SESSION 2, MONDAY, JANUARY 25
Posters can be set up after 8:00 am on Monday

Posters will be available for viewing from 3:30 pm–10:00 pm on Monday. Presenters will be at their posters from 3:30 pm–4:30 pm. Posters must be removed by 10:00 pm on Monday.

POSTER SESSION 3, TUESDAY, JANUARY 26
Posters can be set up after 8:00 am on Tuesday

This is a special session displaying the highest-ranked posters by young investigators. A grand prize and several other prizes will be presented to the best posters. Posters will available for viewing from 3:30 pm–10:00 pm on Tuesday. Presenters will be at their posters from 3:30 pm–4:30 pm and returning for the special session from 6:30 pm–8:30 pm. Posters must be removed by 10:00 pm on Tuesday.

POSTER SESSION 4, WEDNESDAY, JANUARY 27
Posters can be set up after 8:00 am on Wednesday

Posters will be available for viewing from 3:30 pm–10:00 pm on Wednesday. Presenters will be at their posters from 3:30 pm–4:30 pm. Posters must be removed by 10:00 pm on Wednesday.

Please refer to pages 26–33 for a listing of poster sessions.

BREAKFAST is served to all conference delegates on Sunday, January 24 from 7:00 am–8:30 am in the Colorado Ballroom. Tickets are not required for the Sunday breakfast.

Monday through Thursday breakfast will be available from 6:30 am–9:00 am, in the Imperial Ballroom (Coppertop Complex). ***The tickets in your registration packet are required for admission.***

DISCOUNTED SKI LIFT VOUCHERS can be picked up at the WCBR Information Desk. Vouchers can be redeemed only at a Breckenridge ski window. Discounted lift tickets are valid only at the following resorts: Breckenridge, Keystone, Arapahoe Basin, Vail, and Beaver Creek.

BANQUET table sign-up sheets will be posted next to the Information Desk, Monday–Wednesday. Attendees will have the opportunity to reserve a table for the Thursday night banquet. 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 **22** *AMA PRA Category 1 credits*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

Conference Support

EDUCATIONAL GRANTS

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

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50TH WINTER CONFERENCE ON BRAIN RESEARCH

JANUARY 28–FEBRUARY 2, 2017
BIG SKY, MONTANA

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

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Don't forget to visit the posters & exhibits

Events Summary

SATURDAY, JANUARY 23

First Time Attendees, Travel Fellows and Mentors Welcome Reception • 6:00 pm–6:30 pm • Imperial Ballroom

Event begins promptly at 6:00 pm.

Welcome Wine and Cheese Reception • 6:30 pm–7:30 pm • Peak 1–4

SUNDAY, JANUARY 24

Conference Breakfast and Plenary Address • Colorado Ballroom

Breakfast • 7:00 am–8:30 am

Plenary Address • 8:00 am–9:30 am

Brain-machine interfaces: from basic science to neurological rehabilitation

Miguel Nicolelis, M.D., Ph.D., Center for Neuroengineering, Duke University

Dr. Nicolelis' research was named by Science Magazine as one of the top scientific breakthroughs of 2012. There is no question that this pioneer's work is exerting substantial impact on the quality of human life. His efforts in electrophysiology, brain-machine interface and robotics have already realized the goal of reanimation of paralyzed limbs. This extraordinary achievement was highlighted on one of the world's biggest platforms when the FIFA World Cup 2014 was opened with the demonstration of a paraplegic man in a brain-controlled robotic exoskeleton walking up to and kicking a ball, witnessed by an audience of hundreds of millions of people worldwide. Dr. Nicolelis' work also includes recent focus on treatment for neurological and psychiatric disorders. WCBR attendees and members of the Breckenridge community alike will greatly appreciate his amazing science and his inspirational personal story.

Career Development • 2:30 pm–3:30 pm • Peak 11

Travel Fellows are especially encouraged to attend.

Research Science Panelists:

Lakshmi Devi, Ph.D., Chair, Icahn School of Medicine at Mount Sinai
Amy Newman, Ph.D., NIDA-Intramural Research Program, NIH
Matt LaVoie, Ph.D., Harvard University
Laura O'Dell, Ph.D., University of Texas, El Paso
Deanna Benson, Ph.D., Icahn School of Medicine at Mount Sinai
Gretchen Snyder, Ph.D., Intra-Cellular Therapies, Inc.
Matthew Riedy, Ph.D., SPAWAR Systems Center Atlantic

This round-table discussion session will focus on professional development topics such as the individual development plan (IDP), mentoring and being mentored, balancing career and life, and identifying and resolving conflicts. The session is targeted toward junior investigators (including faculty and postdoctoral fellows).

Exhibits and Poster Session • 3:30 pm–4:30 pm • Peak 1–4

Panel Sessions • 4:30 pm–6:30 pm & 7:00 pm–8:30 pm

Light refreshments will be available between sessions.

MONDAY, JANUARY 25

First Meeting of the Board of Directors • 6:30 am–8:30 am • Base 9 Bar

Panel Sessions • 7:30 am–9:30 am

Smitty Stevens Memorial Race Registration Waiver Deadline • 8:00 am • WCBR Information Desk, Floor 3 Foyer

Exhibits and Poster Session • 3:30 pm–4:30 pm • Peak 1–4

Panel Sessions • 4:30 pm–6:30 pm & 7:00 pm–8:30 pm

Light refreshments will be available between sessions.

Brain Talk Town Meeting • 7:00 pm–8:30 pm • Imperial Ballroom

Attendance is open to all.

Beyond boundaries: linking brains to machines to restore neurological functions

Miguel Nicolelis, M.D., Ph.D., Center for Neuroengineering, Duke University

TUESDAY, JANUARY 26

Breakfast for Travel Fellows Meeting • 6:30 am–9:00 am • Base 9 Bar

Panel Sessions • 7:30 am–9:30 am

Exhibits and Poster Session • 3:30 pm–4:30 pm • Peak 1–4

Panel Sessions • 4:30 pm–6:30 pm

Special Poster Session • 6:30 pm–8:30 pm • Peak 1–4

The 25 top-ranked posters submitted by junior investigators will be on display in this special session, accompanied by a wine and cheese reception. Posters will be judged and award-winning posters will be identified. Winners will be announced and prizes will be given at the Closing Banquet on Thursday, January 28.

WEDNESDAY, JANUARY 27

Panel Sessions • 7:30 am–9:30 am

Smitty Stevens Memorial Ski Race • 10:00 am–11:30 am • EpicMix Race location, Sundown Run (Mountain Peak 9)

Registration waivers must be completed no later than 8:00 am on Monday, January 25 at the WCBR Information Desk.

Mountain Lunch • 11:30 am–2:00 pm • Copper Top Bar and Imperial Ballroom

Required lunch ticket is in your registration packet.

Exhibits and Poster Session • 3:30 pm–4:30 pm • Peak 1–4

Panel Sessions • 4:30 pm–6:30 pm

Business Meeting • 6:30 pm • Peak 5

All attendees are encouraged to attend and vote on the Program Chair-elect, Facilities, and Education positions, as well as new board members. Conference updates, future meeting locations and other business will be discussed.

THURSDAY, JANUARY 28

Second Meeting of the Board of Directors • 6:30 am–8:30 am • Base 9 Bar

Panel Sessions • 7:30 am–9:30 am & 4:30 pm–6:00 pm

Reception • 6:30 pm • Floor 3 Foyer

Banquet and Dance • 7:30 pm • Colorado Ballroom

Required dinner ticket is in your registration packet.

Program

SUNDAY, JANUARY 24, 2016

7:00 AM–8:30 AM

Breakfast • Colorado Ballroom

8:00 AM–9:30 AM

Plenary Address • Colorado Ballroom

Brain-machine interfaces: from basic science to neurological rehabilitation

Miguel Nicolelis, M.D., Ph.D.

2:30 PM–3:30 PM

Special Session • Peak 11

Career Development

Lakshmi Devi (Chair), Amy Newman, Matt LaVoie, Laura O'Dell, Deanna Benson, Gretchen Snyder, Matthew Riedy

3:30 PM–4:30 PM

Exhibits and Posters • Peak 1–4

4:30 PM–6:30 PM

1. **Panel** • Peak 5

   The biology of schizophrenia in the 21st century: moving from genetic risk to mechanisms of action

   Thomas Hyde (Chair), Elizabeth Tunbridge, Amanda Law, Andrew Jaffe, Nick Brandon

2. **Panel** • Peak 6–8

   Axonal regeneration in CNS repair: an evolutionary perspective

   Martin Oudega (Chair), Andrew Chisholm, Michael Shifman, Jeffery Plunkett, James Fawcett

3. **Panel** • Peak 9–10

   Alzheimer's disease as an oscillopathy of septohippocampal system dysfunction?

   John Lawrence (Chair), Sylvain Williams (Co-chair), Rory McQuiston, John Huguenard, Andre Fisahn, Philippe Diaz

4. **Panel** • Peak 11–12

   Synaptic regulation of striatal circuits

   David Kupferschmidt, Hitoshi Morikawa, Christopher Ford (Chair), Tianyi Mao

5. **Panel** • Peak 14

   Microglia and their diverse roles in neurodegenerative, psychiatric, and mood disorders

   Gretchen Snyder (Chair), Staci Bilbo, Matthew LaVoie, Elizabeth Bradshaw, Miles Herkenham

6. **Panel** • Peak 15–16

   Opiate-induced plasticity in mesocorticolimbic circuits

   Abigail Polter, Jose Moron-Concepcion, Elena Chartoff, Matthew Hearing (Chair)

7. **Panel** • Peak 17

   Adolescent binge alcohol exposure and decision-making brain circuitry

   Fulton Crews, Justin Gass, Jeremy Clark, Charlotte Boettiger (Chair)

6:30 PM–7:00 PM

Refreshment Break • Floor 3 Foyer

7:00 PM–8:30 PM

8. **Panel** • Peak 5

   Grub and smokes: common downward slope towards food and drug addiction

   Laura O'Dell (Chair), Travis Brown, Katherine Serafine (Co-chair), Carrie Ferrario

9. **Panel** • Peak 6–8

   Biomarkers of blood brain barrier disruption in the injured brain

   Richard Leigh (Chair), Lawrence Latour, Alexis Simpkins

10. **Panel** • Peak 9–10

    Basic and translational findings on ionic mechanisms of peripheral pain sensitization

    Theodore Cummins, Durga Mohaptra, Robert Gereau (Chair)

11. **Panel** • Peak 11–12

    Neuronal injury in the immature brain after seizures and hypoxia-ischemia

    Wendy Macklin (Co-chair), Claude Wasterlain, Paco Herson, Ed Dudek (Chair)

12. **Panel** • Peak 14

    Cell adhesion molecules in synapse function and disease

    Ana Carneiro (Chair), Gabrielle Rudenko, Yu Yamaguchi, Silvia De Rubeis

13. **Panel** • Peak 15–16

    Targeting phosphodiesterases for rescuing cognition in Alzheimer's diseases: from mice to humans

    Hanting Zhang (Chair), Jos Prickaerts, Ying Xu, Mark Gurney, Lawrence Wennogle

14. **Panel** • Peak 17

    What is the difference between a drug-taking brain and a drug-addicted brain? Insights from animal studies

    Leandro Vendruscolo, Benjamin Zimmer, Anna Samaha (Chair)

MONDAY, JANUARY 25, 2016

6:30 AM–9:00 AM

Breakfast • Imperial Ballroom

7:30 AM–9:30 AM

15. **Panel** • Peak 5

    New possibilities with multimodal brain imaging

    Gitte Knudsen (Chair), Christin Sander, Alexandre Franco, Pierre LeVan

16. **Panel** • Peak 6–8

    Novel mechanisms for modulating prefrontal cortical circuitry for the treatment of neuropsychiatric disorders

    Carrie Jones (Chair), Min Wang, Zhen Yan, Steven Siegel, Michael Grannan

17. **Panel** • Peak 9–10

    The ventral tegmental area glutamatergic neurons: neurocircuitry, neurotransmission and behavior

    Marisela Morales (Chair), Seth Taylor, Carlos Mejias-Aponte, Stephen Rayport, Sandra Blaess

18. **Panel** • Peak 11–12

    How and why to study both sexes in basic neuroscience research

    Jill Becker (Chair), Rebecca Shansky, Jaclyn Schwarz, Brian Trainor

19. **Panel** • Peak 14

    Alternative signaling pathways in addiction models

    Alfred Robison, Brad Grueter, David Stellwagen (Chair), Catherine Cahill

20. **Panel** • Peak 15–16

    Using in vivo calcium imaging to understand neural circuit control of dynamic behaviors

    Da-Ting Lin, Jones Parker, Erin Calipari (Chair), Michael Bruchas

21. **Panel** • Peak 17

    Gut feelings: new links between ghrelin and psychiatric disorders

    Jeffrey Zigman, Lorenzo Leggio, Ki Goosens, William Brimijoin (Chair)

3:30 PM–4:30 PM

Exhibits and Posters • Peak1–4

4:30 PM–6:30 PM

22. **Panel** • Peak 5

    The neuro-immune interface in addiction: another vicious cycle

    Kyle Frantz (Chair), Fulton Crews, Michal Bajo, Bryan Yamamoto, Staci Bilbo

23. **Panel** • Peak 6–8

    Regeneration and plasticity after injury: extracellular matrix, inflammation, visual function

    James Fawcett (Chair), Herbert Geller, Larry Benowitz, Ronald Meyer, Keith Martin

24. **Panel** • Peak 9–10

    Novel mechanisms of regulation and signaling at excitatory synapses

    Shernaz Bamji, Andres Barria (Chair), Ulli Bayer, Jean-Claude Beique

25. **Panel** • Peak 11–12

Progesterone receptors: they're not just in the nucleus anymore

Shaila Mani, Kevin Sinchak, Paul Micevych (Chair), Melinda Mittelman-Smith

26. **Panel** • Peak 14

Calcium signaling slopes leading to neurodegeneration

Ilya Bezprozvanny, Mark Dell'Acqua, Grace Stutzmann, Victoria Bolotina (Chair)

27. **Panel** • Peak 15–16

New diagnostic trends in severe epilepsy

Olaf Paulson (Chair), Stefan Posse, Sándor Beniczky, Alexandre Franco, Lars H. Pinborg

28. **Panel** • Peak 17

The NMDA receptor complex—A hub for the developmental convergence of psychosis risk factors

Vibeke Catts, Matthew Puhl, Duncan Sinclair, Heather Brenhouse (Chair)

6:30PM–7:00PM

Refreshment Break • Floor 3 Foyer

7:00 PM–8:30 PM

Brain Talk Town Meeting • Imperial Ballroom • *All are welcome and encouraged to attend*

Beyond boundaries: linking brains to machines to restore neurological functions

Miguel Nicolelis, M.D., Ph.D., Center for Neuroengineering, Duke University

7:00 PM–8:30 PM

29. **Panel** • Peak 5

Brain-driven vulnerability to substance use disorders: do brains make drug abusers?

Noelle Anastasio (Chair), Thomas Crowley (Co-chair), Catharine Winstanley, Patricia Conrod

30. **Panel** • Peak 6–8

CNS drug delivery, biodistribution, and translational aspects of AAV-based gene therapeutics

Carolyn Fairbanks (Chair), R. Scott McIvor, Andreas Beutler

31. **Panel** • Peak 9–10

Not just a relay: dissecting structure and function of the deep cerebellar nuclei in cognition

Abigail Person, Krystal Parker, Erik Carlson (Chair)

32. **Panel** • Peak 11–12

Mechanisms underlying migraine

KC Brennan, Greg Dussor, Andrew Russo (Chair), Leon Garcia-Martinez

33. **Panel** • Peak 14

Little bumps, big bumps: how the environment affects the neural progenitors of the subventricular zone

Steven Levison, Olivier Raineteau, Francis Szele (Chair)

34. **Panel** • Peak 15–16

    Molecular pathways controlling synapse development and plasticity

    Katherine Roche, John Isaac, David Bredt (Chair), Andres Maricq

35. **Panel** • Peak 17

    The neurobiology of eating disorders: translational research of core appetitive, cognitive, and emotional deficits

    David Jimerson, Scott Crow, Kelly Klump (Chair)

TUESDAY, JANUARY 26, 2016

6:30 AM–9:00 AM

Breakfast • Imperial Ballroom

7:30 AM–9:30 AM

36. **Short Course** • Peak 5

    Big data in neuroscience

    Paul Katz (Chair), Jason Gallant, Lloyd Fricker, Andrew Jaffe, Jessica Turner

37. **Panel** • Peak 6–8

    The behavioral and neurobiological consequences of combined psychostimulant and alcohol use

    Dieter Meyerhoff, Lori Knackstedt (Chair), William Griffin, Zachary Rodd

38. **Panel** • Peak 9–10

    Stress effects on endocannabinoid signaling and emotional control

    Sachin Patel, Hsiao-Huei Chen (Chair), Jeffrey Tasker, Jaideep Bains

39. **Panel** • Peak 11–12

    Initiating the turns, elongating the runs, and mtor-ing up the slopes: augmenting neuropsychiatric therapeutic intervention by targeting protein synthesis

    Michael Stefanik (Chair), Mauro Costa-Mattioli, Emanuela Santini, Jacob Beckley

40. **Panel** • Peak 14

    Coerulean fire: norepinephrine, the brain's intrinsic performance enhancing drug

    Barry Waterhouse (Chair), Craig Berridge (Co-chair), Robert Spencer, Rachel Navarra, Jill McGaughy, Elena Vazey

41. **Panel** • Peak 15–16

    Circuit specialization across primary sensory and motor domains of cerebral cortex

    Hysell Oviedo (Co-chair), Bryan Hooks, Samuel Hires, Aaron McGee (Chair)

42. **Panel** • Peak 17

New approaches to targeting opiod receptors for the management of chronic pain

Paul Phillips (Chair), Julius Bourke, Edita Navratilova, Lakshmi Devi, Charles Chavkin

3:30 PM–4:30 PM

Exhibits and Posters • Peak 1–4

4:30 PM–6:30 PM

43. **Short Course** • Peak 5

Will I dream of electric sheep? A primer on brain machine interfaces

David Devilbiss (Chair), Jeremy Hill, Dan Moran, Miguel Nicolelis

44. **Panel** • Peak 6–8

Fear and anxiety: contributions from below the brain

Monika Fleshner, Christopher Lowry, Paul Marvar, Matthew Young (Chair)

45. **Panel** • Peak 9–10

Role of opioid receptors in pain, affective and motivated behavior

Michael Bruchas (Chair), Amynah Pradhan, Jose Moron-Concepcion, Catherine Cahill

46. **Panel** • Peak 11–12

Basal ganglia function in human disease

Stephen Traynelis (Chair), Sharon Swanger, Mark Bevan, Karen Eskow Jaunarajs, Jeff Conn

47. **Panel** • Peak 14

Taming the beast: neuronal populations and signaling systems within the amygdala regulating emotional learning, stress and drug preference

Thomas Kash (Co-chair), Rebecca Shansky, Matthew Hill (Chair), Zoe McElligott, Joshua Gordon

48. **Panel** • Peak 15–16

Voltage-gated ion channels in neurons: disease, activity and location

Angeles B. Ribera, Leonard Kaczmarek, William Catterall, Chen Gu (Chair)

49. **Panel** • Peak 17

Prefrontal cortex neuropeptides: novel targets for the treatment of cognitive and motivational dysfunction

Brian Baldo (Chair), Nicola Grissom, Craig Berridge, Seema Bhatnagar

6:30 PM–8:30 PM

Special Poster Session & Reception • Peak 1–4

WEDNESDAY, JANUARY 27, 2016

6:30 AM–9:00 AM

Breakfast • Imperial Ballroom

7:30 AM–9:30 AM

50. **Panel** • Peak 5

    Vulnerability factors for drug addiction: interactions between natural and drug rewards

    Tod Kippin, Marilyn Carroll, Zuoxin Wang, Lique Coolen (Chair)

51. **Panel** • Peak 6–8

    Traumatic brain injury: complex pathologies contributing to a difficult problem

    Amy Brooks-Kayal, Bret Smith, Catharine Winstanley, Akiva Cohen (Chair)

52. **Panel** • Peak 9–10

    At the nexus between environment and synaptic plasticity, immediate early genes may influence mental illness risk

    Mohamed Kabbaj, Flavio Kapczinski, Amelia Gallitano (Chair), Dietmar Kuhl

53. **Panel** • Peak 11–12

    Behavioral insights into neural circuits for addiction and cognitive function

    Caitlin Orsini (Co-chair), Stephen Chang, Donna Calu, Ryan Lalumiere, Michael Saddoris (Chair)

54. **Panel** • Peak 14

    The epidemic of opiate use disorder

    Kathryn Cunningham (Chair), Phil Skolnick, Kim Janda, Sandra Comer, Harshini Neelakantan

55. **Panel** • Peak 15–16

    Local protein synthesis at synapses, a keynote of plasticity

    Shannon Farris, Deanna Benson, Marius Ifrim, Oswald Steward (Chair)

56. **Panel** • Peak 17

    Hard times, bad timing–epidemiological, cellular and molecular evidence for windows of stress vulnerability across the lifespan

    Hanan Trotman, Eliane Proulx, Kimberly Urban, Duncan Sinclair (Chair)

10:00 AM–11:30 AM

Smitty Stevens Memorial Ski Race • EpicMix Race location, Sundown Run (Mountain Peak 9)

11:30 AM–2:00 PM

Mountain Lunch • Coppertop Bar and Imperial Ballroom

3:30 PM–4:30 PM

Exhibits and Posters • Peak 1–4

4:30 PM–6:30 PM

57. **Panel** • Peak 5

    What had BDNF signaling got to do with addiction?

    Paul Phillips (Chair), Jacqueline McGinty, Anna (Xuan) Li, Shannon Gourley, Dorit Ron

58. **Panel** • Peak 6–8

Astrocytes as central players and a novel target in ALS, AD and stroke

Milos Pekny (Chair), Jin-Moo Lee (Co-chair), Elly Hol, Steven Levison

59. **Panel** • Peak 9–10

Pain mechanisms: from peripheral detection to ascending and descending modulation

Durga Mohaptra (Chair), Andrew Shepherd, Theodore Price, Bryan Copits, Yarimar Carrasquillo

60. **Panel** • Peak 11–12

Orexin/hypocretin neurons: physical activity, sleep, arousal, thermogenesis and hypoglycemia…what's the connection?

Catherine Kotz (Chair), Jennifer Teske, Andrew Whittle, Barry Levin

61. **Panel** • Peak 14

High by design: cellular mechanisms and behavioral models of designer drug use

Carl Lupica (Chair), Ernesto Solis, M. Foster Olive, Alex Hoffman, Jenny Wiley

62. **Panel** • Peak 15–16

Transmitter diversity, co-release and plasticity at central synapses

Shane Hentges (Chair), Thomas Hnasko, Marisela Morales, Louis-Eric Trudeau, Jaideep Bains

63. **Panel** • Peak 17

Double diamonds, no problem: the role of specific inputs to the medial prefrontal cortex in the regulation of fear and anxiety

Joshua Gordon (Chair), Ofer Yizhar, Nancy Padilla Coreano, Celia Kjaerby, Caitlin Vander Weele

6:30 PM

Business Meeting • Peak 5

THURSDAY, JANUARY 28, 2016

6:30 AM–9:00 AM

Breakfast • Imperial Ballroom

7:30 AM–9:30 AM

64. **Panel** • Peak 5

    Searching for neural substrates of PTSD vulnerability in the young, adult, and addicted

    Tania Roth, Almira Vazdarjanova, Marek Schwendt (Chair), Justin Gass

65. **Panel** • Peak 6–8

    Neurocognitive effects of early-life seizures

    Tim Benke (Chair), Rod Scott, Joaquin Lugo

66. **Panel** • Peak 9–10

    The neurobiology of sleep/wake oscillations

    Matt Carter (Chair), Antoine Adamantidis, Kamran Diba, Thien Thanh Dang-Vu

67. **Panel** • Peak 11–12

    Recent updates on incubation of drug craving: environmental enrichment, epigenetics and glutamate receptors

    Marcello Solinas, Yan Dong, Anna (Xuan) Li (Chair), Karen Szumlinski (Co-chair)

68. **Panel** • Peak 14

    The place of the lateral preoptic area–lateral hypothalamic continuum in the control of adaptive and pathological motivated behavior

    Daniel Zahm, Michela Marinelli, David Barker (Chair), Steven Simmons

69. **Panel** • Peak 15–16

    Inflammatory signaling at the crossroads between stress, addiction and psychopathology

    Gretchen Neigh (Chair), Jesse Schank, Jennifer Felger, Georgia Hodes

70. **Panel** • Peak 17

    How cortical inhibitory circuits gate perception and plasticity

    Alfredo Kirkwood (Chair), Li Zhang, Robert Froemke, Elizabeth Quinlan

3:30 PM–4:30 PM

Refreshment Break • Floor 3 Foyer

4:30 PM–6:30 PM

71. **Panel** • Peak 5

    Innovative strategies for detection and treatment of neurogdegenerative diseases

    Greg Gerhardt (Chair), Holly Hunsberger, Miranda Reed, Sid O'Bryant, Richard Grondin

72. **Panel** • Peak 6–8

    Synaptopathies: from the periphery to central and from mechanisms to disease

    Gabriel Corfas (Chair), Mohammed Akaaboune, Christorpher Cowan, Derek Buhl

73. **Panel** • Peak 9–10

Functional implications of the heterogeneous, molecular, physiological, and anatomical organization of forebrain locus coeruleus-norepinephrine projections

Patricia Jensen, Carlos Mejias-Aponte, Barry Waterhouse, David Devilbiss (Chair)

74. **Panel** • Peak 11–12

Transporters on the move–biophysical approaches for direct assessment of protein dynamics

Joeseph Mindell, Michael Kavanaugh, Claus Loland (Chair), Kenneth Madsen

75. **Panel** • Peak 14

Down the slippery slope: new frontiers in addiction-related circuits

Susan Ferguson (Co-chair), Joshua Haight (Chair), Jessica Barson, Thomas Kash, Lindsay Yager

76. **Panel** • Peak 15–16

Nobody plays alone: multisensory connections and plasticity in the primary sensory cortices

Eike Budinger, Huizhong Tao, Hey-Kyoung Lee (Chair), Patrick Kanold (Co-chair)

77. **Panel** • Peak 17

Stress and cocaine: a thorny problem in the PFC-accumbens circuit

Jacqueline McGinty (Chair), Jason Radley, Ben Siemsen, Shannon Gourley, Robert Wheeler

6:30 PM–7:30 PM

Reception • Floor 3 Foyer

7:30 PM–11:30 PM

Banquet and Dance • Colorado Ballroom

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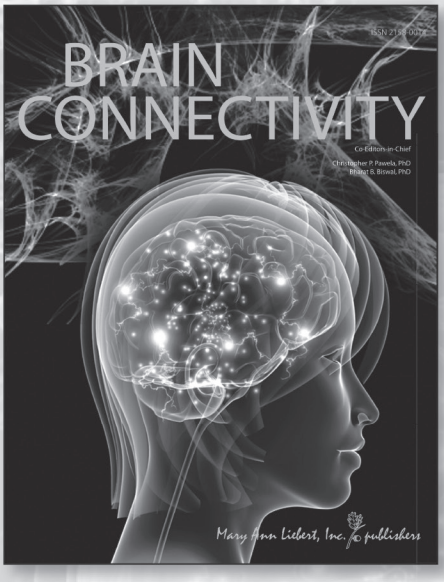

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POSTER SESSION I

SUNDAY, JANUARY 24, 2016 • PEAK 1–4

Posters will be available for viewing from 3:30 pm–10:00 pm on Sunday. Presenters will be at their posters from 3:30 pm–4:30 pm.

Posters may be set up after 12:00 pm on Sunday and must be removed by 10:00 pm on Sunday.

SU1. **Generation of Ca2+-independent CaMKII activity by nitric oxide**

Steven Coultrap

SU2. **RGS14 binds and colocalizes with Rap2 to regulate PC12 cell neurite outgrowth**

Katherine Squires

SU3. **Behavioral phenotyping in ankyrin 3 knockout mice**

Daniel Petrus

SU4. **Inhibition of POMC neuron activity by mu opioid receptors overshadows pre-synaptic disinhibition through GABAergic synapses**

Philip Fox

SU5. **Monosynatic inputs to ventral tegmental area glutamate neurons**

Carlos Mejias-Aponte

SU6. **Characterizing Fos-expressing neuronal ensembles in the nucleus accumbens after amphetamine sensitization in rats**

Rebecca Fallon

SU7. **Effect of cocaine self-administration pattern on reinstatement and corticostriatal activity**

Aaron Garcia

SU8. **Signaling prediction for reward size in rodent medial orbitofrontal cortex during Pavlovian unblocking**

Nina Lopatina

SU9. **A novel method for isolation and quantification of human peripheral cannabinoid receptors**

Ariel Ketcherside

SU11. **Human postmortem brain collection and the study of PTSD**

Michelle Mighdoll

SU12. **TrkB regulates behavioral vulnerabilities to adolescent stress hormone exposure**

Elizabeth Barfield

SU13. **Environmental experience rescues spatial discrimination and gene expression patterns in offspring following prenatal toll-like receptor 4 activation**

Amanda Kentner

SU14. **Effects of risperidone treatment in adolescence on adult neuroinflammation and DA receptors in a developmental model of schizophrenia**

Moazam Cheema

SU15. Changes in synaptic plasticity and the development of an autistic phenotype following kainate induced early life seizure

Paul Bernard

SU16. PI3K-MTOR hyperactivity contributes to cognitive deficits following a single generalized seziure

Anne Anderson

SU17. Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression

Olaf Paulson

SU18. Short general anaesthesia induces prolonged changes in gene expression in the mouse hippocampus

Tulen Pekny

SU19. Peripheral and central deficits contributing to manual function in patients with Type II Diabetes

Stacey Gorniak

SU20. Multiple Sclerosis patients show less flexible reallocation of cognitive resources during dual-task walking: a mobile brain/body imaging (MoBI) study

Elizabeth Chernyak

SU21. Nicotinic acetylcholine receptors in inflammation and immunity–multiple sclerosis

Ronald Lukas

SU22. Attenuation of reactive gliosis slows down progression of amyotrophic lateral sclerosis (ALS) in mice

Roy Pekny

SU23. JZP-110: A dopamine-norepinephrine reuptake inhibitor (DNRI) with robust wake-promoting effects and low abuse potential

Lawrence Carter

SU24. Improving therapeutic efficacy on Alzheimer's pathology using transcranial MRI-guided focused ultrasound

Kelly Markham-Coultes

SU25. The presence and identity of a companion affects neural responses to group separation in rhesus macaques (Macaca mulatta)

Tamara Weinstein

POSTER SESSION 2

MONDAY, JANUARY 25, 2016 • PEAK 1–4

Posters will be available for viewing from 3:30 pm–10:00 pm on Monday. Presenters will be at their posters from 3:30 pm–4:30 pm.

Posters may be set up after 8:00 am on Monday and must be removed by 10:00 pm on Monday.

MO1. The 2.2-angstrom crystal structure of carboxy-terminal region of ataxin-3

Meewhi Kim

MO2. The role of CSPGs in neuronal differentiation of stem cells from the adult zebrafish brainstem

Jeffery Plunkett

MO3. Late mTOR inhibition suppresses established epilepsy in the NS-Pten KO mouse model of cortical dysplasia

Angus Wilfong

MO4. MTOR signaling in oligodendrocyte differentiation during developmental myelination and remyelination

Teresa Wood

MO5. Behavioural assessment of mice with mosaic expression of ATRX in the CNS

Renee Tamming

MO6. Borders of primary sensory areas reflect natural variation in parenting received, and exogenous exposure to oxytocin, in prairie voles

Karen Bales

MO7. A specialized pro-resolution mediator approach to cognitive performance in the Ts65Dn mouse model of down syndrome

Eric Hamlett

MO8. Early maternal deprivation in the rat alters cortical structure and function in adulthood

Sarine Janetsian

MO9. Chemogenetic inactivation of the rat medial prefrontal cortex attenuates methamphetamine- and mating-induced neuronal activity, but not behavior

Lindsey Bishop

MO10. A novel mouse model of resistance to drugs to treat alcohol binge drinking

John Crabbe

MO11. Presynaptic inhibition of identified excitatory inputs to dorsomedial striatum

William Birdsong

MO12. Corticotropin-releasing factor (CRF) impairs prefrontal cortex-dependent cognitive processes

Sofiya Hupalo

MO13. Alterations in hypoglossal neuron activity in a mouse model of DiGeorge/22q11.2 Deletion Syndrome

David Mendelowitz

MO14. To study the effect of electroconvulsive therapy on visuospatial memory in rats

Navya Lakkappa

MO15. Why biperiden is a better model for memory impairments in dementia than scopolamine

Arjan Blokland

MO16. Postnatal Arc/Arg3.1 ablation causes profound impairments in long-term memory consolidation

Ora Ohana

MO17. Nrf2-ARE activator carnosic acid decreases mitochondrial dysfunction, oxidative damage and neuronal cytoskeletal degradation following traumatic brain injury in mice

Edward Hall

MO18. Diminished amygdala activation and behavioral threat response following traumatic brain injury

Christopher Palmer

MO19. Cerebrospinal fluid from HD subjects seeds aggregation of mutant huntingtin

Steven Potkin

MO20. Real-time striatal measurements of oxidative stress and dopamine in the dyskinetic rat during chronic L-Dopa treatment for Parkinson's disease

Leslie Sombers

MO21. The circadian variation of sleep and alertness is advanced in women

Diane Boivin

MO22. Human brain collection core: a valuable free resource to study brain disorders

Jonathan Sirovatka

MO23. The changing face of acute neurology: experience from two decades of the Cambridge Neurology Emergency Clinic

Sybil Stacpoole

MO24. An immersive 3D brain simulation that future health professionals explore via the Oculus Rift™ virtual reality headset

Bradley Tanner

MO25. Gene X smoking interactions in the ventromedial PFC: alpha 5 nicotinic cholinergic receptor gene variation and smoking effects on adolescent grey matter

Hugh Garavan

POSTER SESSION 3

TUESDAY, JANUARY 27, 2015 • PEAK 1–4

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 at their posters from 3:30 pm–4:30 pm and returning for the special session from 6:30 pm–8:30 pm.

Posters may be set up after 8:00 am on Tuesday and must be removed by 10:00 pm on Tuesday.

TU1. Throughout life, multisensory connections of primary sensory cortices develop within five phases

Julia Henschke

TU2. Characterization of neuregulin 3 subclass expression across cortical development, in affective disorders, and genetic regulation by risk variation

Clare Paterson

TU3. Microglia establish region specific phenotypes in the basal ganglia and exhibit variable responses to normal aging

Lindsay De Biase

TU4. VTA dopamine activation regulates neuroplasticity and sensitized psychostimulant reward following sexual experience in male rats

Lauren Beloate

TU5. Estrous cycle modulates inhibition of dorsal vagal motor neurons

Carie Boychuk

TU6. GIRK channels in VTA DA neurons regulate sensitivity to cocaine-related behaviors

Nora McCall

TU7. The lateral habenula receives an unexpected glutamatergic input from the lateral preoptic area

David Barker

TU8. Ca2+-dependent and -independent inhibition of GABA release onto POMC neurons by presynaptic inhibitory GPCRs

Reagan Pennock

TU9. Optogenetic assessment of dynamic input integration in the ventral striatum

Julie Brooks

TU10. Reversal of morphine-induced cell-type specific synaptic plasticity in the nucleus accumbens shell blocks reinstatement

Matthew Hearing

TU11. Methylphenidate enhances early sensory signal processing in the rat visual thalamus through noradrenergic signaling

Rachel Navarra

TU12. β-Arrestin D2-receptor biased ligand, UNC9994, increases the excitability of prefrontal fast-spiking interneurons

Steven Gee

TU13. DAPK1 functions in NMDA receptor dependent synaptic long-term depression

Dayton Goodell

TU14. NMDA efficiently evokes dendritic release of neuropeptides: a quantitative real time assessment

Soledad Pitra

TU15. Observing and controlling projection-defined medial prefrontal cortex subpopulations in reward and aversion

Caitlin Vander Weele

TU16. Synthetic activation of infralimbic cortex inhibits cocaine seeking via efferents to the nucleus accumbens shell

Jamie Peters

TU17. Regulation of goal-directed action selection by cocaine, MDMA, and orbitofrontal BDNF-TrkB

Elizabeth Pitts

TU18. Subanesthetic ketamine reduces the incentive-motivational value of reward cues in sign-tracking individuals: implications for addiction treatment

Jonathan Morrow

TU19. An evaluative conditioning approach to alter behavioral and neuronal responses to visual food cues

Kristina Legget

TU20. The role of Akt3 in neurocognitive dysfunction: linking GWAS and function in schizophrenia

Kristy Howell

TU21. Movement modulates phase-locking between neuronal discharge in human STN and cortical oscillations

Witold Lipski

TU22. Preventing calcium dysregulation and synaptic loss in Huntington's disease: an evaluation of sigma-1 receptor agonists in corticostriatal co-cultures from YAC128 mice

Daniel Ryskamp

TU23. Alzheimer-associated Aβ oligomers impact the central nervous system to induce peripheral metabolic deregulation

Natalia Silva

TU24. Differential mechanisms of action of monoacylglycerol lipase inhibition on blood-brain-barrier integrity following inflammatory or ischemic insults

Justin Piro

TU25. Effects of controlled cortical impact brain injury on cell loss and neurogenesis in the mouse dentate gyrus

Jeffery Boychuk

POSTER SESSION 4

Wednesday, January 28 • Peak 1–4

Posters will be available for viewing from 3:30 pm–10:00 pm on Wednesday. Presenters will be at their posters from 3:30 pm–4:30 pm.

Posters may be set up after 8:00 am on Wednesday and must be removed by 10:00 pm on Wednesday.

WE1. **Neuronal Pentraxin 1 is essential for neuronal activity dependent mitochondrial dynamics**

Ramon Trullas

WE2. **Sirtuin3 regulates mitochondrial fusion by optic atrophy 1 deacetylation**

Kimberly Kleinschmidt

WE3. **Regulation of the actin interacting protein drebrin by mutations in HspB1**

David Fink

WE5. **Knocking down targets in the CNS: antisense oligonucleotide distribution and pharmacodynamics in the rat CNS**

Fredrik Kamme

WE6. **The desensitization of midbrain dopamine D2 receptors**

Brooks Robinson

WE7. **Diametric changes in cue-elicited phasic dopamine release mediate drug-taking and drug-seeking**

Lauren Burgeno

WE8. **C-Fos expression in the striatal circuitry following reinstatement in differentially reared rats**

Margaret Gill

WE10. **Extrasynaptic NMDA receptor signaling under astrocyte control contributes to central neuropeptide regulation of hypothalamic neuronal activity and sympathetic control**

Javier Stern

WE11. **Contingent exposure to a high-fat diet alters reward circuitry and increases "craving-like" behaviors over a period of abstinence**

Paige Dingess

WE12. **The effects of AgRP neuron stimulation on food intake during appetite suppression**

Alison Smith

WE13. **The presence or absence of QTc prolongation in buprenorphine-naloxone among youth with opioid dependence**

George Woody

WE14. Neuropathic pain alters reward and affect via kappa opioid receptor (KOR) upregulation

Shiwei Liu

WE15. Mechanisms of tolerance to the antinociceptive effects of Δ9-THC in the formalin test of inflammatory pain

Daniel Morgan

WE16. Novel anti-inflammatory TNF-alpha synthesis inhibitors derived from the backbone of thalidomide

Nigel Greig

WE17. Whole-brain mapping of neuronal activity in the learned helplessness model of depression

Yongsoo Kim

WE18. AgRP neurons disrupt sleep/wake architecture and cause deficits in rapid eye movement (REM) sleep

Kelsey Loy

WE19. Sleep disorder impact on efficacy of prolonged exposure therapy for PTSD

Christopher Reist

WE20. Salivary biomarkers for Huntington's disease

Elizabeth Thomas

WE21. A novel LRRK2 radioligand demonstrates increased active LRRK2 in sporadic Parkinson's disease brain

Warren Hirst

WE22. Anterior cingulate cortex and cognitive aging: mechanisms

Jose Pardo

WE23. Acute effects of kainic acid induced early life seizures

Heather Caballes

WE24. Assessment of skiing-related concussion and mild traumatic brain injury using multivariate signatures from combined portable telemetric EEG and cognitive testing data

David Devilbiss

WE25. Validity of the chronic social defeat stress model on sex differences in glutamate homeostasis

Akiko Shimamoto

Panel Session Abstracts

SUNDAY, JANUARY 24, 2016

Sunday Early Evening Panel Sessions

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 5

1. The biology of schizophrenia in the 21st century: moving from genetic risk to mechanisms of action

Chair: Thomas Hyde
Presenters: Elizabeth Tunbridge, Amanda Law, Andrew Jaffe, Nick Brandon

Genome-wide association studies have identified over 100 polymorphisms (SNPs) conferring risk for schizophrenia. Deciphering the molecular mechanisms by which these SNPs increase risk for illness is a daunting task. However, unraveling the mechanism of risk is a critical step in identifying new targets for therapy. Elizabeth Tunbridge (Oxford) will discuss how multimodal neuroimaging might be used to shed light on the neural circuits mediating disease risk. She will focus on ZNF804A, a gene robustly associated with increased risk of psychosis, and expressed in the developing brain, but whose neurobiological impact is obscure. Amanda Law (U of Colorado, Denver, School of Medicine) will present novel data charting the pre-and postnatal developmental trajectory of AKT1, AKT2 and AKT3 expression in human hippocampus and prefrontal cortex, and in patients with schizophrenia (SZ). She will discuss how schizophrenia genome-wide significant variants in the AKT3 gene may impact splicing of the AKT3/SDCCAG8 genic region in brain. Andrew Jaffe (Lieber Institute) has identified widespread changes in DNA methylation (DNAm) levels at the transition from prenatal to postnatal life that manifest in the transcriptome, correlate strongly with a shifting cellular landscape, and overlap regions of genetic risk for schizophrenia. He also identified a subset of sites that differ between patients and controls, enriched for genes related to development and differentiation, strongly correlate with the changes related to the prenatal-postnatal transition, and were enriched for GWAS risk loci. His findings support an epigenetic component to the developmental origins of schizophrenia. Finally, Nick Brandon (AstraZeneca) will discuss the interrogation of the PGC2 GWAS hot-spot at 10q24.32. Specifically schizophrenia-associated SNPs in this region are in high LD with a VNTR in the first exon of a gene known as arsenic methyltransferase (AS3MT). The risk allele leads to increased expression of a shorter isoform of AS3MT

known as AS3MTd2d3. Understanding the function of this variant in the context of schizophrenia will be described. This session will provide a window into the next phase of research in schizophrenia and related psychotic disorders, decoding the mechanism of action of population-derived genetic risk factors.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 6–8

2. Axonal regeneration in CNS repair: an evolutionary perspective

Chair: Martin Oudega
Presenters: Andrew Chisholm, Michael Shifman, Jeffery Plunkett, James Fawcett

Regeneration of axons is important for recovery of function after CNS injury. The degree of axon regeneration in damaged nervous tissue is determined by the interplay between intrinsic, axonal, growth-pathways and extrinsic, environmental, growth-promoting and growth-inhibitory cues. Evolutionarily older organisms are able to regenerate damaged axons and repair the mature CNS while younger organisms are not. Which molecules are involved in the successful axon regeneration in non-mammals and are these conserved? Is axon regeneration in non-mammals successful because growth-inhibitory molecules are absent? And if these molecules are expressed do they have perhaps a different role? Why does the regenerative ability of mammalian neurons diminish with maturity? These and other intriguing questions will be discussed in this panel. Dr. Andrew Chisholm (UCSD, USA) will discuss the growth and guidance of axons during development and after injury in C. elegans. Recent studies showed that some key intrinsic mechanisms in regeneration (e.g. DLK) are highly conserved in worm, fly, and mouse, underscoring the value of our comparative approach. Dr. Michael Shifman (Temple University, USA) will discuss the role of guidance molecules in axonal regeneration in the injured spinal cord in the lamprey. Dr. Jeffery Plunkett (St. Thomas University, USA) will discuss spinal cord repair and the role of CSPGs therein in the zebrafish. Dr. James Fawcett (University of Cambridge, UK) will discuss the question why CNS axons lose their intrinsic regenerative ability as they mature.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 9–10

3. Alzheimer's disease as an oscillopathy of septohippocampal system dysfunction?

Co-chairs: John Lawrence, Sylvain Williams
Presenters: Rory McQuiston, John Huguenard, Andre Fisahn, Philippe Diaz

Alzheimer's disease (AD) has historically been described as a disorder of cognitive impairment attributable to the loss of cholinergic neurons in the basal forebrain and medial septum-diagonal band of Broca (MS-DBB). Brain

rhythms, neuronal oscillations that support cognitive function, require precise coordination and synchronization in interconnected networks across MS-DBB and hippocampus. As this complex synaptic interconnectivity between MS-DBB and hippocampus becomes better resolved, hypotheses relating the loss of connectivity to cognitive impairment are emerging. Drawing on expertise spanning molecular to network levels, we discuss challenges ahead in describing AD as an oscillopathy of circuit dysfunction within and between MS-DBB and hippocampus. Dr. McQuiston will introduce cholinergically-induced hippocampal rhythms, describe known synaptic relationships between MS-DBB cholinergic neurons and their hippocampal targets, survey the cholinergic receptors engaged, discuss consequences of cholinergic fiber loss, and describe beneficial effects of acetylcholinesterase inhibitors. The discussion will then turn to long-distance GABAergic projections between MS-DBB and hippocampus. Dr. Williams will discuss MS-DBB GABAergic circuits projecting to the hippocampus and the potential consequences of their loss or dysfunction in memory and in rhythmogenesis. Dr. Lawrence will describe synaptic relationships between MS-DBB GABAergic neurons and hippocampal targets and the complex interplay between cholinergic and GABAergic modulation. Dr. Huguenard will discuss the hippocamposeptal projection to the MS-DBB and the potential consequences of cellular loss in rhythmogenesis and in cognitive function. Dr. Andre Fisahn will discuss A-beta toxicity, its effects on oscillations, potential underlying mechanisms, and future therapeutic strategies. Finally, Dr. Diaz will discuss novel drug targets that may prevent the loss of cholinergic and/or GABAergic connectivity in AD.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 11–12

4. Synaptic regulation of striatal circuits

Chair: Christopher Ford
Presenters: David Kupferschmidt, Hitoshi Morikawa, Christopher Ford, Tianyi Mao

The striatum forms the major input to the basal ganglia and is critical for integrating action and motivation. Exhibiting a heterogeneous mix of cell types, the striatum is a convergence point for excitatory inputs that arise from the cortex and thalamus as well as modulatory inputs such as dopamine from midbrain neurons and acetylcholine from local interneurons. In this panel, speakers will discuss recent work examining the synaptic mechanisms and plasticity by which these inputs regulate the activity of striatal circuits. First, David Kupferschmidt (NIAAA, NIH) will discuss work using in vivo fiber photometry of corticostriatal inputs during motor skill learning to determine whether changes in the activity of discrete projections represent alterations in circuit recruitment or modulation of presynaptic inputs in the striatum.

Hitoshi Morikawa (University of Texas, Austin) will present data about how phasic dopamine transients differentially regulate calcium signals in two subpopulations of medium spiny neurons (MSNs) in the nucleus accumbens and dopamine-timing-dependence of this regulation. Christopher Ford (Case Western) will talk about how the firing patterns of cholinergic interneurons are temporally encoded by muscarinic M4-receptors within MSNs as spontaneous transient events and the connectivity that exists between cholinergic interneurons and MSNs at muscarinic synapses. Lastly, Tianyi Mao (Vollum Institute) will talk about the sub-region dependent plasticity of thalamostriatal pathway and how opiates differentially modulate this plasticity.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 14

5. Microglia and their diverse roles in neurodegenerative, psychiatric and mood disorders

Chair: Gretchen Snyder

Presenters: Staci Bilbo, Matthew LaVoie, Elizabeth Bradshaw, Miles Herkenham

Immune cells, including microglia, play an active and fundamental role in the development and maintenance of normal central nervous system function. This panel will explore the evidence for microglial involvement in normal brain development and in diverse brain disorders, including neurodegenerative and psychiatric diseases and mood disturbances. Staci Bilbo (Duke) will describe how marked sex differences in the prevalence and age of onset of psychiatric disorders are paralleled by striking sex differences in the pattern and gene expression of microglial colonization of the developing rodent brain. The influence of sex differences in immune system development will be discussed as a potential influence on neural development and susceptibility to psychiatric disease. Matt LaVoie (Harvard) will describe the emerging role for microglial dysfunction in adult onset neurodegenerative diseases, focusing on the impact of pathogenic mutations in LRRK2 on microglial responses and alpha-synuclein proteostasis. Elizabeth Bradshaw (Harvard) will discuss the involvement of innate immune cells in Alzheimer's disease and the genetic associations that have thrust them into the spotlight for AD susceptibility. Miles Herkenham (NIMH) will show that microglia derived from mice that were either susceptible to or resilient against chronic social defeat display different activity profiles when studied ex vivo. Microglia from "susceptible" mice are relatively more phagocytic, secrete molecules that break down the blood-brain barrier, and hinder new neuron growth in hippocampal neurospheres, compared to cells from "resilient" mice, suggesting a role for microglia in the development of depressive behaviors in chronic stress. Together, the panelists will highlight the diverse influences of brain immune status on early brain development and brain disease.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 15-16

6. Opiate-induced plasticity in mesocorticolimbic circuits

Chair: Matthew Hearing
Presenters: Abigail Polter, Jose Moron-Concepcion, Elena Chartoff, Matthew Hearing

Opioid-based drugs remain clinical mainstays for pain management despite the increasing diversion of these readily available compounds for non-therapeutic use. While reducing vulnerability to relapse affords an opportunity for pharmacotherapeutic intervention, a distinct lack of knowledge of the cellular plasticity underlying opioid-induced changes in behavior impedes our ability to effectively confront opiate addiction. Presenting mostly unpublished data, this panel examines synaptic plasticity in cortico-limbic brain regions produced by morphine and stress, at the cellular, molecular and structural level, and how they relate to negative affective states, reward conditioning, and reward-seeking. Abigail Polter will report on divergent mechanisms underlying stress- versus opiate-induced disruption of synaptic strength at ventral tegmental area dopamine neuron GABAergic synapses, with a focus on modality-specific changes in opioid receptor function. Jose Moron-Concepcion will discuss the context-specific nature of morphine-associated alterations in hippocampal CA1 pyramidal cell dendritic spine morphology, alterations in RhoA kinase and NMDAR expression, and the involvement of Rho kinase (ROCK) in the development of morphine place preference. Elena Chartoff will discuss withdrawal-dependent changes in phosphorylation and trafficking of GluA1 AMPAR subunit in the nucleus accumbens (NAc), and how selective antagonism of NAc AMPAR signaling blocks withdrawal-induced decreases in sensitivity to brain stimulation reward as well as the development of conditioned place aversion. Matthew Hearing will present data showing that repeated morphine promotes bidirectional changes in synaptic strength, transmitter release probability, and GluA2-lacking AMPAR subunit expression in NAc shell medium spiny neurons containing the dopamine D1 vs D2 receptor, and that optogenetic and pharmacological reversal of this plasticity blocks reinstatement of morphine reward-seeking.

PANEL • SUNDAY, 4:30 PM–6:30 PM • PEAK 17

7. Adolescent binge alcohol exposure and decision-making brain circuitry

Chair: Charlotte Boettiger
Presenters: Fulton Crews, Justin Gass, Jeremy Clark, Charlotte Boettiger

Binge drinking peaks in adolescence, and the maturing adolescent brain is uniquely sensitive to alcohol insult, producing persistent neurological and behavioral effects that can be detected in adulthood. Moreover, a growing

literature indicates that brain circuits essential for advantageous decision-making, including the prefrontal cortex (PFC) are disrupted by adolescent alcohol exposure. Abnormal functioning in PFC circuitry may contribute to the elevated risk for substance use disorders associated with adolescent alcohol exposure. The central goal of this panel is to bring together diverse researchers in the alcohol research field using a wide variety of techniques to probe the unique sensitivity of decision-making brain circuitry in the adolescent brain to binge alcohol exposure, with a strong translational emphasis from rodents to human studies. First, Fulton Crews (University of North Carolina, Chapel Hill, USA) will describe experiments finding that adolescent intermittent alcohol exposure results in neuroimmune gene induction, altered cholinergic and serotonergic neurons, and altered PFC responses to alcohol and reversal learning tasks in adulthood. Then, Justin Gass (Medical University of South Carolina, USA) will discuss the role of mGluR5 in deficits in PFC-dependent behaviors in adulthood, consequent to adolescent intermittent alcohol exposure. Jeremy Clark (University of Washington, USA) will present data dissecting the role of mesolimbic dopamine circuitry in maladaptive decision-making of adult rats following adolescent alcohol intake. Finally, Charlotte Boettiger (University of North Carolina, Chapel Hill, USA) will present fMRI data showing that, in humans, adolescent binge alcohol exposure is associated with hyper-connectivity between mesolimbic dopamine and ventrolateral PFC regions. Together these presentations will relate PFC function to decision-making and how this is altered by adolescent binge drinking.

Sunday Evening Panel Sessions

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 5

8. Grub and smokes: common downward slope towards food and drug addiction

Co-chairs: Laura O'Dell, Katherine Serafine
Presenters: Laura O'Dell, Travis Brown, Katherine Serafine, Carrie Ferrario

Peptides regulating feeding and appetite are also positioned to modulate the central processes that modulate the rewarding effects of drugs of abuse. Thus, overlapping substrates sub-serving drug reward and feeding may be under control of similar and/or convergent neural processes. This panel will explore the mechanisms by which changes in feeding regulatory systems alter neuronal signaling in reward pathways in a manner that confer enhanced long-term vulnerability to drug abuse. The panel includes researchers working at various levels of analysis to provide a broad discussion of the role of central neurotransmitter systems and reward-related brain circuitry in the development of food addiction and overeating behavior. First, Dr. Laura O'Dell (University

of Texas El Paso) will provide introductory comments and a discussion of brain systems believed to modulate insulin regulation of enhanced nicotine intake in rodent models of diabetes. Second, Dr. Carrie Ferrario (University of Michigan) will discuss the role of cues that elicit "craving" for palatable foods and the underlying mechanisms that confer enhanced long-term cue-triggered motivation in obesity. Third, Dr. Travis Brown (University of Wyoming) will discuss time-dependent increases in high-fat diet-induced reward seeking in rodent models and the underlying changes in cortical spine density that are believed to confer enhanced vulnerability to obesity and drug addiction. Fourth, Dr. Katherine Serafine (University of Texas El Paso) will present findings on the long-term behavioral effects of eating a high-fat diet on sensitivity to drugs acting on dopamine systems. Lastly, the panelists will provide an overview of the implications of identifying neurobiological risk factors that lead to compulsive eating and drug use.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 6–8

9. Biomarkers of blood brain barrier disruption in the injured brain

Chair: Richard Leigh
Presenters: Richard Leigh, Lawrence Latour, Alexis Simpkins

The interface between the central nervous system (CNS) and the peripheral circulation is highly regulated by the neurovascular unit (NVU). The NVU maintains this blood-brain barrier (BBB) through complex interactions between the endothelium, neurons, astrocytes, pericytes and the extracellular matrix. BBB disruption has been recognized as a marker for a variety of neurologic diseases. New biomarkers using magnetic resonance imaging (MRI) to detect BBB disruption in human brain injury have provided insight into possible mechanisms for a variety of neuropathologic states. In this panel, several novel methods for detecting BBB disruption with MRI will be described. Using these methods, new findings of BBB disruption in cerebral ischemia and traumatic brain injury will be presented. By combining these methods with serum markers of CNS injury, potential blood biomarkers for diagnosis, prognosis and treatment of disease will be reviewed. With his first presentation entitled "Disruption in Acute Cerebral Ischemia," Richard Leigh will begin the panel. Animal models of cerebral ischemia have classically demonstrated a bi-phasic opening of the BBB with an initial early, potentially reversible, phase and a later inflammatory phase. In human acute ischemic stroke (AIS), the presence of BBB disruption has been linked to hemorrhagic transformation and poor outcome, particularly when patients are treated with tissue plasminogen activator (tPA). The National Institutes of Health (NIH) intramural stroke branch has been collecting serial MRI scans on patients suffering from AIS as part of a natural history study for more than a decade. This has led to the

identification of several methods for detecting BBB disruption that are much more sensitive and quantitative than classic post-contrast T1 imaging. Using these methods, a dose-dependence between BBB disruption and subsequent tPA-associated intracranial hemorrhage (ICH) has been identified (1). In this presentation, the relationship between tissue injury, BBB disruption, reperfusion and treatment effects of patients suffering from AIS will be explored using a novel marker of BBB disruption. With a second presentation entitled "BBB Disruption in Vascular Cognitive Impairment," Dr. Leigh will continue this panel. With age, the human brain develops T2 hyperintensities in the deep white matter on MRI. The development of these white matter hyperintensities (WMH) is accelerated in individuals with vascular risk factors. WMH have been associated with vascular cognitive impairment (VCI), Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA) and often precede the development of dementia. BBB disruption has been detected in patients with WMH, typically using dynamic contrast enhanced (DCE) MRI. However DCE MRI requires a lengthy acquisition time and is not a standard clinical scan. Newer methods of BBB measurement have revealed information about BBB disruption associated with WMD from the NIH natural history study cohort by retrospectively post-processing perfusion weighted imaging. In this presentation, changing patterns of WMH associated BBB disruption will be demonstrated in relation to risk factors, demographics, progression of disease and response to therapy. Dr. Latour will proceed with a presentation entitled "Disruption in Traumatic Brain Injury (TBI)." Damage to the brain, vasculature, and meninges occur as a direct result of mechanical forces during head trauma. Inelastic deformation of the brain following impact injures neurons and glia, while shearing results in disruption of axons. With increasing severity there is vessel rupture with hemorrhage into the parenchyma and in the extra-axial spaces. Autoregulation is lost, and both ischemic and coagulation cascades can be triggered. The integrity of the BBB can be compromised exposing the brain to molecules from the serum. Edema develops secondary to these events with a concomitant inflammatory response. Inflammation and cell death continues for days to weeks, and the endogenous process of neovascularization forms leaky vessels. Most of what is known about BBB disruption in TBI comes from data on pre-clinical models or severe injury in humans. There is growing evidence that BBB disruption occurs following mild TBI, or concussion. This may represent the vast majority of patients who sustain a head injury. In this presentation, recent data on the relevance of BBB disruption to mild TBI, imaging of brain injury and BBB integrity, and the potential deleterious sequelae will be explored. Dr. Simpkins will conclude the panel with a presentation entitled "Blood Biomarkers for BBB Disruption." Quantifying BBB in the clinical setting by molecular means has been challenging. Direct measurements of blood brain barrier damage via invasive techniques such as lumbar puncture is not feasible in stroke or TBI patients given the need for rapid clinical assessment and medical management. A more practical alternative

has been whole blood analysis. Several blood biomarkers for BBB have been identified, such as SB100, matrix metalloproteinase 9, neuron-specific enolase, glial fibrillary-associated protein, and brain natriuretic peptide. However, their clinical use has been limited given the low levels of detection in the whole blood and non-specificity of these biomarkers. Diagnostic and prognostic yield is increased when multiple markers are used as a panel, but the clinical utility has still been somewhat limited. Genomic analysis of blood has identified mRNA biomarkers predictive of hemorrhagic transformation in ischemic stroke using microarray detection. A benefit of RNA analysis is the ability to detect the changes in gene expression triggered by injury before the protein is expressed. More recently, newer second generation whole blood genomic analysis such as RNA sequencing has become available and provides even more sensitive detection of changes in gene expression. Currently at the NIH, a clinical natural history study is being conducted, which combines patterns of micro RNA and messenger RNA profiles from whole blood samples collected serially at multiple time points during the acute presentation of ischemic stroke with simultaneously acquired multi-modal MRI. Using this approach, we aim to identify and validate more specific and predictive models of BBB damage using non-invasive methods. In this presentation a review of the known literature will be followed by a discussion of the methodology, preliminary findings and future directions for the study of BBB blood biomarkers.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 9–10

10. Basic and translational findings on ionic mechanisms of peripheral pain sensitization

Chair: Robert Gereau

Presenters: Theodore Cummins, Durga Mohaptra, Robert Gereau

Chronic pain is a major source of human suffering, and has been imposing a steady and significant economic burden on society. Currently available therapeutics are only partially effective and have multiple side effects, resulting in under-management of chronic pain. Although identification of basic neurobiological mechanisms and in vivo testing of such mechanistic findings in rodent models of pain have been widely pursued, many potential therapeutics based on these findings have failed in clinical trials. This symposium will provide a combination of basic mechanistic understanding of sensory neuron excitation, involving excitatory ion channels in both rodent and human sensory neurons, and development of clinically relevant rodent models of chronic pain conditions. Dr. Gereau (Chair, Washington University) will provide a brief introduction on the ionic mechanisms of sensory neuron excitation in peripheral pain transmission, and will moderate discussions. Dr. Cummins (Indiana University) will present research findings on specific voltage-gated

Na+ channels in sensory neurons, their excitation and specific functional modifications under pain conditions, including modifications caused by mutant Na+ channels identified in human pain conditions. Dr. Mohapatra (Washington University) will present recent findings on the development of clinically relevant mouse models of chronic pain in human metastatic bone cancers for investigating ionic mechanisms of peripheral sensitization. Finally, Dr. Gereau will present recent findings on translational pain research, focusing on characterization of ionic mechanisms of peripheral pain sensitization in human sensory neurons. Recent developments on the utilization of optogenetic approaches in human sensory neurons for propelling fast translation of basic science to therapeutic developments for chronic pain conditions in humans will also be discussed.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 11–12

11. Neuronal injury in the immature brain after seizures and hypoxia-ischemia

Co-chairs: Ed Dudek, Wendy Macklin
Presenters: Wendy Macklin, Claude Wasterlain, Paco Herson, Ed Dudek

Hypoxia-ischemia (HI), with or without seizures, is known to cause injury to the immature brain, and these types of injuries can be devastating and have life-long consequences. Similarly, early-life seizures, with or without hypoxic-ischemic injury, are risk factors for several negative neurological outcomes, such as cerebral palsy and epilepsy. The effects of HI and seizures on the immature brain, however, depend on numerous clinical and experimental variables, such as age-of-occurrence and brain temperature. In spite of the enormous potential value of translational research in this area, progress has been difficult and results have been controversial. The speakers in this session will report recent findings from their laboratories and will discuss how issues such as age at the time of the insult and ambient temperature can greatly alter the effects of HI and seizures. Claude Wasterlain will provide an initial overview of the clinical problems and the relevant issues; he will then discuss the effect of brain temperature on the level of neuronal injury after induction of repetitive seizures in the neonatal brain (postnatal day 7, PND7). Wendy Macklin and Paco Herson will describe results from their studies using the middle cerebral artery occlusion model at PND25; Paco Herson will focus on recovery of electrophysiological alterations, while Wendy Macklin will describe the remarkable preservation of vasculature and myelinating oligodendrocytes, despite dramatic loss of striatal neurons. Ed Dudek will discuss the impact of HI versus hypoxia-induced seizures alone at PND7 on neuronal survival and possible epilepsy. Together, these data sets will lead to a lively discussion that will focus on how HI and seizures alter the neonatal brain.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 14

12. Cell adhesion molecules in synapse function and disease

Chair: Ana Carneiro
Presenters: Ana Carneiro, Gabrielle Rudenko, Yu Yamaguchi, Silvia De Rubeis

Multiple cell adhesion receptor genes have been associated with Autism Spectrum Disorder (ASD), including neurexins and neuroligins, integrins, and cadherins. Cell adhesion receptors are plasma membrane glycoproteins that mediate cell-extracellular matrix and cell-cell interactions. Besides having an adhesive function, they orchestrate complex protein interaction networks in the synaptic cleft, providing key points of regulation during synapse development and stabilization. In this panel, we will discuss the function of cell adhesion molecules in multiple levels of biological organization, from the single molecule level to the whole organism. The panel chair, Dr. Ana Carneiro, will give an introduction of the cell adhesion receptor family, and how they promote cell polarization and motility, contextualizing these biological phenomena within cellular phenotypes observed in ASD patients. Dr. Gabrielle Rudenko will discuss the molecular structure of the neurexin 1a-neuroligin complex, and the mechanisms by which this complex organizes synaptic protein interaction networks. The consequences of loss of integrin-binding heparan sulfate proteoglycans (HSPGs) will be discussed by Dr. Yu Yamaguchi. The loss of HSPGs leads to a reduction in the level of synaptically localized glutamate receptors, which are paralleled by multiple behavioral deficits in core phenotypes linked to symptoms of ASD. Finally, Dr. Silvia de Rubeis will provide an update on the contribution of cell adhesion genes to the complex genetic basis of ASDs. Her group has recently finished the analyses on 3,871 autism cases and 9,937 ancestry-matched or parental controls revealing an enrichment of genes targeted by RNA-binding proteins, and genes encoding synaptic components, including adhesion molecules. In closing, Dr. Ana Carneiro will discuss how the analyses of genetic interactions can inform on the molecular and cellular underpinnings of ASD.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 15–16

13. Targeting phosphodiesterases for rescuing cognition in Alzheimer's diseases: from mice to humans

Chair: Hanting Zhang
Presenters: Jos Prickaerts, Ying Xu, Mark Gurney, Lawrence Wennogle

Cognitive deficits are one of the characteristic symptoms of degenerative diseases, in particular Alzheimer's disease (AD). Phosphodiseterases (PDEs), a superfamily of 11 enzymes (PDE1-11) that hydrolyzes cyclic

nucleotides (cAMP and cGMP), have been implicated in cognition in AD and other degenerative diseases. However, their roles in cognition remain largely unknown. The speakers in this panel consisting of both junior and senior neuroscientists, who are well recognized in this area, will present the latest advances in studies of PDEs in degenerative diseases. Specifically, Jos Prickaerts (Maastricht U, The Netherlands) will give an overview of recent findings of inhibition of PDE2, PDE4, or PDE5 on cognition and its implication in treatment of AD. The focus will be on memory processes and its translation of animals to humans, with treatment of PDE4 or PDE5 inhibitors. Ying Xu (SUNY Buffalo) will provide solid evidence for the role of PDE2 in mediating memory in AD. In the triple transgenic mouse model of AD (3xTg-AD), lentiviral miRNA-mediated PDE2A knockdown mimicked the ability of PDE2A inhibition to reverse memory deficits, neuronal atrophy, apoptotic and inflammatory responses, and low levels of cAMP/cGMP in the hippocampus. Mark Gurney (Tetra Discovery Partners) will focus on PDE4D, one of the four PDE4 isoforms, and discuss the design of subtype, negative allosteric modulators (PDE4D-NAMs), which have potent cognitive benefit by augmenting signaling through the cAMP/PKA/CREB pathway for memory consolidation, with limited side effects. Thus, PDE4 isoforms provide rich opportunities for the development of mechanistically novel drugs to treat cognitive deficits in AD. Lawrence Wennogle (Intra-Cellular Therapies) will demonstrate the potent effects of PDE1 inhibitors on cognition in degenerative disorders, including AD and Parkinson's disease. He will highlight the safety and tolerance of the novel PDE1 inhibitor ITI-214 in the four human clinical Phase 1 studies completed recently. Evidence also will be summarized to support the cognitive enhancing potential of PDE1 inhibitors, a role in inflammatory conditions and fibrosis.

PANEL • SUNDAY, 7:00 PM–8:30 PM • PEAK 17

14. What is the difference between a drug-taking brain and a drug-addicted brain? Insights from animal studies

Chair: Anna Samaha
Presenters: Leandro Vendruscolo, Benjamin Zimmer, Anna Samaha

In spite of much research, medications for addiction are lacking. Part of the reason comes down to our animal models. Preclinical tests are often conducted in animals that take drugs, but that do not necessarily show addiction-like traits. The brain changes seen in these animals could be causally linked to addiction, but they could also result from simply taking drugs. Here, we present work that is honing in on a fundamental question in addiction; what is the difference between a drug-taking brain and a drug-addicted brain? The answers are helping to move the addictions field forward. What is the role of stress in compulsive alcohol drinking? Leandro Vendruscolo (NIH/NIDA, US) will speak about the

critical influence of glucocorticoid receptors (GR). Rats were made dependent on alcohol by being exposed to its vapour. Compared to nondependent rats, these rats drank more, worked harder for alcohol, and drank in spite of punishment. Studying these two groups also shows that GR signalling mediates compulsive, but not moderate alcohol drinking. What pattern of drug use pushes the addiction process forward most effectively? Benjamin Zimmer (Medical University of South Carolina, US) will present surprising answers to this question. His work shows that multiple fast-rising "spikes" in cocaine levels produce greater increases in the motivation to take cocaine than continuously high drug levels. Thus, when it comes to producing an addiction phenotype, how often brain levels of drug rise and fall could be more important than how much drug is taken. Can the speed of drug delivery to the brain predict addiction? Anna Samaha (Université de Montréal, Canada) presents data showing that even when cumulative cocaine intake is the same, rats taking rapid injections of cocaine later show excessive motivation to obtain the drug, but rats taking slower injections of the drug maintain controlled drug use. Comparing these two groups also reveals a causal role for glutamate mGlu2/3 receptors in regulating pathological cocaine use.

MONDAY, JANUARY 25, 2016

Monday Morning Panel Seesions

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 5

15. New possibilities with multimodal brain imaging

Chair: Gitte Knudsen
Presenters: Gitte Knudsen, Christin Sander, Alexandre Franco, Pierre LeVan

The number of neuroimaging techniques is rapidly expanding and currently include, e.g., electroencephalography (EEG), magnetoencephalography (MEG), computer tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). When it comes to sensitivity and specificity, spatial and temporal resolution, each modality has its own advantages and disadvantages. The use of different imaging modalities is advantageous since they supply complementary information about the brain. However, traditionally researchers have clustered around a certain imaging modality and have not gained the benefit of combining technologies. Moreover, the fusion of different modalities is not straightforward and combining images requires advanced image processing techniques. With the recent introduction of combined PET-MRI and EEG-MRI scanners that allow for simultaneous data acquisitions, it has become possible to harvest some of the benefits of

combining these two modalities. So far, however, the number of sites with combined PET-MRI and EEG-MRI scanners is limited. Gitte Knudsen will present the Cimbi database that includes data from over a 1000 subjects (healthy controls and patients) that include PET and structural and functional MRI data. She will also report on recent results showing the relationship between the serotonin (5-HT) system and intrinsic functional connectivity, as measured with resting state fMRI. Christin Sander will discuss how combined, simultaneous PET-MRI can be used in for assessment of pharmaco-dynamic effects within the dopaminergic and the opiod system. Alexandre Rosa Franco will report on the use of joint independent component analysis for combing PET images (microglia activation maker—11C-(R)-PK11195 radioligand) with intrinsic functional connectivity data on patients with multiple sclerosis. He will also present the results of using the same technique for combining diffusion tensor imaging and fMRI data. Pierre LeVan will present the latest technological developments in simultaneous EEG and functional MRI acquisitions and present applications of the technique for the investigation of resting-state networks in healthy controls and epilepsy patients.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 6–8

16. Novel mechanism for modulating prefrontal cortical circuitry for the treatment of neuropsychiatric disorders

Chair: Carrie Jones

Presenters: Min Wang, Zhen Yan, Steven Siegel, Michael Grannan

Disruptions in prefrontal cortical circuitry are associated with many neuropsychiatric disorders, including schizophrenia and autism spectrum disorder (ASD). This panel will focus on understanding the molecular influences on normal and impaired prefrontal cortical function with important implications for novel treatment development. Dr. Min Wang, working in the laboratory of Dr. Amy Arnsten (Yale University) will first describe how persistent activation of the dorsolateral prefrontal cortex (dlPFC) in monkeys during working memory tasks depends on activation of N-methyl-d-aspartate glutamate receptors (NMDAR); and that stimulation of nicotinic alpha7 (nic-α7) receptors provides the permissive membrane depolarization required for NMDAR actions in the dlPFC. These data support nic-α7 agonists for the amelioration of the cognitive deficits in schizophrenia. Dr. Steve Siegel (University of Pennsylvania) will discuss how constitutive reductions of the obligatory NMDAR subunit NR1 or selective reduction of NR1 restricted to prefrontal cortical pyramidal neurons in genetically modified mice result in altered patterns of cortical activity, including increased resting high frequency EEG power, as observed in schizophrenia. Next, Michael Grannan from Dr. Carrie Jones' lab (Vanderbilt Center for Neuroscience Drug Discovery) will

discuss how selective positive allosteric modulators of the M4 muscarinic acetylcholine receptor subtype can reverse impairments in prefrontal cortical-mediated physiology, behaviors, and/or cognitive functions observed in NR1 knockdown (KD) mice. Finally, Dr. Zhen Yan (University of Buffalo) will describe how genetic deletion of Shank3, a key scaffolding protein organizing the assembly of postsynaptic proteins at glutamatergic synapses, in mice decreases prefrontal cortical NMDAR synaptic functions and distribution and induces autism-like behavioral and cognitive deficits, which can be restored using actin regulators of cofilin and Rac 1.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 9–10

17. The ventral tegmental area glutamatergic neurons: neurocircuitry, neurotransmission and behavior

Chair: Marisela Morales

Presenters: Seth Taylor, Carlos Mejias-Aponte, Stephen Rayport, Sandra Blaess

The ventral tegmental area (VTA) contains, dopaminergic, GABAergic and glutamatergic neurons. VTA-glutamatergic neurons form local synapses with neighboring neurons, but they are also part of the mesocorticolimbic system. In this panel, we will present recent findings on the complexities of the cellular composition of VTA-glutamatergic neurons, their connectivity and relation to psychiatric disorders and modulation of behavior. First, Dr. Marisela Morales (National Institute on Drug Abuse) will provide introductory remarks. Dr. Seth Taylor (University of California San Diego) will provide an overview on the brain distribution of VTA-glutamatergic-efferents and their comparison with the distribution of VTA-GABA-efferents and VTA-dopamine-efferents. Dr. Carlos Mejias-Aponte (National Institute on Drug Abuse) will present findings on structures that provide monosynaptic inputs to VTA-glutamatergic neurons. Dr. Stephen Rayport (Columbia University) will present electrophysiological evidence on glutamatergic neurotransmission by inputs of dopamine neurons in different brain areas. Dr. Sandra Blaess (University of Bonn) will provide converging evidence leading to the functional characterization of the VTA-glutamatergic inputs by dopamine neurons on prefrontal cortex GABA-interneurons and the role of these inputs in perseverative behavior.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 11–12

18. How and why to study both sexes in basic neuroscience research

Chair: Jill Becker
Presenters: Jill Becker, Rebecca Shansky, Jaclyn Schwarz, Brian Trainor

Despite substantial evidence for sexual dimorphism in brain structure and function, the vast majority of basic science research is conducted in male subjects. The importance of considering both sexes is becoming increasingly recognized by the scientific community. The National Institutes of Health (NIH) are promoting efforts to enhance and stimulate research examining the role of sex in health and disease. Yet it is unclear to many who study rodents how best to economically and efficiently include both males and females in their research programs. This expert panel will lead an interactive discussion of practical approaches to sex differences research, including grant proposal considerations as well as experimental design and procedures. Jill Becker will discuss practical aspects to including both males and females in research designs. For example, when do you need to look at the estrous cycle or manipulate hormones vs. using intact animals? Jackie Schwartz will discuss the importance of looking at sex differences during development as well as practical aspects of how to sex developing mice and rats. Rebecca Shansky will discuss new NIH policies on "Sex as a Biological Variable," which will become implemented immediately after WCBR. Brian Trainor will discuss key sexual dimorphisms in neurotransmitter & neuropeptide systems that should be considered in experimental design. All presenters will use examples from their own research to illustrate why it is important to study both males and females and how both sexes can be incorporated into research programs. The audience is invited to bring their questions for this interactive panel.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 14

19. Alternative signaling pathways in addiction models

Chair: David Stellwagen
Presenters: Alfred Robison, Brad Grueter, David Stellwagen, Catherine Cahill

Drug addiction is a chronic and debilitating disorder that has an immense social and financial impact on individuals and society. Despite our understanding of the primary molecular action of drugs of abuse, the modifications of neural circuitry underlying addiction remains poorly understood. While much work has focused on the primary signaling pathways initiated by drugs of abuse, the lasting changes in reward circuitry likely depend on secondary signaling systems, including epigenetic changes in gene regulation and activation of

microglia and other elements of the innate immune system. The talks will address how these additional signaling pathways shape the changes in reward function during addiction. AJ Robison (Michigan State University) will discuss how chronic cocaine exposure induces deltaFosB in hippocampus via histone demethylation, and this is required for rewarding and contextual associative aspects of cocaine. Brad Grueter (Vanderbilt University) is investigating the interaction between TLR4, synaptic physiology, and drug-reward behavior related to the NAc. He finds that TLR4 knockout mice have an attenuated learning response to cocaine conditioning. Consistent with these behavioral findings, there is decreased synaptic strength on neurons in the NAc and the absence of NMDAR-dependent LTD. David Stellwagen (McGill University) will talk about the role of tumor necrosis factor alpha (TNF) in modulating the response to cocaine, where drug-activated microglia release TNF to suppress both the synaptic and behavioral changes induced by cocaine. Further, reactivation of microglia can suppress already established changes in the behavioral response to drug. Catherine Cahill (UC Irvine) will discuss how opioid dependence initiates microglial activation in limbic structures including the ventral tegmental area, and how microglial-derived BDNF causes changes in dopamine output leading to changes in the reward response to drugs of abuse including morphine and cocaine.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 15–16

20. Using in vivo calcium imaging to understand neural circuit control of dynamic behaviors

Chair: Erin Calipari

Presenters: Da-Ting Lin, Jones Parker, Erin Calipari, Michael Bruchas

Advances in calcium imaging techniques have provided a number of powerful tools to probe how the brain responds to various neurochemical and behavioral stimuli, and the use of these techniques in in vivo models of psychiatric disease are quickly leading to a more in depth understanding of the neural basis of emotional processing, cognition, learning, and motivated behaviors. While a large amount of previous work has focused on electrophysiological recordings as well as optogenetic stimulation of distinct subpopulations of cells, only recently have advances in calcium imaging made it possible to record the activity of genetically distinct and pathway specific subpopulations of neurons in freely-moving animals. This session will discuss a number of calcium imaging approaches, which give unprecedented access to the temporal profile of activity from genetically distinct cell populations orchestrating behavior. Specifically, the speakers will focus on how temporally specific signaling from distinct cell-types control the encoding reward-related behaviors and associated motor outputs and how these signals are dysregualted in psychiatric disease.

First, Dr. Erin Calipari will start with a brief introduction to calcium imaging as a technique and how it has expanded the ability to define the distinct and temporally specific neuronal circuit control of complex and dynamic behaviors. Dr. Da-Ting Lin will present data invalidating the dogma, derived from optogenetic studies, that striatal D1 medium spiny neurons (MSNs) promote behavior while D2 MSNs inhibit it. Dr. Jones Parker will then discuss his work outlining how dysfunction of distinct striatal ensembles underlies the parkinsonian state. Dr. Erin Calipari will present her data outlining how temporally specific D1 and D2 MSN signals encode cue-reward associations for cocaine and how cocaine-induced dysfunction in D1 MSNs underlies relapse. Finally, Dr. Michael Bruchas will present single cell imaging data that identifies the role of hippocampal ensembles in conditioned associations for nicotine reward. This session will showcase the novel technology integrated into discussion of how applications of these technologies are expanding the scope of addressable scientific questions and how these advances can be applied to the study of psychiatric disorders and designing therapeutic interventions.

PANEL • MONDAY, 7:30 AM–9:30 AM • PEAK 17

21. Gut feelings: new links between ghrelin and psychiatric disorders

Chair: William Brimijoin
Presenters: Jeffrey Zigman, Lorenzo Leggio, Ki Goosens, William Brimijoin

Ghrelin is a neuropeptide released into the bloodstream by many organs, especially the stomach. It is secreted continuously, but its levels are influenced by many factors, including hunger and stress. In its active form, ghrelin can cross the blood-brain barrier and bind to GHSR-1a, a G-protein coupled receptor expressed in hypothalamus, hippocampus, amygdala, neocortex, and other brain regions. Increasing evidence shows that, apart from effects on feeding behavior, ghrelin also has a powerful modulatory influence on brain circuits for cognition and emotion, where the sensitivity to this hormone appears to be highly regulated. Emerging studies suggest that dysregulated ghrelin signaling may underlie numerous psychiatric disorders. This panel will consider the newest developments in that rapidly developing area of research. First, Jeffrey Zigman will discuss the role of ghrelin in brain circuits that regulate reward processing. He will also consider how this signaling modulates complex eating disorders and depression, conditions associated with both aberrant reward processing and metabolism. Next, Lorenzo Leggio will consider how ghrelin's impact on reward processing affects craving in alcoholic individuals. Ki Goosens will then explore the role of ghrelin in brain circuits during normal fear learning and pathological fear states, such as post-traumatic stress disorder. Finally, Steve Brimijoin will discuss a role for ghrelin in aggression and anxiety, as well as the

therapeutic potential of long-term modification of ghrelin levels by viral gene transfer. Overall, the panelists will provide new insights into the mechanisms by which changes in ghrelin can lead to psychiatric disease, and will consider the value of targeting ghrelin in treating these disorders.

Monday Early Evening Panel Sessions

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 5

22. The neuro-immune interface in addiction: another vicious cycle

Chair: Kyle Frantz
Presenters: Fulton Crews, Michal Bajo, Bryan Yamamoto, Staci Bilbo

Drug addiction is among the many diseases influenced by interactions between the nervous and immune systems. Neuroimmune responses to drugs may initially protect but ultimately exacerbate drug-related behavior, toxicity and neurodegeneration. Other environmental and developmental stressors also activate neuroimmune signaling and glial cells, thereby altering acute and long-term drug responsivity. Speakers on this panel use animal models to investigate neuroimmune mechanisms for the molecular, cellular and behavioral effects of ethanol, methamphetamine and opioid drugs. First, Fulton Crews will discuss Toll-like receptor (TLR) expression and signaling in the brain, with focus on alcohol-induced innate immune gene induction and neurodegeneration. He will present findings on ethanol-induced neuronal and glial cell signaling through HMGB1-TLR4 and miRNA-TLR7 pathways. Next, Michal Bajo will explore the role of cytokines in the effects of ethanol on cellular properties and physiology of neurons in the central amygdala. Specifically he will show that the pro-inflammatory cytokine IL-1, which is critical in ethanol-induced neuroinflammation, also regulates inhibitory GABAergic transmission and modulates ethanol's effects at GABAergic synapses. Bryan Yamamoto will then discuss the role of inflammation in the neurotoxic effects of methamphetamine, including results indicating that serial exposure of rats to chronic stress exacerbates methamphetamine-induced depletions of monoamines through inflammation-associated mechanisms. He will also show that methamphetamine compromises the blood-brain barrier through neuroinflammation. Finally, Staci Bilbo will link early maternal care to permanent alterations in brain glial cell function, with long-term consequences for neural function and behavior such as relapse to opioid-seeking. Overall, this work provides insight into the bidirectional interactions between abused drugs and the innate immune system in the cycle of addiction.

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 6–8

23. Regeneration and plasticity after injury: extracellular matrix, inflammation, visual function

Chair: James Fawcett
Presenters: Herbert Geller, Larry Benowitz, Ronald Meyer, Keith Martin

The damaged adult mammalian nervous system has some ability to recover function after neuronal damage due to physical damage, degeneration or ageing. This is mainly through plasticity; the formation of new connections through sprouting and rewiring through change in strength of existing synapses. The ability of axons to regenerate for long distances is very limited. In fish and amphibia, however, long distance regeneration and reformation of functional connections in some pathways is very successful. A key controller of plasticity is the extracellular matrix in the form of perineuronal nets, which are responsible for turning off plasticity in adults at the end of critical periods. The success of failure of axon regeneration depends on the balance between inhibitory molecules in the extracellular matrix and on myelin and on the intrinsic regenerative ability of the neurons. The panel will focus on mechanisms of plasticity and regeneration and the factors that can suppress them in the mammalian nervous system or encourage them in fish or amphibia. James Fawcett will be chairman. Herb Geller's presentation will discuss the inhibitory effects of molecules in the extracellular matrix, and their relation to the proteoglycan receptor PTPsigma. Keith Martin will discuss restoration of function in the eye after damage by glaucoma and other conditions, with a focus on retinal transplantation and retinal ganglion cell protection and regeneration. Ron Meyer will discuss the formation of functional connections during regeneration of optic axons in the fish visual system focusing on the compensatory up-regulation of postsynaptic activity and the importance of the convergence of axons to effectively drive postsynaptic neurons.. Larry Benowitz will highlight the role of inflammation and oncomodulin in stimulating regeneration, the restoration of central connections using combinatorial therapies, and ongoing studies on zinc signaling as a major regulator of regeneration.

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 9–10

24. Novel mechanisms of regulation and signaling at excitatory synapses

Chair: Andres Barria
Presenters: Shernaz Bamji, Andres Barria, Ulli Bayer, Jean-Claude Beique

Changes in synaptic strength are generally thought to be one of the cellular bases for learning and memory and critical for the establishment and

maturation of functional neural circuits during development. The vast majority of excitatory neurotransmission in the brain is mediated by glutamate and its ionotropic receptors, AMPA- and NMDA-type glutamate receptors. Unique properties allow the NMDAR to initiate changes in synaptic strength that is normally expressed as changes in the number and properties of AMPARs. This panel will discuss novel signaling cascades and molecular events that regulate synaptic glutamate receptors with consequences for synaptic plasticity and development of neuronal circuits. Dr. Shernaz Bamji (University of British Columbia) will discuss how neuronal activity can drive post-translational modification (palmitoylation) of synaptic substrates leading to long term strengthening of synaptic connections. Dr. Andres Barria (University of Washington) will present evidence that non-canonical Wnt signaling cascades regulate trafficking of NMDARs. Due to their importance in synaptic function, regulation of NMDARs by Wnt signaling provides a mechanism for Wnt ligands to modulate basal synaptic transmission, synaptic plasticity, and brain functions acutely beyond embryonic development. Dr. Ulli Bayer (University of Colorado Denver) will present mechanisms for bi-directional control of excitatory synapse strength by CaMKII. This will include mechanisms for input specificity as well as for trans-synaptic communication. Implications for neurological diseases will be discussed. Dr. Jean-Claude Béïque (University of Ottawa) will describe how NMDAR activation during early postnatal development triggers a non-canonical calcium signaling that imparts spatial attributes to plasticity rules. By favoring the spatial clustering of synaptic weights along dendrites, these mechanisms may instruct the assembly of microcircuit motifs during network development.

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 11–12

25. Progesterone receptors: they're not just in the nucleus anymore

Chair: Paul Micevych
Presenters: Shaila Mani, Kevin Sinchak, Paul Micevych, Melinda Mittelman-Smith

Over the years, our ideas about estrogen signaling in the brain have been greatly expanded due to results that demonstrate membrane-initiated actions. These estradiol membrane-initiated signaling (EMS) events have been demonstrated for morphological plasticity, neuroprotection, reproduction, drug addiction and nociception. More recent experiments have demonstrated that progesterone, whether from the ovary or produced in the brain, also has significant membrane-initiated actions that impact behavior, plasticity and reproductive physiology. Importantly, estrogen and progestin actions are integrated and require both classical nuclear as well as membrane actions. Participants will provide novel behavioral, anatomical and neurochemical results demonstrating the integration of estradiol and progesterone activation of various signaling

pathways to regulate sexual behavior, morphological plasticity and ovulation. Previously, these neural effects of progesterone were solely ascribed to transcriptional regulation through interactions of progesterone receptor (PR) with the nuclear progesterone response element (PRE). Mani will discuss the role of a novel set of membrane PRs, Sinchak will highlight how activation nuclear PR on the membrane facilitates sexual receptivity and Micevych will describe how EMS induced morphological plasticity is modulated by progesterone at both pre- and post-synaptic sites. Mittelman-Smith will provide information on in integration of estradiol signaling, both nuclear and EM, with neuroprogesterone signaling to regulate the luteinizing hormone surge through kisspeptin neurons.

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 14

26. Calcium signaling slopes leading to neurodegeneration

Chair: Victoria Bolotina

Presenters: Ilya Bezprozvanny, Mark Dell'Acqua, Grace Stutzmann, Victoria Bolotina

Recent discoveries revealed new Ca2+signaling origins of Alzheimer's (AD) and Parkinson's disease (PD). A brief introduction will guide through a dangerous terrain of Ca2+ signaling towards the AD and PD slopes. Ilya Bezprozvanny will focus on AD and the role of neuronal store-operated Ca2+ entry (nSOC) in stability of synaptic spines. They discovered that nSOC pathway is critical for maintenance of mushroom synaptic spines, and that synaptic nSOC pathway is compromised in aging and AD brains. Recently they explore the ways to target nSOC pathway therapeutically to prevent synaptic and memory loss in AD. Mark Dell'Acqua will focus on overproduction of beta amyloid in AD and its association with changes in Ca2+ signaling and disrupted synaptic plasticity. He will present recent work on the role of Ca2+-activated phosphatase calcineurin, and its anchoring to the postsynaptic scaffold protein AKAP150 in beta amyloid mediated synaptic dysfunction. Beth Stutzmann will describe early Ca2+ signaling abnormalities in AD, and how this contributes to structural and functional deficits in synapses. She will show that stabilizing intracellular Ca2+ release is one of the effective means to preserve synaptic function and prevent AD pathology. Victoria Bolotina will focus on PD, and present their recent discovery of a previously unknown sequence of pathological events that leads to the death of dopaminergic neurons in SNc. She will show that idiopathic PD is associated with impairment of PARK14-dependent Ca2+ signaling, and can be mimicked in a new mouse model: genetic impairment of PARK14 results in the loss of SOCE, depletion of Ca2+ stores, autophagic dysfunction, progressive death of DA neurons in SNc and age-dependent PD-like motor dysfunction. Altogether, this session will demonstrate that defects in Ca2+ signaling can trigger pathological events in specific neurons and neuronal structures. Restoration of Ca2+ function can be a new strategy for treatment of AD and PD.

27. New diagnostic trends in severe epilepsy

Chair: Olaf Paulson

Presenters: Stefan Posse, Sándor Beniczky, Alexandre Franco, Lars H. Pinborg

Medically refractory focal epilepsy is potentially treatable by surgery. The identification of the epileptogenic zone requires a multidisciplinary systematic approach. In all epilepsy surgery centres the components of the presurgical evaluation include interictal/ictal EEG-video recordings to document seizure semiology and EEG changes, structural MRI, neuropsychology and psychiatry. If the data are discordant placement of intracranial EEG electrodes may in some cases lead to identification of the epileptogenic zone and the neural networks underlying seizures. The present panel deals with new approaches in the investigation of severe epilepsy in order to further elucidate the pathophysiology. The long term goal is to use this new knowledge in the preoperative planning in epilepsy surgery and thereby to render more patients seizure free as well as to be able to offer surgery to more patients. The measures to be considered are functional magnetic resonance (fMRI), electromyography (EMG), combined electroencephalography (EEG) and fMRI (EEG-fMRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). Olaf Paulson will provide introductory comments and lead discussion of the presentations. Stefan Posse will discuss the use of high speed fMRI with time of repetition below .5 sec compared to the classical value of 2 sec yielding a much improved temporal resolution. The short time of repetition has special interest when combining fMRI with EEG. Sándor Beniczky will report on identifying and characterising epileptic seizures using signals from the muscles (surface electromyography). Alexandre Rosa Franco will discuss the use of fMRI for presurgical planning in resecting the epileptic region and detailing its strengths and limitations. Lars Pinborg will finally report on the use of SPECT and PET in focal epilepsy, both with classical radioligands for measurement of blood flow and glucose consumption, and with newer ligands for receptor mapping.

PANEL • MONDAY, 4:30 PM–6:30 PM • PEAK 17

28. The NMDA receptor complex- A hub for the developmental convergence of psychosis risk factors

Chair: Heather Brenhouse

Presenters: Vibeke Catts, Matthew Puhl, Duncan Sinclair, Heather Brenhouse

Psychotic symptoms can be induced by NMDA receptor antagonism, while in the brains of individuals with schizophrenia, postmortem NMDA receptor abnormalities have been reported. However, it is unclear whether NMDA dysfunction is central to the etiology of schizophrenia, or is a consequence of other pathophysiological factors. In this session, we discuss evidence that putative risk factors for schizophrenia- maternal infection, sex and early life stress- influence NMDA signaling, supporting a causal link between NMDA dysfunction and psychotic illness. Vibeke Catts (University of New South Wales) will review evidence for NMDA dysfunction in schizophrenia, including data showing altered postsynaptic NMDA receptor subunit expression in the illness. She will also describe the impacts of maternal immune activation on NMDA receptor gene expression and binding. Matthew Puhl (McLean Hospital) will discuss work in a mouse model of NMDA receptor hypofunction in which neuroanatomical, neurochemical and molecular abnormalities analogous to deficits in schizophrenia are seen, highlighting the value of rodent models in translational studies of NMDA signaling. Duncan Sinclair (University of Pennsylvania) will present evidence that male and female rodents differ in the composition, phosphorylation and function of NMDA receptor complexes at the synapse, around the equivalent postnatal age that sex differences in schizophrenia emerge. Finally, Heather Brenhouse (Northeastern University) will present data illustrating that early life stress results in NMDA receptor-mediated interneuron dysfunction and abnormal behavior in adolescent rodents, which can be remediated by uncoupling of NR2A and PSD95. Together, these presentations support the hypothesis that NMDA receptor signaling is a hub for the developmental convergence of risk factors involved in the pathogenesis of schizophrenia.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 5

29. Brain-driven vulnerability to substance use disorders: do brains make drug abusers?

Co-chairs: Noelle Anastasio, Thomas Crowley
Presenters: Noelle Anastasio, Thomas Crowley, Catharine Winstanley, Patricia Conrod

Externalizing behaviors of human children and adolescents (impulsivity, risk-taking) predict adolescent and adult substance use disorders. Our translational studies of substance-naïve human and non-human subjects suggest that aberrant brain function underlies aberrant early behaviors and reflects a neural vulnerability to substance use disorders. Dr. Anastasio will discuss an imbalance in the cortical glutamatergic system as an underpinning of inherent impulsivity in rodents. She will show that inherent impulsivity may be driven by dysregulation of N-methyl-D-aspartate receptor signaling and that selective NMDAR potentiation may rescue high inherent impulsivity. Dr. Crowley previously showed with fMRI that during risky decision-making adolescents with substance and conduct problems had widespread brain hypoactivity. He will highlight that drug-naïve 9-11 year-olds playing the same decision game as those with the aberrant behaviors mentioned above similarly show widespread aberrant brain function. Dr. Winstanley's work shows that risk-preferring rodents demonstrate enhanced cocaine-seeking, with incubation of craving one month after withdrawal. Risk-preferring decision strategies worsen during cocaine self-administration; the advantageous choice strategies are unaffected by cocaine, indicating risky decision-making is an important contributor to substance use vulnerability. Dr. Conrod will present data from the IMAGEN study, a longitudinal cohort of 2200 adolescents who underwent genetic, neuroimaging and behavioral assessments. She will present correlates of factors of psychopathology within a hierarchical structural model associated with psychiatric conditions, including substance use disorder. This panel will emphasize that a greater understanding of the vulnerability to the development of substance use disorders requires the cross-talk and contribution of cross-discipline, cross-species studies.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 6–8

30. CNS drug delivery, biodistribution, and translational aspects of AAV-based gene therapeutics

Chair: Carolyn Fairbanks
Presenters: Carolyn Fairbanks, R. Scott McIvor, Andreas Beutler

Gene therapy may offer specific advantages over traditional pharmacotherapies including, the potential for continuous release and ultralocalized delivery of biotherapeutics which may avoid many adverse or contraindicating side

effects common with pharmacotherapies. Compared to pharmacotherapy, gene therapy remains nearly at the beginning of understanding of the unique challenges associated with translation. These include optimization of gene vectors tools, gene delivery approaches, biodistribution, and understanding duration of efficacy as well off-target and toxicity effects some of which are unique and unlike those encountered with pharmacotherapy. In this session, we feature pre-clinical work using adeno-associated viral vector strategies for overexpressiing diverse therapeutic proteins/neuropeptides for chronic pain and other CNS therapeutic functions. Dr. Carolyn Fairbanks of the University of Minnesota will moderate and discuss issues associated with biodistribution and tropism of AAV vectors in general and present data on the impact of site-specific overexpression of arginine decarboxylase for the treatment of chronic pain and prevention of opioid analgesic tolerance Dr. R. Scott McIvor of the University of Minnesota will compare the effectiveness of route of administration and AAV vector subtype to achieve target broad expression of alpha-L-iduronidase to address neurological sequelae associated with lysosomal storage disorders. Andreas Beutler of the Mayo Clinic will feature important considerations for scale-up to larger animals and humans and translation of gene therapeutic technology for clinical applications. Translational challenges aside, the long term potential to ultra-selectively target specific regions and cell populations relevant to pain pathways and endogenous analgesic systems could greatly expand the therapeutic window of treatments intended to control pain and to treat other CNS therapeutic dysfunction.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 9–10

31. Not just a relay: dissecting structure and function of the deep cerebellar nuclei in cognition

Chair: Erik Carlson
Presenters: Abigail Person, Krystal Parker, Erik Carlson

Traditionally, the deep cerebellar nuclei were characterized as relays encoding plastic changes occurring in the cerebellar cortex. Recent studies of anatomy and function have challenged this view, in the context of multiple cerebellar functions including cognition. Erik Carlson (University of Washington) will discuss the identification of a novel population of dopamine D1 receptor positive neurons within the lateral nucleus of the cerebellum (LNC) that are anatomically segregated and have molecular, electrophysiological, and anatomical profiles of inhibitory neurons. Silencing of these neurons disrupts specific non-motor behaviors, including spatial memory, social preference, and anxiety without altering motor coordination or motivation. These findings provide direct evidence of anatomically restricted cell types within the LNC that influence specific cerebellar operations. Krystal Parker (University of Iowa) will discuss data providing novel insight into how the cerebellum

contributes to cognition, which may inspire cerebellar-targeted therapeutics for schizophrenia. Cerebellar stimulation is safe and effective in reducing negative and cognitive symptoms, yet the underlying neural mechanisms are unknown. Using tract-tracing, neuronal ensemble recording, pharmacology, and optogenetics in rodents performing an interval timing task, we investigate how stimulating cerebellar dentatothalamic projections rescues timing impairments and neuronal abnormalities caused by frontal dysfunction. Abigail Person (University of Colorado) will discuss an interoceptive system that allows the cerebellum to monitor its own output via collaterizing cerebellar output neurons. Anatomical and physiological experiments in my lab are uncovering roles for corollary discharge signals in amplifying and suppressing coincident reafferent signals in the granule cell layer, highlighting the importance of the integrative properties—rather than simple relay properties—of the granule cell layer.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 11–12

32. Mechanisms underlying migraine

Chair: Andrew Russo
Presenters: KC Brennan, Greg Dussor, Andrew Russo, Leon Garcia-Martinez

This session will address new perspectives on migraine from preclinical models and clinical trials. The recent success of CGRP monoclonal antibodies for preventing migraine makes this session very timely. The speakers will describe how ion channels, cortical spreading depression (CSD), and the neuropeptide CGRP are ideally placed at the intersection of the periphery and the brain to play key roles in migraine. Dr. Brennan will first describe the pathophysiology and circuit mechanisms of migraine that cause a disorder of altered sensory gain. This will include the trigeminovascular system upon which migraine is thought to act, and CSD, which is the proposed mechanism of migraine aura. This will set the stage for understanding the cellular mechanisms discussed in Dr. Dussor's and Dr. Russo's talks. Dr. Dussor will describe mechanisms leading to afferent nociceptive signaling from the cranial meninges, the likely source of migraine pain. His talk will include receptors and signaling molecules that activate trigeminal nerve endings in the dura mater, including a contribution from non-neuronal cells in the dura (fibroblasts) and how these cells can play a previously unrecognized role in migraine. Dr. Russo will discuss translational studies looking at CGRP using light aversive behavior in mouse models as a surrogate for migraine-associated photophobia. The findings will be discussed in the context of CGRP activities in the periphery and central nervous system. This will provide a foundation for the clinical trials discussed in Dr. Garcia-Martinez's talk. Dr. Garcia-Martinez will end the session with an update on the

discovery of antibodies targeting the CGRP pathway and on their performance in clinical trials. Three antibodies directed against CGRP and one against the CGRP receptor have all reported positive data in early trials. It now appears that antibodies targeting the CGRP pathway are a promising new drug class to prevent migraines in many patients.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 14

33. Little bumps, big bumps: how the environment affects the neural progenitors of the subventricular zone

Chair: Francis Szele
Presenters: Steven Levison, Olivier Raineteau, Francis Szele

The subventricular zone (SVZ) is the largest neurogenic stem cell niche in the postnatal and adult mammalian brain. This panel will explore how environmental signals mediate different populations of stem and progenitor cells in the SVZ. Steve Levison will discuss fascinating work from his group revealing multiple classes of bipotential and tripotential SVZ cells. The different classes respond variously to diffusible ligands and also react heterogeneously to injury. Steve's FACsorting protocols now allow the SVZ field to study in more detail than ever possible the behaviour of these distinct cells. Olivier Raineteau will then speak about a very complementary bioinformatics approach to dissecting signalling pathways that differ between the dorsal and lateral SVZ. These studies are essential in understanding molecular diversity between these two SVZ subregions which derive from pallial and subpallial origins, respectively. He then will describe integrated genomics approaches to discover small molecules that can target these specific pathways. These exciting experiments from Olivier's group are likely to lead to druggable targets for stimulating endogenous stem cell mediated repair. Finally Francis Szele will speak about two mechanisms that mediate the function of the pro-inflammatory molecule Galectin-3 (Gal-3) in the lateral SVZ. Francis' group has shown that Gal-3 binds to b-Catenin and diminshes Wnt signalling. This finding suggested decreased proliferation and they showed that Gal-3 over expression in vivo via electroporation caused decreased proliferation. Gal-3 overexpression also increased astrocyte genessis from the postnatal SVZ which was accompanied by increased BMP signalling. This work shows that Gal-3 is uniquely co-regulates Wnt and BMP signalling in the SVZ stem cell niche.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 15–16

34. Molecular pathways controlling synapse development and plasticity

Chair: David Bredt
Presenters: Katherine Roche, John Isaac, David Bredt, Andres Maricq

Organization of receptors at postsynaptic sites is precisely controlled during development. Furthermore, receptor density at synapses is dynamically regulated in the plasticity that underlies learning and memory. The panel will describe molecular and cellular proteins and pathways that determine the distribution and function of synaptic neurotransmitter receptors and associated signaling machinery. Roche will present recent findings on the role of phosphorylation in the regulation of neuroligin (NLGN) trafficking and function. The C-termini of NLGNs are phosphorylated by a variety of kinases, often in an isoform-specific manner. Roche will discuss specific phosphorylation sites recently identified on NLGN1 and NLGN2 and their potential roles in regulating binding to other excitatory and inhibitory molecules, respectively. Isaac will present evidence that re-expression of GluN2B at thalamocortical synapses underlies the reactivation of synaptic plasticity in adult somatosensory cortex following sensory afferent denervation. Trafficking and function of ligand-gated ion channel in neurons often involves both principle and auxiliary subunits. Bredt will present data demonstrating that assembly of neurotransmitter receptors can also require channel-specific chaperones. Maricq will discuss machinery regulating the delivery and removal of synaptic AMPARs. Kinesin-1 mediates the transport of AMPARs and CaMKII is a key regulator of this process. He will present results from recent genetic studies, which identify new molecular components, including putative adaptor proteins and kinases.

PANEL • MONDAY, 7:00 PM–8:30 PM • PEAK 17

35. The neurobiology of eating disorders: translational research of core appetitive, cognitive, and emotional deficits

Chair: Kelly Klump
Presenters: David Jimerson, Scott Crow, Kelly Klump

Eating disorders (i.e., anorexia nervosa, bulimia nervosa) are serious forms of mental illness whose etiology remain poorly understood. Research has traditionally focused on psychosocial and cultural contributions to these disorders, with little attention paid to neurobiology. However, emerging data strongly implicate several biological systems in the etiology of the core features

of the disorders. This panel will describe the state-of-the-science in this area, focusing on neurobiological contributions to pervasive appetitive, cognitive, and emotional abnormalities intrinsic to the disorders. An emphasis will be placed on describing data from clinical and pre-clinical models in order to reflect the growing translational focus of the field. Dr. Klump will begin the panel by reviewing data from human and animal models showing the significant effects of gonadal hormones on phenotypic and genetic risk for the overeating and binge eating behaviors that are common to eating disorders. She will discuss how these hormones likely contribute to the disorders' female predominance and may impact non-appetitive features of the disorders and other neurobiological systems (e.g., serotonin). Dr. Jimerson will build upon this presentation by providing an overview of clinical investigations implicating CNS serotonin dysregulation in eating disorder symptomatology in women. He will then discuss recent preclinical data in female rats suggesting that impaired serotonin function in the prefrontal cortex may specifically contribute to symptoms of impaired cognitive flexibility characteristic of anorexia nervosa. Dr. Crow will end by describing emotion regulation deficits that are common in eating disorders and also linked to frontal regions. He will review new data supporting diminished fronto-limbic activity in response to emotional cues in women who are acutely ill with AN.

TUESDAY, JANUARY 26, 2016

Tuesday Morning Panel Sessions

SHORT COURSE • TUESDAY, 7:00 AM–9:30 AM • PEAK 5

36. SHORT COURSE: Big data in neuroscience

Chair: Paul Katz
Presenters: Jason Gallant, Lloyd Fricker, Andrew Jaffe, Jessica Turner

Advances in computing, sequencing, and imaging technology have created new research opportunities in neuroscience. This short course provides an introduction to several "big data" approaches used in neuroscience. In addition to presenting basic concepts and methodology for those interested in using the techniques, this session will discuss the interpretation of data for participants to better understand published reports. Jason Gallant will discuss how RNA-seq can be used to test for differences in expression of tens of thousands of genes simultaneously at low cost even without a reference genome. He will introduce the RNA-seq workflow and illustrate best practices in experimental design and data analysis. Lloyd Fricker will introduce proteomics and the related field of peptidomics, which provide a profile of the proteins/peptides in a biological

sample. The strengths and weaknesses of the techniques will be discussed, including potential biases in the results. Andrew Jaffe will discuss integrating genetic variation with DNA methylation and gene expression data in the human brain. He will talk about analytic methods for methylation and expression quantitative trait loci (meQTL and eQTL, respectively) analyses to better understand the functional correlates of genetic risk variation for common disease. Finally, Jessica Turner will discuss how to integrate neuroimaging and genetics. Efforts are underway to identify genetic effects on measures of brain volume and function based genome-wide and whole-genome scans for common and rare variants in combination with large neuroimaging datasets. She will assess issues of interpreting results in light of rapidly developing imaging and genetics knowledge and resources. These lectures will provide participants with a basis for understanding the published literature on producing and analyzing large data sets. It could also provide inspiration for beginning new projects. Ample time will be allowed for questions and discussion.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 6-8

37. The behavioral and neurobiological consequences of combined psychostimulant and alcohol use

Chair: Lori Knackstedt

Presenters: Dieter Meyerhoff, Lori Knackstedt, William Griffin, Zachary Rodd

The majority of addicted individuals are polysubstance users (PSU), consuming more than one addictive drug at once. Particularly common is the combination of alcohol and psychostimulants: 60-90% of alcoholics (ALC) are also addicted to nicotine and 50-90% of cocaine users abuse alcohol. Poorer health outcomes and greater resistance to treatment are reported for patients with PSU. Despite the prevalence of PSU, few studies have directly examined its behavioral or neurobiological underpinnings. Dr. Meyerhoff will begin the panel by presenting data regarding neuroimaging and neurocognitive differences between PSU and ALC. Comparing these populations revealed that PSU and ALC differ in prefrontal cortex (PFC) adaptations, including the prominence of neuronal injury/glial changes in PSU. Dr. Knackstedt has developed a novel rodent model of combined intravenous cocaine and oral alcohol (Coc+EtoH) self-administration which reveals that unlike after Coc alone, glutamate transmission in the nucleus accumbens (NA) core does not mediate relapse to cocaine-seeking in Coc+EtOH rats. Ceftriaxone, which targets glutamate, does not prevent relapse in Coc+EtOH rats as it does after Coc alone. Dr. Griffin found that the combination of caffeine and alcohol (Caf+EtOH) resulted in greater EtOH consumption than access to EtOH without Caf.

Repeated exposure to Caf+EtOH produced significant locomotor sensitization and reduced the ataxia caused by ethanol challenge. Dr. Rodd developed an oral nicotine (Nic) and EtOH self-administration model in rats. Nic+EtOH increased sensitivity to the rewarding properties of Nic in the NA shell and the posterior ventral tegmental area (pVTA). Nic+ EtOH self-administration increased basal glutamate in the mPFC and NA shell while EtOH and Nic alone did not alter glutamate. Thus, the present lack of efficacious treatments for drug addiction may be the result of a failure to understand the distinct correlates of combined ethanol and psychostimulant abuse.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 9–10

38. Stress effects on endocannabinoid signaling and emotional control

Chair: Hsiao-Huei Chen
Presenters: Sachin Patel, Hsiao-Huei Chen, Jeffrey Tasker, Jaideep Bains

Hsiao-Huei Chen (Ottawa Hospital Research Institute) will introduce the panel and summarize the current status of the field of endocannabinoids in the control of anxiety, raising the key questions that need to be answered in future work. Sachin Patel (Vanderbilt University) will discuss how 2-Arachidonoylglycerol (2-AG) signalling promotes emotional resiliency and the translational implications for therapeutics development. In particular, this presentation will focus on pharmacological augmentation of 2-AG signalling to promote stress-resiliency and as a possible treatment approach for anxiety and stress-related psychiatric disorders. Hsiao-Huei Chen (Ottawa Hospital Research Institute) will discuss how a serendipitous observation of anxiety behaviors in transgenic mice with brain insulin and leptin resistance led to the discovery of a novel amygdalar intracellular cascade that impairs endocannabinoid signalling and underlies stress-induced anxiety disorders. In particular, how activation of the protein tyrosine phosphatase PTP1B disrupts 2-AG production and the therapeutic potential of PTP1B inhibition to treat stress-induced anxiety disorders. Jeffrey Tasker (Tulane University) will discuss how stress induces anxiogenesis via glucocorticoid-mediated endocannabinoid suppression of inhibition in the basolateral amygdala (BLA). He will present how acute stress causes a long-term depression of synaptic inhibition in BLA neurons by activation of a membrane-associated glucocorticoid receptor and retrograde release of 2-AG at GABA synapses. Jaideep Bains (University of Calgary) will discuss why salience matters in stress and endocannabinoids. He will present his exciting findings focusing on how stress can bi-directionally control the efficacy of retrograde endocannabinoid signaling in the hypothalamus.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 11–12

39. Initiating the turns, elongating the runs, and mtor-ing up the slopes: augmenting neuropsychiatric therapeutic intervention by targeting protein synthesis

Chair: Michael Stefanik

Presenters: Mauro Costa-Mattioli, Emanuela Santini, Jacob Beckley

The ability to quickly adapt may save your life on the slopes immediately, but the ability to learn from that experience, store that information, and produce long lasting changes in behavior (so you miss that tree on the next run) requires synaptic modifications dependent on the synthesis of new proteins. When these processes are interfered with, changes in protein synthesis produce profound alterations in synapse and circuit function. This panel will present data elaborating on the role protein synthesis plays in maintaining adaptations in a number of synaptic processes (LTP, LTD) and neuropsychiatric conditions, ranging from Autism Spectrum Disorder to addiction. It will also discuss translation as a target for therapeutic intervention. Mauro Costa-Mattioli (Baylor College of Medicine) will present on the most recent advances of how protein synthesis regulates both increases and decreases in synaptic strength (LTP and LTD, respectively) in the brain. Additionally, he will discuss new findings regarding the role of translational control of pathological learning. Second, Emanuela Santini (NYU) will speak on the role of protein synthesis in Autism Spectrum Disorder. She will present data indicating that dysregulated protein synthesis generates behavioral and synaptic ASD-like phenotypes in a novel rodent model, and show how dysregulation of some of these signaling pathways contributes to the generation of these phenotypes. Michael Stefanik (Rosalind Franklin University) will describe a novel role for protein synthesis in maintaining pathological adaptations in the nucleus accumbens that underlie the incubation of cocaine craving following extended withdrawal. Jacob Beckley (UCSF) will conclude the session by presenting evidence that the first experience with alcohol triggers mTORC1 activation and synaptic plasticity in dopamine D1-receptor neurons selectively in the nucleus accumbens shell.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 14

40. Coerulean fire: norepinephrine, the brain's intrinsic performance enhancing drug

Co-chairs: Barry Waterhouse, Craig Berridge
Presenters: Robert Spencer, Rachel Navarra, Jill McGaughy, Elena Vazey

Many studies have shown that local administration of norepinephrine (NE) or activation of the locus coeruleus (LC)-NE projection system can facilitate signal transmission through sensory and executive networks in the mammalian brain; however, the context in which these actions manifest themselves and impact behavioral outcomes have not been fully identified. Methylphenidate (MPH), a prescription stimulant used to treat attention deficit hyperactivity disorder elevates catecholamine levels in central circuits through blockade of NE and dopamine reuptake. Off-label use of MPH for performance enhancement in healthy individuals is becoming increasingly popular, suggesting that NE and dopamine represent the neural substrates through which MPH exerts influences on cognitive and sensorimotor processes resulting in performance enhancement. The panel will focus on recent evidence implicating noradrenergic neurotransmission in optimizing behavioral performance in adults and adolescents as revealed by psychostimulant drug actions, receptor specificity, and LC influences on cortical and sub-cortical circuits that are responsible for goal directed behavior.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 15–16

41. Circuit specialization across primary sensory and motor domains of cerebral cortex

Co-chairs: Aaron McGee, Hysell Oviedo
Presenters: Hysell Oviedo, Bryan Hooks, Samuel Hires, Aaron McGee

The primary sensory cortices (A1, S1, and V1) and primary motor cortex (M1) are the gateways to sensing and responding to our environment. These regions share a common developmental trajectory, composition of excitatory and inhibitory neurons, and lamination. Yet within the constraints of this architecture, primary sensory and motor cortex remodel the canonical cortical circuit map to subserve the unique characteristics of each modality. The tools needed to identify these differences between cortical circuits are being rapidly developed, including viral tracing methods, conditional mutant and transgenic mice, optogenetics, and circuit mapping approaches compatible with in vitro and in vivo physiology. This panel will present new information on the specialization of cortical circuits obtained with these emerging techniques and

discuss differences in circuitry between domains within cortex, the functional implications of these adaptations, and the consequences of disruption of these circuits in neurologic disorders. First, Hysell V. Oviedo will provide brief introductory comments and describe refinements within primary auditory cortex that may contribute to the lateralized processing of sounds, and the role of sensory experience in shaping these specializations. Next, Mac Hooks will present recent work employing optogenetics and circuit-mapping to characterize how both thalamic and local network inputs sculpt feed-forward excitation and inhibition in primary motor cortex. Then Andrew Hires will discuss circuit mechanisms of touch perception based on recordings in S1 during whisker-guided object localization. Last, Aaron McGee will describe recent work employing conditional mouse genetics to dissect the maturation of circuitry in primary visual cortex with the close of the critical period.

PANEL • TUESDAY, 7:00 AM–9:30 AM • PEAK 17

42. New approaches to targeting opioid receptors for the management of chronic pain

Chair: Paul Phillips

Presenters: Julius Bourke, Edita Navratilova, Lakshmi Devi, Charles Chavkin

A third of all Americans and over 20 % of the world's population suffers from chronic pain. While opiate analgesics can be effective in the management of chronic pain, they have high abuse liability. Diversion of opiate pain medications represents the fastest growing area of substance abuse in the USA and this trend is being repeated across the globe. Consequently the FDA and other regulatory bodies have greatly limited prescribing practices of opiates. This panel explores strategies to find alternative means of targeting opioid receptors that produce analgesic effects but minimize abuse potential. Julius Bourke (St Barts Hospital) will discuss maladaptations in D2 and mu-opioid midbrain systems in two chronic pain disorders and how these may represent valid pharmacological targets but in a manner that represents a paradigmatic shift in the treatment of pain. He will further highlight how objective tests may be used to identify vulnerable individuals and provide greater group homogeneity for future research. Edita Navratilova (Univ Arizona) will continue the discussion on the role of endogenous dopamine and opioid brain circuits for relief of pain and describe the neural mechanisms of affective and motivational features of pain. She will further discuss how brain adaptations in chronic pain may influence motivational learning. Next, Lakshmi Devi (Mount Sinai) will discuss heterodimerization of opioid receptors and their regulation by chaperone proteins. She will show the mu-delta heterodimers unique pharmacological profiles that could be targeted for specific therapeutic effects.

Finally, Charles Chavkin (Univ Washington) will describe how ligand-directed signaling at mu and kappa opioid receptors have important implications for the design of new medications for the treatment of pain. Specifically, he will demonstrate that G-protein-dependent and arrestin-dependent signaling pathways have differential effects on analgesia and motivational processes.

Tuesday Evening Panel Sessions

SHORT COURSE • TUESDAY, 4:30 PM–6:30 PM • PEAK 5

43. SHORT COURSE: Will I dream of electric sheep? A primer on brain-machine interfaces

Chair: David Devilbiss
Presenters: Jeremy Hill, Dan Moran, Miguel Nicolelis

Direct control of machines by human thought was first reported in the 1960's, almost 10 years before microprocessors were available for computers. In this early experiment, electrodes implanted in the human motor cortex were used to advance a slide projector. Since then, neural relations with machines continue to evolve allowing more complex interactions and control. We are on the threshold of an era where brain machine interfaces (BMI) will become common for the enhancement of sensory and motor functions and the monitoring and control of dysfunctional brain activity. This short course will focus on engineering and neurocomputational concepts to enable the general neuroscientist to begin to use these tools to study the causal relationship between neural signaling and behavior. Jeremy Hill will describe the BCI2000 general-purpose framework for BMI research. His presentation will include an overview of the necessary measurement systems, signal processing, effector systems, and how BMI learns a mapping between neural activities and their physical actions. He will conclude with an application of this technology to allow people with severe neurodegeneration and a loss of all motor control to communicate and interact in their environment. Dan Moran will describe the advantages and limitations of different neural signals for use in BMI and how electrocorticography (ECoG) for BMI provides balance between signal quality and safety. He will also discuss the advantages of particular ECoG features for the control of neuroprosthetics. Finally he will describe the design considerations and development of an implantable bi-directional BMI system. Miguel Nicolelis will describe the fundamental concepts of a Brainet and the materials and resources needed to perform neural stimulation and recordings of large scale brain activity in freely moving animals. He will conclude with a description of the computational approaches used to describe the organization and function of large neural ensembles. These presentations will overview the

leading-edge of BMI technologies and provide resources and tools for better understanding the neural bases of behavior. Questions and discussion will be encouraged throughout the course, and BMI technology will be available for experimentation.

PANEL • TUESDAY, 4:30 PM–6:30 PM • PEAK 6–8

44. Fear and anxiety: contributions from below the brain

Chair: Matthew Young
Presenters: Monika Fleshner, Christopher Lowry, Paul Marvar, Matthew Young

Fear/anxiety disorders such as post-traumatic stress disorder (PTSD) occur at a lifetime prevalence of ~30% in the US. Vulnerability to fear/anxiety disorders is increased by chronic and acute traumatic psychological stress. While the focus of most fear/anxiety research has focused within the brain, the response to a significant or chronic stressor occurs in regulatory systems throughout the body. Mounting evidence increasingly indicates that peripheral stress response systems have significant behavioral consequences that are potentially relevant to the development and treatment of stress-induced fear/anxiety disorders. In this panel, we will present evidence for biological mechanisms through which peripheral systems contribute to stress-associated fear and anxiety behaviors in rodents. Matthew Young (Emory University) will discuss a proinflammatory immune response to fear memory retrieval, and how the effect of that response on the subsequent maintenance of a fear memory may contribute to the persistent and profound memories for a traumatic experience in PTSD. Paul Marvar (George Washington University) will discuss shared hormonal-immune signaling mechanisms that may contribute to common hypertension and fear memory symptoms in PTSD. Monika Fleshner (University of Colorado Boulder) will discuss recent evidence that interventions that induce changes in the gut microbiota can facilitate stress resistance/resiliency and prevent the development of stress-induced anxiety- and depression-like behaviors. Finally, Christopher Lowry (University of Colorado Boulder) will discuss how immunization with heat-killed preparations of immunoregulatory bacteria prevents stress-enhanced fear responsivity and fear extinction deficits, and how novel strategies might be developed for preventing stress-related psychiatric disorders in vulnerable individuals.

45. Role of opioid receptors in pain, affective and motivated behavior

Chair: Michael Bruchas
Presenters: Michael Bruchas, Amynah Pradhan, Jose Moron-Concepcion, Catherine Cahill

This symposium is geared toward increasing our knowledge of the cellular and neural mechanisms underlying the regulation of motivational and affective state in the presence of pain. Speakers will provide knowledge in the use of state-of-art and innovative tools in order to dissect out the neural mechanisms underlying pain-induced alterations in behavioral states. Talks presented in this symposium are likely to have a significant impact in the neurobiology of pain, addiction and affective disorders for the following reasons: 1) The symposium will highlight the functional relationship between pain, opioid receptor dysregulation, and motivated and affective behavior, 2) the symposium will provide new insights into the critical neurochemical and neuroanatomical mechanisms that underlie pain-induced changes in opioid reward and comorbid affective disorders, 3) the symposium will also discuss novel opioid-based therapeutic strategies for the treatment of trigeminovascular pain/migraine. First, Dr. Bruchas (Washington University) will present recent data highlighting the role of two different subpopulations of dynorphin neurons in the nucleus accumbens that drive either aversion or reward. Then, Dr. Amynah Pradhan will discuss the role of opioid receptors in trigeminovascular pain/migraine. Her talk will focus on animal models of migraine, and the potential of delta opioid receptor agonists as novel anti-migraine therapies. Dr Moron-Concepcion (Columbia University) will talk about his recent findings in relation to the involvement of the kappa opioid receptor system in the alterations in motivated behavior in the presence of inflammatory pain and how persistent inflammation alters the patterns of opioid intake using the rat model of intravenous drug self-administration. Lastly, Dr Cahill (University of California at Irvine) will focus her talk on pain-induced changes in the kappa opioid receptor and dynorphin. She will present evidence that kappa opioid receptor activation contributes to negative affect induced by chronic pain as well as evidence the tonic aversive component of pain is partially driven by activation of the kappa opioid receptor in specific limbic structures known to be involved in aversion and reward.

PANEL • TUESDAY, 4:30 PM–6:30 PM • PEAK 11–12

46. Basal ganglia function in human disease

Chair: Stephen Traynelis
Presenters: Sharon Swanger, Mark Bevan, Karen Eskow Jaunarajs, Jeff Conn

The basal ganglia consists of a collection of interconnected nuclei that process a wide range of information, and play an important role in cognition and movement. A number of neurological disorders have been associated with basal ganglia pathology, and include Parkinson's disease and dystonia. In this session, we focus on new findings in the subthalamic nucleus and striatum that are relevant to these two conditions. Talks will discuss basic advances in understanding the neurobiology of these two brain regions, as well as touch on therapeutically relevant concepts relating to their role in disease. Dr. Sharon Swanger (Dept of Pharmacology, Emory University) will initially present new data on postsynaptic receptor identity in excitatory afferent input to the subthalamic nucleus. Dr. Mark Bevan (Dept of Physiology, Northwestern University) will discuss the molecular, cellular and circuit mechanisms underlying pathological activity of the subthalamic nucleus in experimental Parkinson's disease. Dr. Karen Jaunarajs (Dept of Neurology, University of Alabama-Birmingham) will present new data that provides evidence of a central role for striatal cholinergic interneuron dysfunction in the pathophysiology of dystonia. Finally, Dr. Jeffery Conn (Dept of Pharmacology, Vanderbilt University) will discuss M4 muscarinic receptor modulation of dopamine release through actions on D1-expressing medium spiny neurons to trigger release of an endocannabinoid that acts on CB2 receptors on dopaminergic terminals to inhibit release. These talks together will provide basic information on the pharmacology and physiology of subthalamic and striatal circuits, and provide new information about their role in basal ganglia disorders.

PANEL • TUESDAY, 4:30 PM–6:30 PM • PEAK 14

47. Taming the beast: neuronal populations and signaling systems within the amygdala regulating emotional learning, stress and drug preference

Co-chairs: Matthew Hill, Thomas Kash
Presenters: Rebecca Shansky, Matthew Hill, Zoe McElligott, Joshua Gordon

The amygdala is a complex structure divided into several distinct anatomical nuclei that regulates and wide array of behaviors, including stress perception, emotional learning and motivation. Employing rapidly emerging technologies, a growing body of research has determined how the amygdala regulates these behaviors with greater precision. While complex, these studies have elucidated

both local chemical signaling systems within the amygdala, and dissect local anatomical circuits and neuronal populations across various amygdalar nuclei (such as the basolateral (BLA) and central (CeA) nuclei), to map out the nature by which the amygdala regulates these processes. Using a wide array of techniques, ranging from optogenetics, chemogenetics, cell type reporter mice, viral manipulations and electrophysiology, this panel will discuss recent findings relating to the mechanisms by which the amygdala regulates behavioral processes, such as anxiety, emotional learning and motivation. First, Tom Kash (University of North Carolina), will provide introductory comments introducing the area. Rebecca Shansky (Northeastern University) will present new data demonstrating unique structural features in BLA neurons that are recruited by cued fear conditioning using an Arc-dVenus reporter mice, as well as potential sex differences within these processes. Matthew Hill (University of Calgary) will discuss new findings regarding the importance of enzymes regulating endocannabinoid hydrolysis within principal neurons of the BLA, through viral manipulation of expression levels, and the impact this has on stress, anxiety and emotional learning. Zoe McElligott (University of North Carolina) will present novel data regarding the importance of a subset of CeA neurons expressing neurotensin in the regulation of the effects of ethanol, including ethanol consumption and the development of ethanol preference. Josh Gordon (Columbia University) will describe evidence for contrasting roles for somatostatin- and parvalbumin-expressing interneurons in the BLA in fear expression and extinction, using a combination of behavioral optogenetics and neurophysiology.

PANEL • TUESDAY, 4:30 PM–6:30 PM • PEAK 15–16

48. Voltage-gated ion channels in neurons: disease, activity and location

Chair: Chen Gu

Presenters: Angeles B. Ribera, Leonard K. Kaczmarek, William Catterall, Chen Gu

Voltage-gated ion channels play significant roles in regulating neuronal intrinsic excitability and synaptic transmission. This panel will present several findings that exemplify the regulation of these channels in three neuronal compartments, dendritic postsynaptic regions, axons and presynaptic terminals. Voltage-gated (Nav) sodium channels are concentrated at the axonal initial segment and nodes of Ranvier. Angeles B. Ribera (University of Colorado Anschutz Medical Campus) will discuss how zebrafish touch-insensitive mutants are shedding light on mechanisms that underlie the maintenance of Nav channel intracellular pools. Kv3.3 voltage-gated K^+ (Kv) channel is mainly localized in dendrites to regulate dendritic integration and action potential firing. Leonard 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. Voltage-gate Ca^{2+} (Cav) channels are localized in presynaptic terminals to induce neurotransmitter release. William Catterall (University of Washington) will describe new findings on the regulation of presynaptic Cav channels by calmodulin and related calcium sensor proteins, and its role in short-term synaptic plasticity and in spatial learning and memory. Chen Gu (Ohio State University) will describe long-distance delivery of Nav and Kv1 channels along axons that is distinctively regulated by kinesin motors and ankyrin adaptors, and its impact on action potential firing. Mutations of these channel genes are linked with various neurological disorders in humans. These studies invite discussion regarding the roles of voltage-gated ion channels in different neuronal compartments under physiological and pathological conditions.

PANEL • TUESDAY, 4:30 PM–6:30 PM • PEAK 17

49. Prefrontal cortex neuropeptides: novel targets for the treatment of cognitive and motivational dysfunction

Chair: Brian Baldo

Presenters: Brian Baldo, Nicola Grissom, Craig Berridge, Seema Bhatnagar

The prefrontal cortex (PFC) plays a pivotal role in cognitive and motivational processes that are impaired in a variety of psychiatric disorders. Currently, our ability to treat PFC dysfunction is limited to monoamine-targeting drugs. Alternative targets, including neuropeptide systems, are greatly understudied. We will discuss new evidence that neuropeptides act locally within the PFC to modulate behavioral and cognitive function; in some cases, producing unique effects relative to other PFC-based neuromodulators. Brian Baldo (U. Wisconsin–Madison) will outline how intra-PFC mu-opioid signaling produces abnormally strong food motivation and impulsivity, which are features of binge-type eating disorders. These opioid-driven effects are not reproduced by a variety of intra-PFC monoamine agonists or antagonists. Nicola Grissom (U. Cincinnati) will present data demonstrating a link between PFC opioid receptor expression and 5-CSRT performance, a measure of PFC-based attentional/executive function. Moreover, she will describe how epigenetic regulation and expression of PFC opioid receptors are sensitive to obesogenic diets consumed both during adulthood and maternally, and how this receptor regulation can impact corticostriatal cognition. Craig Berridge (U. Wisconsin-Madison) will describe how corticotropin releasing factor (CRF) signaling in the dorsal caudomedial PFC impairs performance in a delayed-alternation test of working memory, while blocking CRF receptors in this region improves

this performance, identically to all FDA-approved ADHD treatments. Finally, Seema Bhatnagar (U. Pennsylvania) will discuss evidence that hypothalamic projections of orexin/hypocretin to the PFC modulate both neuroendocrine stress responses and PFC-based cognitive functions. Collectively, these findings suggest that targeting peptide systems may represent a novel and powerful approach for the treatment of PFC-based cognitive and motivational dysfunction in psychiatric illness.

WEDNESDAY, JANUARY 27, 2016

Wednesday Morning Panel Sessions

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 5

50. Vulnerability factors for drug addiction: interactions between natural and drug rewards

Chair: Lique Coolen
Presenters: Tod Kippin, Marilyn Carroll, Zuoxin Wang, Lique Coolen

Some individuals are more vulnerable to development of substance abuse; yet the causes of these individual differences remain unclear. This symposium will highlight recent research in animal models showing protective effects of pair bonding and sucrose exposure and increased vulnerability influenced by early life exposure, gender, and natural reward deprivation. Moreover, the neurobiological underpinnings of these interactions and influences on substance abuse will be discussed. A cardinal characteristic of addiction is the choice to take or seek drugs over other activities. Consistent with differential addiction vulnerability in humans, emerging studies demonstrate substantial individual variability in the propensity for animals to take or seek-out drugs. Dr. Tod Kippin will describe evidence that the selection between cocaine reinforcement versus a competing reinforcer (food) exhibits high individual variation with the majority of rats exhibiting strong preferences for either food or cocaine. Further, he will discuss sex differences suggesting increased vulnerability towards selecting cocaine over food as well as the hormonal basis of this choice behavior. In contrast, sweet substances reduce drug-seeking behavior in all aspects of addiction and Dr. Marilyn Carroll will demonstrate that in rats bred for high versus low sweet intake, the High Sweet Intake rats are more prone to all aspects of drug addiction than Low Sweet Intake rats. Moreover, combining treatments such as progesterone or atomoxetine, with nondrug rewards (saccharin or exercise) reduces all aspects of addiction more than either treatment alone in rats and monkeys. The next two presentations will unravel the neurobiology of interactions between natural and drug reward

actions within the complex networks that mediate goal directed behaviors, using molecular, pharmacological, and chemogenic approaches to. Dr. Zuoxin Wang will demonstrate that dopamine and oxytocin regulate an interaction between amphetamine and social bonding interaction in monogamous prairie voles. He will demonstrate amphetamine exposure impairs pair bonding whereas pair bonding experience attenuates the rewarding value of amphetamine. In addition, nucleus accumbens dopamine mediates such amphetamine–social bonding interaction and oxytocin in the medial prefrontal cortex reveres impaired pair bonding by amphetamine via interaction with nucleus accumbens dopamine. Finally, Dr. Lique Coolen will show that psychostimulants act on the neural plasticity mechanisms that mediate learning and memory of the natural reward behavior sex. Moreover, she will show evidence for the role of dopamine and glutamate in the nucleus accumbens in mediating the consequences of deprivation of sexual reward on the cross-sensitization of psychostimulant reward seeking. Together, these presentations highlight an area of research that is novel and innovative and will be of interest to a broad neuroscience audience.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 6–8

51. Traumatic brain injury: complex pathologies contributing to a difficult problem

Chair: Akiva Cohen

Presenters: Amy Brooks-Kayal, Bret Smith, Catharine Winstanley, Akiva Cohen

More than 1% of Americans suffer a traumatic brain injury (TBI) each year with a significant number of these cases coming from alpine activities including skiing, snowboarding and sledding. Despite its prevalence, no therapy currently exists to treat the alterations underlying pathologies caused by brain injury. In order to develop putative therapeutics it is necessary to understand the cellular and circuit based alterations caused by TBI that underlie and contribute to the cognitive impairment and reduction in seizure threshold. The central goal of this panel is to highlight a comprehensive approach to delineate alterations in the hippocampus and frontal cortex that may contribute to the behavioral impairments caused by brain injury. Specifically this panel will focus on diverse elements i.e., newborn cells in the dentate gyrus and hippocampal GABAergic receptors. Cortical neuroinflammation and increased cocaine seeking behavior and alterations in in vivo electrical activity during a hippocampal behavioral task. First, Akiva S. Cohen (Children's Hospital of Philadelphia) will provide introductory comments. Then Bret Smith (U. Kentucky) will discuss effects of modulating mTOR activity on adult neurogenesis and synaptic neuroplasticity in the dentate gyrus after focal TBI. Catharine Winstanley (U. British Columbia) will then present novel data documenting increased impulsivity after

milder and more severe TBI centered over the frontal cortex in rats, as well as elevated cocaine self-administration that could be related to neuroinflammation in key frontal areas. Amy Brooks-Kayal (Univ. of Colorado) will then discuss alterations in JAK/STAT pathway regulation of GABAA receptor expression and effects of JAK/STAT inhibition on behavioral outcomes after TBI. Finally, Akiva Cohen will discuss alterations in hippocampal in vivo electrical activity which underlie and contribute to injury-induced alterations in behavior.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 9–10

52. At the nexus between environment and synaptic plasticity, immediate early genes may influence mental illness risk

Chair: Amelia Gallitano
Presenters: Mohamed Kabbaj, Flavio Kapczinski, Amelia Gallitano, Dietmar Kuhl

The unique roles of immediate early genes (IEGs), which are rapidly activated in the brain in response to environmental events, make them ideal candidates to account for both environmental and genetic determinants of mental illnesses. This panel will explore the roles of IEG transcription factors early growth response gene 1 (Egr1, aka zif268), Egr3, and their target gene the effector IEG activity-regulated cytoskeleton-associated protein (ARC/Arg3.1), in molecular processes thought to underlie the cognitive, perceptual, and emotional symptoms of psychiatric illnesses. Each of these genes is required for memory formation and synaptic plasticity, and each has been implicated in human mental illness. Dr. Kabbaj (Florida State University) will present functional studies demonstrating a role for Egr1 in determining sex differences in social anxiety, and report on novel gene targets regulated by Egr1 in the prefrontal cortex of male and female rats. Dr. Kapczinski (Federal University UFRGS, Brazil) will discuss his findings of decreased EGR3 expression levels in the post-mortem prefrontal cortex of bipolar disorder patients compared with controls. Dr. Gallitano (University of Arizona) will present findings demonstrating that Egr3 regulates expression of the serotonin 2A receptor in response to stress and show that disruption of this interaction is responsible for mental-illness related phenotypes of Egr3-/- mice. Finally, Dr. Kuhl (University of Hamburg) will describe results of altered synaptic plasticity in a novel mouse model in which all functions of Arc/Arg3.1 have been preserved except transport of the Arg3.1/Arc mRNA into dendrites. The panel will conclude with brief remarks summarizing how these genes and their targets constitute a biological pathway linking environmental events into neurobiological processes that, when dysfunctional, may create the symptoms of mental illness.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 11–12

53. Behavioral insights into neural circuits for addiction and cognitive function

Co-chairs: Michael Saddoris, Caitlin Orsini
Presenters: Stephen Chang, Donna Calu, Ryan Lalumiere, Michael Saddoris

Drug addiction is a disorder marked by abnormal preoccupation with drugs and related stimuli, along with diminished interest in previously rewarding activities. This complex constellation of behavioral changes in the transition to addiction involves a host of changes in the neural circuits typically associated with learning, reward and motivation. Indeed, these changes typically last well after abstinence from the drug, suggesting that addiction can induce persistent plastic changes in neural circuits that can impact normal cognitive function. Multiple studies have now a variety of deficits in decision making, reward evaluation, and associative learning following experience with cocaine, with the most severe deficits typically manifest in cognitively demanding tasks. Critically, these studies demonstrate the importance of using sophisticated behavioral designs to unmask the subtle contributions of different circuits (e.g., prefrontal cortex, striatum, dopamine) and how these pathways can be differentially impacted by exposure to drugs of abuse. By exploring the intersection of behavior, learning and neural circuits, contemporary studies have the potential to illuminate specific pathologies associated with drug abuse, and can provide a critical basis for potential treatments of addiction. In this panel, Steve Chang (Dartmouth College) will discuss how ventral pallidal neurons encode information necessary for motivational processes. Donna Calu (University of Maryland) will look at how behavioral variability inform subsequent behavior and neural encoding during natural reward learning. Ryan LaLumiere (University of Iowa) will discuss recent findings, using different behavioral paradigms, focused on elucidating the precise roles of regions of the medial prefrontal cortex and insular cortex with regard to both cocaine- and food-seeking behavior in rats. Michael Saddoris (University of Colorado Boulder) will examine how cocaine self-administration disrupts reward-related rapid dopamine signaling in drug-abstinent rats.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 14

54. The epidemic of opiate use disorder

Chair: Kathryn Cunningham
Presenters: Phil Skolnick, Kim Janda, Sandra Comer, Harshini Neelakantan

Opioid use disorder (OUD) affects ~1.8 million people in the U.S., and is a catastrophic public health problem with significant morbidity and mortality. One facet of the public health burden of OUDs is the annual estimates of

>24,000 deaths and >500,000 emergency room visits due to opioid (including heroin) overdose. Problematic OUD that escalates into chronic, relapsing illness also requires long-term behavioral and medication therapy to maintain abstinence. The present symposium will probe the state of contemporary and emerging strategies to reverse overdose, manage detoxification and sustain abstinence in OUD. Dr. Phil Skolnick will discuss the use of naloxone in the management of opioid overdose, and the development of intuitive, intranasal delivery devices that are as effective as parenterally administered naloxone in reversing overdose. Dr. Kim Janda will present his research on perfecting vaccines against heroin and synthetic opiates. Special attention in his lecture will be given to optimizing a vaccine's response through chemistry centric and immunological wisdom. Dr. Sandra Comer will discuss the efficacy of the glial activation inhibitor ibudilast to reduce opioid withdrawal symptoms, craving, and reinforcing effects in human research volunteers with OUD. Dr. Harshini Neelakantan will discuss the role of serotonin 5-HT2C receptor (5-HT2CR) hypofunction in relapse vulnerability related to impulsivity and reactivity to drug-associated cues. She will demonstrate that the FDA-approved 5-HT2CR agonist lorcaserin suppresses cue reactivity in rats trained to self-administer oxycodone, setting the stage for translational research in human trials. Thus, this panel will provide insight into mechanisms underlying OUD and the further development of therapeutic strategies for its treatment.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 15–16

55. Local protein synthesis at synapses, a keystone of plasticity

Chair: Oswald Steward

Presenters: Shannon Farris, Deanna Benson, Marius Ifrim, Oswald Steward

This session will present new insights into the mechanisms and functional significance of local protein synthesis in dendrites. Despite 3 decades of research, there is still an incomplete understanding of whether different cell types have a different compliment of dendritic mRNAs, why certain proteins are locally synthesized and how translation of particular mRNAs is regulated. Shannon Farris will report novel findings on the compliment of dendritic mRNAs in the unique population of pyramidal neurons present in hippocampal subfield CA2, where some synapses do not undergo typical long-term potentiation (LTP), but do express potentiation in response to neuromodulators. Dendritic mRNAs were isolated from dissected dendrites from CA2 and sequenced, and transcript localization was verified by single molecule fluorescent in situ hybiridization. mRNAs for proteins involved in calcium signaling (Pcp4 and S100b) were found in high levels along with the non-coding RNA BC1, which represses translation. Comparisons

between the dendritic transcriptome of CA2 vs. other hippocampal subfields suggest how local translation might limit CA2 synaptic plasticity. Deanna Benson will describe studies defining the biological effects of proteins that are synthesized locally at synapses. Novel strategies to detect and suppress particular locally synthesized proteins reveal that local synthesis of p35 regulates synapse function. Marius Ifrim will discuss how the Fragile X Mental Retardation protein, FMRP, regulates mRNA translation within dendrites. Using fluorescence complementation and single-molecule assay that allows visualization of de novo ubiquitination in dendrites, he will show that FMRP ubiquitination within dendrites is triggered glutamate receptor stimulation, suggesting a dynamic mechanism to remove translational repression. Os Steward will describe studies documenting that synaptic activity that triggers late-phase LTP is accompanied by strong activation of markers of mTOR-dependent protein synthesis (specifically, phosphorylation of ribosomal protein S6). Surprisingly, despite robust activation of S6 phosphorylation, overall levels of protein synthesis are remarkably stable. These results suggest complimentary shifts in mRNAs from translating to non-translating pools.

PANEL • WEDNESDAY, 7:30 AM–9:30 AM • PEAK 17

56. Hard times, bad timing- epidemiological, cellular and molecular evidence for windows of stress vulnerability across the lifespan

Chair: Duncan Sinclair
Presenters: Hanan Trotman, Eliane Proulx, Kimberly Urban, Duncan Sinclair

Although the old adage 'what doesn't kill me only makes me stronger' may apply to the bump runs at Breckenridge, in other contexts the experience of stress and trauma can have profound, detrimental effects on our mental health. In this session, we will explore how the timing of stress exposure, particularly during windows of vulnerability, determines the severity of its consequences. Hanan Trotman will review epidemiological evidence that stress at key developmental stages impacts future risk of psychosis. She will also describe relationships between adolescent stress exposure, stress sensitivity, stress hormone dysregulation and prodromal symptoms in youth at high risk of psychosis. Eliane Proulx will describe cellular mechanisms underlying the enduring effects of early life stress, focusing on how early maternal separation disrupts the adolescent maturation of muscarinic signaling in the rodent prefrontal cortex. Kimberly Urban will discuss the heightened consequences of stress in adolescence relative to adulthood, presenting evidence that stress during mid-adolescence in the rat causes changes to passive membrane properties and excitability of cortical pyramidal neurons. Finally, Duncan Sinclair will describe developmental changes in molecular

stress response mechanisms in the human prefrontal cortex, which reveal a possible molecular and cellular basis for windows of neonatal and adolescent stress vulnerability. He will also highlight approaches to studying molecular stress signaling pathways in human populations, focusing on the use of blood cells and biopsy-derived in vitro olfactory neuroepithelial cells to study cellular stress vulnerability in living individuals. Together, these presentations will outline the evidence for heightened stress susceptibility in childhood and adolescence, detail the consequences of stress exposure during these windows of vulnerability, and suggest opportunities for early identification of vulnerable individuals.

Wednesday Evening Panel Sessions

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 5

57. What has BDNF signaling got to do with addiction?

Chair: Paul Phillips
Presenters: Jacqueline McGinty, Anna (Xuan) Li, Shannon Gourley, Dorit Ron

Biochemical analyses in animals used to model features of addiction following chronic drug use have repeatedly identified alterations in the expression of the neuropeptide, brain-derived neurotropic factor (BDNF), and its molecular partners. This panel will explore the role of BDNF-TrkB signaling in corticostriatal and amygdala circuits in the regulation of addiction-like behaviors. First, Jacqueline McGinty (Med Univ SC) will highlight the role of BDNF signaling in averting cocaine abstinence-induced neuroadaptations. Specifically, she will talk about the role of GluN2A and GluN2B-containing NMDA receptors and Src family kinases underlying the ability of an intra-prefrontal cortical BDNF infusion to suppress cocaine-seeking behavior. Next, Anna Li (NIDA IRP) will discuss the role of rat striatal BDNF in incubation of cocaine and methamphetamine craving. She will talk about the complex roles of BDNF-TrkB signaling in incubation of cocaine craving and its interaction with glutamate transmission in NAc and about the distinct changes of BDNF and TrkB expression in dorsal striatal neurons activated by cue-induced extinction tests after prolonged abstinence. Shannon Gourley (Emory Univ) will address evidence that cocaine exposure induces failures in goal-directed decision-making, resulting in maladaptive habits. Bdnf knockdown in the orbitofrontal prefrontal cortex (oPFC) induces the same deficiencies by weakening oPFC-amygdala interactions. Meanwhile, deficits caused by knockdown or cocaine can be reversed by BDNF- and trkB-stimulating drugs, including low-dose MDMA and 7,8-dihydroxyflavone which appear to enhance new learning regarding the predictive relationship between actions and outcomes, thereby combatting the long-term effects of cocaine on decision-making strategies. Finally, Dorit Ron

(UCSF) will present data suggesting that genetic and epigenetic modifications of corticostriatal BDNF drive the transition from recreational to compulsive alcohol use in rodents.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 6–8

58. Astrocytes as central players and a novel target in ALS, AD and stroke

Co-chairs: Milos Pekny, Jin-Moo Lee
Presenters: Milos Pekny, Jin-Moo Lee, Elly Hol, Steven Levison

Prominent astrocyte activation and reactive gliosis accompany both stroke and many neurodegenerative diseases affecting both the acute neurodegenerative process and subsequent plasticity responses. This panel will present some of the most recent findings shedding light on the molecular mechanisms of this process, will show some of the relevant research tools such as the identification of astrocyte subpopulations by singe cell gene expression profiling, and outline the differences between an immature and adult brain. Milos Pekny (University of Gothenburg, Sweden) will give the introduction, present data on the usefulness of single cell gene expression profiling to identify subpopulations of astrocytes in the physiological and disease context, and show the outcome of modulation of reactive gliosis in ALS. Jin-Moo Lee (Washington University, Saint Louis, USA) will present data demonstrating the role of reactive astrocytes in the progression of Alzheimer's disease (AD) and will explore the common molecular themes in neurodegeneration in stroke and AD. Elly Hol (University Medical Center Utrecht, The Netherlands) will discuss genome-wide transcriptional responses in astrocytes in AD and present data on functional changes in astrocytes in AD. Steve Levison (New Jersey Medical School, USA) will discuss the differences in astrocytes participation in stroke in the immature vs. the adult brain and how this affects the outcome.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 9–10

59. Pain mechanisms: from peripheral detection to ascending and descending modulation

Chair: Durga Mohaptra
Presenters: Andrew Shepherd, Theodore Price, Bryan Copits, Yarimar Carrasquillo

Pain is considered a principal symptom in many medical conditions, with >100 million Americans suffering from chronic pain that costs >US$600 billion annually. However, many pain conditions are undermanaged with current therapeutic regimens. A lack of precise understanding of the neurobiological mechanisms for specific pain pathologies impedes the development of

efficacious analgesics. Recent advances in neuroscience have enabled us to better understand the critical molecular/cellular mechanisms and neural circuitry for the detection, transmission and coding of pain signals. This symposium will provide a collective synthesis of novel recent findings on 1) the molecular & cellular events, and mechanisms underlying the detection of painful stimuli by peripheral nerve fibers, 2) mechanisms underlying transmission of painful sensory signals from periphery to spinal cord to brain, and their modulation under specific painful pathologies, and 3) pain-coding circuits in the central nervous system. Dr. Mohapatra (Chair) will provide a brief introduction on pain transmission, and will moderate discussion of the presentations. Dr. Shepherd will present his recent findings on the molecular, cellular and anatomical mechanisms underlying peripheral detection of painful stimuli in injury/inflammation. Next, Dr. Price will present his findings on spinal mechanisms of painful signal transmission, with special emphasis on the critical role of spinal dopaminergic projections in the transition of adaptive to pathological pain states. Dr. Copits will then present his recent findings on brainstem circuits modulating pain transmission and the use of novel optogenetic tools to explore the roles of opioid receptors in these systems. Finally, Dr. Carrasquillo will present her findings on altered excitability and ionic mechanisms of pain signal processing in the amygdala. Collectively, this symposium will uncover the mechanisms underlying peripheral-to-brain neural signal processing of pain.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 11–12

60. Orexin/hypocretin neurons: physical activity, sleep, arousal, thermogenesis and hypoglycemia…what's the connection?

Chair: Catherine Kotz
Presenters: Catherine Kotz, Jennifer Teske, Andrew Whittle, Barry Levin

The hypothalamic orexin/hypocretin neurons are strongly implicated in several metabolic, physiologic and behavioral outcomes that influence body weight, and this panel will cover their recent work in understanding the role of these neurons in these processes. Catherine Kotz will start off by presenting evidence that these neurons can be stimulated and inhibited using optogenetic and DREADDs to influence physical activity and whole body energy expenditure to reduce weight gain in mice on obesogenic diets. Next, Jennifer Teske will discuss her work on orexin in a rodent sleep deprivation model and the impact of sleep extension on weight gain associated with sleep deprivation. Andrew Whittle will then present recent work on neural circuits regulating thermogenesis, and discuss his studies using DREADDs and optogenetics to stimulate and inhibit locus coeruleus neurons in mice on high fat or normal

diets under thermoneutrality. Barry Levin will wrap up the session by discussing the orexin/hypocretin neurons that project to the adrenal medulla which are activated during hypoglycemia. His work has shown that orexin receptor inhibition blunts the epinephrine and feeding responses to hypoglycemia, and the arousal and awareness that leads to a reversal of a learned conditioned place preference following a single hypoglycemic bout. His findings suggest that the orexin/hypocretin neurons play a role in both hypoglycemia-induced neurohumoral and awareness responses and their blunting after recurrent bouts of hypoglycemia. Together, this panel will shed cohesive new light on the role of these neurons in body weight regulation.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 14

61. High by design: cellular mechanisms and behavioral models of designer drug use

Chair: Carl Lupica

Presenters: Ernesto Solis, M. Foster Olive, Alex Hoffman, Jenny Wiley

"Designer drugs" are psychoactive molecules that are often synthesized in clandestine laboratories by amateur chemists. The fact that these molecules are made in illicit laboratories without regulatory control often leads to exposure to unknown concentrations, as well as to adulterants and contaminants, resulting in unintended toxicity. This, together with the increased availability of these compounds, has resulted in a large number of adverse medical events, and significant public health risks. However, despite the widespread and growing use of these drugs, their safety is untested, and in many cases a complete understanding of their pharmacological sites and mechanisms of action are lacking. This panel will present recent research involving 2 of the most widely used classes of designer drugs; designer cannabinoids, found in herbal synthetic marijuana preparations, such as "Spice" and "K2", and the designer synthetic cathinones found in psychoactive preparations known as "bath salts". Carl Lupica (NIDA-IRP) will provide introductory remarks. Ernesto Solis (Virginia Commonwealth University) will discuss the actions of cathinone "bath salts" constituents, including methylenedioxypyrovalerone (MDPV), on the dopamine transporter (DAT), heterologously expressed in Xenopus oocytes. Foster Olive (Arizona State University) will present data examining the effects of binge MDPV self-administration on cognitive function in rodents, and will discuss studies aimed at identifying brain regions and neuronal phenotypes where neurodegeneration occurs to produce cognitive deficits. Alex Hoffman (NIDA-IRP) will discuss the actions of several synthetic cannabinoid molecules, recently identified in illicit herbal preparations, on neurotransmission at glutamate synapses in the mouse hippocampus, and compare these effects with those of Δ9-THC, the psychoactive constituent of

marijuana. Finally, Jenny Wiley (Research Triangle Institute) will discuss the structures and behavioral effects of several synthetic cannabinoids and their derivatives in drug discrimination models in mice. This panel will provide an up to date assessment of the most recently isolated designer compounds and the mechanisms through which they affect brain function.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 15–16

62. Transmitter diversity, co-release and plasticity at central synapses

Chair: Shane Hentges
Presenters: Thomas Hnasko, Marisela Morales, Louis-Eric Trudeau, Jaideep Bains

It is becoming increasingly clear that neurons in the central nervous system can utilize multiple transmitters either at once, or by switching transmitter phenotype in a dynamic manner. These and other novel forms of plasticity are particularly well illustrated in midbrain dopamine neurons and hypothalamic neurons. Following a brief introduction by Shane Hentges (Colorado State University), Louis-Eric Trudeau (University of Montreal) will give an overview regarding the heterogeneity in neurochemical identity of mesencephalic dopamine neurons and present studies focusing on the ontogeny and roles of glutamate release by dopamine neurons. Tom Hnasko (UC San Diego Health Sciences) will discuss transmitter diversity in dopamine neurons focusing particularly on the roles of neurotransmitter co-release in reward-related behaviors. Marisela Morales (National Institute on Drug Abuse) will discuss mechanisms and localization of glutamate release from dopaminergic axons. Jaideep Bains (University of Calgary) will present date on transmitter co-release and plasticity in the hypothalamus in response to stress, specifically focusing on opposing forms of plasticity that are evident during distinct temporal windows after stress.

PANEL • WEDNESDAY, 4:30 PM–6:30 PM • PEAK 17

63. Double diamonds, no problem: the role of specific inputs to the medial prefrontal cortex in the regulation of fear and anxiety

Chair: Joshua Gordon
Presenters: Ofer Yizhar, Nancy Padilla Coreano, Celia Kjaerby, Caitlin Vander Weele

The medial prefrontal cortex (mPFC) plays a key role in the expression and modulation of learned fear and innate anxiety, as do many of the key brain regions which provide its primary and modulatory inputs. Yet the specific roles of these various afferent pathways in anxiety-related behaviors have not been

thoroughly explored. Here, each of the four speakers will discuss experiments applying optogenetics, neurophysiology, and calcium imaging to examine the role of specific inputs to the mPFC in fear and anxiety. The first two talks will focus on major glutamatergic inputs to the mPFC. First, Ofer Yizhar will present the results of experiments aimed at manipulating inputs from the basolateral amygdala, showing that long-term depression of amygdala-mPFC neurotransmission in vivo results in impaired fear learning and facilitation of extinction. Second, Nancy Padilla Coreano will show how optogenetic inhibition of ventral hippocampal inputs reduces anxiety-like behaviour as well as neural representations of aversion in the mPFC. The next two talks will cover neuromodulatory inputs. Celia Kjaerby will present experiments exploring how serotonin modulates inputs to the mPFC, and how these actions can alter anxiety-related behaviour. Finally, Caitlin Vander Weele will show how aversive stimuli alter dopamine release in the mPFC, and how this dopamine release may influence activity in projection-defined mPFC subpopulations which influence behavioral responses. Together, these presentations will provide a framework for understanding how the mPFC integrates diverse inputs to modulate fear and anxiety.

THURSDAY, JANUARY 28, 2016

Thursday Morning Panel Sessions

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 5

64. Searching for neural substrates of PTSD vulnerability in the young, adult, and addicted

Chair: Marek Schwendt
Presenters: Tania Roth, Almira Vazdarjanova, Marek Schwendt, Justin Gass

Post-traumatic stress disorder (PTSD) is a chronic, debilitating disorder that develops in reaction to traumatic life events. Importantly, PTSD symptoms such as lasting anxiety, avoidance, and flashbacks develop only in a subpopulation of trauma-exposed individuals. It is believed that individual vulnerability to develop PTSD arises from gene-environment interactions that also co-vary with age. As such, early life stress, co-morbidity with other psychiatric disorders, and substance abuse all elevate the risk of onset, severity of PTSD symptoms, and resistance to treatment. Presenters in this session will discuss their findings on neurobiological substrates and possible treatment of PTSD using diverse animal models that address the effects of age, individual stress-reactivity, and substance abuse comorbidity. First, Dr. Tania Roth will present data on epigenetic alterations within the brain anxiety circuitry produced by

an animal model of early-life stress (caregiver maltreatment) or by traumatic psychosocial stress in adulthood and discuss her findings in relation to age-dependent PTSD vulnerability. Second, Dr. Vazdarjanova will discuss whether individual reactivity to a mild stressor correlates with future susceptibility to develop PTSD; with the focus on stress-induced changes in immediate early gene expression and HPA axis activity as predictors of PTSD susceptibility in rats. Next, Dr. Marek Schwendt will present findings on neuroadaptations within the amygdala-PFC circuitry that emerge with resilience to develop prolonged PTSD-like anxiety in rodents exposed to a single traumatic stress. He will also discuss different propensity for relapse to cocaine-seeking in animals with vulnerability vs. resilience to develop PTSD. Finally, Dr. Justin Gass has developed a rodent model of PTSD-alcohol comorbidity and will present novel data on the role of mGluR5 receptors in attenuating alcohol consumption and alcohol-induced deficits in fear extinction in PTSD-like rats.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 6–8

65. Neurocognitive effects of early-life seizures

Chair: Tim Benke
Presenters: Tim Benke, Rod Scott, Joaquin Lugo

Seizures occur most commonly in infancy compared to any other time in life. Despite this, effective anticonvulsants for babies with seizures are non-existent. Further, it remains unclear whether or not the seizures or the inciting insult are causative in chronic sequelae including neurocognitive deficits and epilepsy. There is a long standing hypothesis that epileptic seizures and interictal discharges alter neural networks in a way that is responsible for neurocognitive impairments. This is derived from correlations between epileptic phenomena and cognitive outcomes observed in humans. Multiple animal models have been employed to approach this experimentally. Tim Benke (University of Colorado, School of Medicine) and Rod Scott (University of Vermont College of Medicine) will first discuss the clinical issues. Joaquin Lugo (Baylor University) will present his work on the autistic-like phenotype that results from daily repeated flurothyl seizures during early development in mice. He will also present his work on the effect of early-life status epilepticus on sex-specific effects on ultrasonic vocalizations in mice. Rod Scott will discuss how etiology, the inciting insult, is the major predictor of outcome. Here, animal models are used to dissociate epileptic phenomena, epilepsy and neurocognitive outcome. These models are used to identify network level abnormalities that could provide systems level targets for novel therapeutic interventions that could ultimately improve outcomes. Tim Benke will discuss mechanistic causes for acute and chronic alterations in synaptic plasticity and autistic-like behavior following kainate-induced early life seizures. Chronic alterations in LTP

and mGluR-LTD involve alterations in FMRP-mediated signaling, CaMKII and L-type calcium channels. These studies provide additional targets for therapeutic interventions that can rescue altered synaptic plasticity.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 9–10

66. The neurobiology of sleep/wake oscillations

Chair: Matt Carter

Presenters: Matt Carter, Antoine Adamantidis, Kamran Diba, Thien Thanh Dang-Vu

In mammals, there are three general states of vigilance: wakefulness, slow-wave sleep (also called non-rapid eye movement "NREM" sleep), and rapid eye movement (REM) sleep. All mammals exhibit a characteristic pattern of sleep/wake oscillations in which they transition from one vigilance state to the next throughout their active and inactive periods. Despite much progress in recent years, the neural basis of sleep/wake oscillations is relatively unknown, as are their function. This session will explore current research in the neurobiology of sleep/wake oscillations using a variety of methods and perspectives. Dr. Matt Carter (Williams College) will begin the session by briefly introducing concepts in sleep/wake neurobiology for non-experts. He will then present recent findings using optogenetic techniques into how neurons traditionally involved in food intake can influence sleep/wake architecture in mice. Dr. Antoine Adamantidis (University of Bern) will present findings that establish a direct causal link between REM sleep and memory consolidation in mice. Specifically, he will show how REM-specific optogenetic silencing of GABAergic neurons in the medial septum impairs declarative and fear-conditioned memories. Dr. Kamran Diba (University of Wisconsin at Milwaukee) will talk about how the firing rates of cortical neurons change dynamically both within REM and NREM sleep epochs and across extended sequences of REM and NREM. He will also discuss the possible mechanisms driving these changes. Finally, Dr. Thien Thanh Dang-Vu (Concordia University) will talk about human electroencephalography and neuroimaging studies investigating mechanisms and functions of sleep/wake oscillations in healthy and disrupted sleep. Taken together, this panel will explore sleep/wake oscillations from a variety of perspectives and should be of great interest to a broad neuroscience audience.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 11–12

67. Recent updates on incubation of drug craving: environmental enrichment, epigenetics and glutamate receptors

Co-chairs: Anna (Xuan) Li, Karen Szumlinski
Presenters: Marcello Solinas, Yan Dong, Anna (Xuan) Li, Karen Szumlinski

Incubation of drug craving refers to the time-dependent increases in cue-induced drug seeking after withdrawal from drug self-administration. Our panel will provide recent updates on incubation of psychostimulants and alcohol craving, focusing on environmental enrichment, epigenetics and glutamate receptors. Marcello Solinas (INSERM, France) will present results showing that housing conditions during withdrawal influence incubation of craving. In particular, he will show that exposure to environmental enrichment during periods of abstinence prevents incubation of cocaine and alcohol craving. Yan Dong (U Pittsburgh) will present data on experimental improvement REM sleep or exposure to enriched environment, two noninvasive behavioral strategies, regulates synaptic trafficking of calcium-permeable AMPARs in the nucleus accumbens and decreases incubation of cocaine craving. Anna (Xuan) Li (NIDA, Baltimore) will describe the role of striatal histone deacetylase 5 in incubation of methamphetamine craving and the unique genetic profile of selectively activated neurons that contributes to incubation of methamphetamine craving. Karen Szumlinski (UC Santa Barbara) will describe recent data pertaining to the dysregulation of excitatory signaling within the prefrontal cortex as it relates to cue-reactivity during protracted withdrawal.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 14

68. The place of the lateral preoptic area-lateral hypothalamic continuum in the control of adaptive and pathological motivated behavior

Chair: David Barker
Presenters: Daniel Zahm, Michela Marinelli, David Barker, Steven Simmons

Neurons in the lateral preoptic area (LPO) and lateral hypothalamus (LH) provide substantial input to midbrain and epithalamic areas, including the ventral tegmental area (VTA), the lateral habenula (LHb) and rostromedial tegmental nucleus (RMTg), that are implicated in processing rewarding and aversive stimuli. The role that specific subcircuits within this portion of the basal forebrain play in behavior and psychopathologies, including drug-addiction and depression, has been the object of recent studies. This panel explores new

findings on the neuroanatomical organization of the related connections of the VTA, LHb and RMTg, electrophysiological and phenotypic characteristics of LPO-LH outputs to the VTA, LHb and RMTg, and the role that specific circuits play in behavior and psychopathology. Scott Zahm will discuss the related connectivities of the VTA, LHb and RMTg with emphasis on outputs from the LPO and LH to these structures. Next, Michela Marinelli will discuss the functional relevance of the LPO on VTA activity. She will present pharmacology, chemogenetics, and optogenetics data showing functional specificity of LPO projections to the VTA, including evidence that this projection targets mainly VTA GABA neurons. She will also show that the LPO plays a role in cocaine-seeking behavior. David Barker will then discuss evidence from retrograde tracing, in situ hybridization, and electron microscopy showing an unexpected glutamatergic projection from the LPO to the LHb as well as behavioral evidence from mice transfected with channelrhodopsin demonstrating that this pathway participates in aversion. Steven Simmons will conclude the panel by discussing how LH orexin neurons, which predominantly target the VTA, participate in generating motivation underlying drug seeking behavior. He will also provide evidence showing that the first FDA-approved drug targeting orexin signaling, suvorexant, may be therapeutic for treating substance abuse disorders.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 15–16

69. Inflammatory signaling at the crossroads between stress, addiction and psychopathology

Chair: Gretchen Neigh

Presenters: Gretchen Neigh, Jesse Schank, Jennifer Felger, Georgia Hodes

A diverse literature exists detailing the role of increased inflammatory signaling in the brain and its implications for affective disorders such as depression and anxiety. More recently, it has come to light that immune signaling pathways are involved in other stress-related psychopathologies such as the addiction process, particularly in the case of alcohol abuse. Indeed, whereas increased peripheral immune cell activation and prolonged exposure to high levels of inflammatory cytokines may decrease reward sensitivity and confer susceptibility to stress-induced depressive behavior, inflammatory signaling molecules such as nuclear factor kappa B (NFkB) have been found to mediate the rewarding properties of alcohol. Therefore, immune signaling in the brain is a fundamental process involved in a wide range of neuropsychiatric disorders and may serve as a viable target for development of novel treatment strategies. Furthermore, stress is known to have a profound influence on both affective disorders and addiction. This process may involve intricate interactions between glucocorticoids (a main effector of the stress response) and inflammatory signaling pathways.

The current symposium will draw on evidence from the study of inflammation effects on the brain, stress-induced immune activation, and the role of immune signaling in addiction to illustrate the diverse relationships between inflammation and neural function and the potential influence of stress in affective disorders and addiction. Goals of symposium: 1) to provide insight and fundamental knowledge regarding the contribution of immune signaling to affective disorders and addiction, 2) to illustrate immunologic and neurobiologic mechanisms by which inflammation may contribute to these disorders, 3) to build a framework based on knowledge of the interaction between brain immune signaling and behavior which can inform treatment strategies and experimental approaches.

PANEL • THURSDAY, 7:30 AM–9:30 AM • PEAK 17

70. How cortical inhibitory circuits gate perception and plasticity

Chair: Alfredo Kirkwood

Presenters: Alfredo Kirkwood, Li Zhang, Robert Froemke, Elizabeth Quinlan

Inhibitory circuits are essential for information processing as they shape the temporal and spatial propagation of neural activity. Indeed, a powerful emerging notion in cortical function is that the dynamic control of balanced excitation and inhibition (E/I) is crucial for gating sensory perception and plasticity. The talks in this panel were arranged to illustrate these points in a comprehensive manner. Alfredo Kirkwood (Johns Hopkins) will present unique properties of short-term plasticity of the synapses made by fast spiking (FS) interneurons onto pyramidal cells, and he will discuss how these properties are key to effectively control postsynaptic firing over wide range of cortical activities. Li Zhang (U. Southern California) will discuss how the differential recruitment of feedforward inhibitory circuit modules in the auditory cortex shape spectral, temporal and amplitopic relationships, and how this process is relevant for understanding functional processing. Robert Froemke (NYU) will compare and contrast the noradrenergic, cholinergic, and oxytocin modulatory systems that regulate cortical inhibition, control synaptic plasticity, and produce changes in auditory perception and behavior. This presentation will be complemented by new data on direct recordings from neuromodulatory neurons, to determine the conditions under which each system is activated by sensory input or forms of experience.Elizabeth Quinlan (U. Maryland) will address the central role that FS interneurons play in the regulation of critical periods for synaptic plasticity. Dr Quinlan will focus on how molecular manipulations that enhance or decrease the excitatory drive onto FS also alter the initiation and termination of the critical period for visual cortical plasticity. Importantly, these approaches can be used to promote the recovery of visual function in an eye deprived of vision from birth.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 5

71. Innovative strategies for detection and treatment of neurodegenerative diseases

Chair: Greg Gerhardt
Presenters: Holly Hunsberger, Miranda Reed, Sid O'Bryant, Richard Grondin

Neurodegenerative diseases, characterized by the slow and progressive loss of neurons, are becoming more prevalent, and although the speed of research has increased, clinical trials have yielded unsatisfactory results. Neurodegenerative disorders, such as Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD), can disrupt molecular pathways, synapses, local circuitry, and higher order neural networks. However, many researchers are now targeting earlier changes in the disease process in hopes of preventing the downstream effects, including neuronal loss and abnormal protein assembly. This panel will present innovative advances for treatments in the area of neurodegeneration. Holly Hunsberger will focus on the possible treatment of AD through regulation of the glutamatergic system using riluzole, an FDA-approved drug for treatment of amyotrophic lateral sclerosis (ALS), which decreases glutamate release and increases glutamate clearance in the extracellular space. Richard Grondin will present his work in nonhuman primates on targeting HD and PD progression using RNA interference therapy. He will discuss a possible treatment to silence the expression of the disease-causing gene by injecting directly into the brain Adeno Associated Virus (AAV) vectors carrying short hairpin ribonucleic acid (shRNA) constructs or constant infusion of silencing ribonucleic acid (siRNA's) designed to reduce production of target proteins such as huntingtin and α-synuclein. Because early treatment strategies also require rapid and cost-effective biomarkers, Sid O'Byrant aims to generate and refine a biomarker algorithm in human blood that will yield excellent accuracy for identification of neurodegenerative diseases and their subtypes. He will discuss the identification and use of a blood-based AD and PD screening tool. Greg Gerhardt will expand on his recent work with PD patients undergoing deep brain stimulation therapy. He will discuss Phase I clinical trials involving implantation of peripheral nerve allografts into the substantia nigra or nucleus basalis of Meynert as adjunct therapies to DBS. Collectively, the presentations will highlight innovative approaches in mice, non-human primates, and humans, transitioning from bench to bedside.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 6–8

72. Synaptopathies: from the periphery to central and from mechanisms to disease

Chair: Gabriel Corfas
Presenters: Gabriel Corfas, Mohammed Akaaboune, Christorpher Cowan, Derek Buhl

The focus of this panel will be to discuss recent findings on the mechanisms of synaptopathies; i.e. disease states that are primarily caused by structural and functional disruption of synapses, and how this knowledge might help in the development of new therapies for diverse disorders, from hearing loss and neuromuscular diseases to autism and psychiatric disorders. Gabriel Corfas (University of Michigan) will provide introductory remarks and will present findings on the cellular and molecular mechanisms that regulate the formation of inner ear synapses and how this knowledge can be leveraged to promote synapse regeneration and restoration of hearing after noise exposure. Mohammed Akaaboune (University of Michigan) will discuss his studies on the formation and maintenance of the vertebrate neuromuscular synapse, focusing on mechanisms that regulate the stability of the postsynaptic receptors through a ubiquitin-proteasome (UPS) dependent mechanism. Christopher Cowan (McLean Hospital) will then review his studies on the regulation of inhibitory and excitatory synapse development in cortical neurons by the MEF2C transcription factor and its potential implications for endophenotypes of autism, intellectual disability and schizophrenia. Finally, Derek Buhl (Pfizer) will discuss his findings on the effects that mutation of Shank2 have on synaptic function and plasticity as well as behavior, and the relevance of these phenotypes to Autism Spectrum Disorder.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 9–10

73. Functional implications of the heterogeneous, molecular, physiological, and anatomical organization of forebrain locus coeruleus-norepinephrine projections

Chair: David Devilbiss
Presenters: Patricia Jensen, Carlos Mejias-Aponte, Barry Waterhouse, David Devilbiss

The noradrenergic (NE)—locus coeruleus (LC) is the principle nucleus of several adrenergic loci that innervate and modulate the function of nearly every forebrain region. Generally, the LC is viewed as a homogeneous nuclei of neurons that discharge en masse to release norepinephrine and other co-transmitters uniformly throughout the CNS. However, a growing body of evidence indicates that the LC and other pontine NE cell groups (A5 and A7)

differentially regulate information processing and cognitive functions across brain regions. This panel will review recent evidence that the LC and other NE loci can bias neuromodulation to selectively optimize sensorimotor versus executive functions through a number of anatomically-specific projection patterns, NE release volumes, physiological properties, and molecular expression patterns. Patricia Jensen will provide new evidence for genetically defined subpopulations of NE neurons that innervate unique target brain regions. Elucidation of such an organizational schema provides new inroads to understanding the myriad of functions regulated by the noradrenergic system. Carlos Mejias-Aponte will present further anatomical evidence supporting a differential release of NE across target forebrain regions. Such mismatch in NE efflux across target brain regions likely acts to optimize different cognitive functions as arousal levels increase. Barry Waterhouse will present recent work demonstrating that LC neurons may be organized into functional cliques having similar electrophysiological properties and anatomical targets. Such functional organization may be critical for orchestrating orienting, executive, and sensorimotor functions. David Devilbiss will describe some of the functional consequences of heterogeneous innervation of LC-NE to target forebrain circuitry. Selective optimization of target network function across cortical and subcortical regions is likely critical for normal adaptive cognitive function and behavior.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 11-12

74. Transporters on the move—biophysical approaches for direct assessment of protein dynamics

Chair: Claus Loland

Presenters: Joeseph Mindell, Michael Kavanaugh, Claus Loland, Kenneth Madsen

Transporter proteins play critical roles in the nervous system. Our understanding of these proteins has grown by leaps and bounds in recent years, in part due to dramatic advances in structural biology, yielding atomic resolution of many transporters. However, since these structures represent snapshots in the complex functional landscapes of these proteins, it is essential to use orthogonal approaches to put structural information into functional context. These include assessment of protein dynamics, signaling, and regulation. This panel will describe how the rapidly evolving biophysical approaches can provide fundamentally new insights for direct assessment of transporter function and interaction. Using combinations of computational modeling and protein biochemistry, Joseph Mindell has revealed the outward facing structure of the Na+/succinate transporter VcINDY, demonstrating that transport involves a substantial elevator-like movement of the protein's transport domain, paralleling that seen the glutamate transporter (EAAT)

homolog, Gltph. Michael Kavanaugh presents optical and electrophysiological data elucidating how EAATs help shape the responses of glutamate receptors in the brain. Notably, he will show that the family also includes transporters for L-Ser/D-Ser and that members of this transporter gene family may modulate NMDAR responses to D-Ser as well as L-Glu. Claus J. Loland will introduce transition metal ion FRET (tmFRET) in the neurotransmitter:sodium symporter, LeuT. tmFRET is distance-dependent quenching of an incorporated fluorescent probe by bound Ni2+. The direct monitoring of conformational changes provides deeper insight into protein dynamics in e.g. gating domains. Kenneth L. Madsen will describe how quantitative confocal microscopy on cell membrane sheets can characterize multivalent binding kinetics and dynamics of scaffolding proteins to the exposed intracellular C-termini of proteins embedded in their native membrane environment.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 14

75. Down the slippery slope: new frontiers in addiction-related circuits

Co-chairs: Joshua Haight, Susan Ferguson

Presenters: Susan Ferguson, Joshua Haight, Jessica Barson, Thomas Kash, Lindsay Yager

Addiction is a neuropsychiatric disease characterized by compulsive drug-seeking and drug–taking and a high propensity for relapse even after long periods of abstinence. Unfortunately, much of the neural circuitry underlying this debilitating disorder has yet to be elucidated. This panel will cover recent work in this area, highlighting cutting-edge approaches, theories, and breakthroughs in understanding how diverse reward and motivational circuits give rise to maladaptive behavior. First, Dr. Susan Ferguson will give a brief introduction to the panel. Next, Joshua Haight will discuss the role of the paraventricular nucleus of the thalamus (PVT) in incentive salience attribution to reward-paired cues. Specifically, lesion studies, neuronal mapping, and chemogenetic techniques show that prelimbic cortical afferents to the PVT may control the attribution of incentive salience to reward paired cues. Continuing with the PVT, Dr. Jessica Barson will discuss data demonstrating that the PVT is an important part of the addiction neurocircuitry. In the anterior PVT, hypothalamic orexin is released in response to ethanol bingeing, which then increases local neuronal activity and levels of substance P that promote further drinking. Next, Dr. Thomas Kash will present recent findings indicating that corticotrophin releasing factor containing neurons in the bed nucleus of the stria terminalis regulate binge-like alcohol consumption, including unpublished findings which highlight both upstream and downstream anatomical structures that regulate this process. Last, Dr. Lindsay Yager will discuss ongoing work using targeted expression of DREADDs (Designer Receptors Exclusively

Activated by Designer Drugs) and two-photon imaging of genetically encoded calcium indicators to better define the role of dorsal striatal circuitry in several behavioral measures of compulsive drug use characteristic of addiction.

PANEL • THURSDAY, 4:30 PM–6:30 PM • PEAK 15-16

76. Nobody plays alone: multisensory connections and plasticity in the primary sensory cortices

Co-chairs: Hey-Kyoung Lee, Patrick Kanold
Presenters: Eike Budinger, Huizhong Tao, Hey-Kyoung Lee, Patrick Kanold

There is emerging evidence that primary sensory cortices are functionally influenced by other senses beyond their primary inputs. Such multisensory influences are thought to affect normal sensory processing and allow multisensory integration even at this early stage of cortical processing. In this panel, we will discuss the anatomical pathways that allow multisensory information to influence primary sensory cortices, how these inputs alter functional tuning of cortical neurons, and undergo plastic changes to allow sensory compensation in the event of losing a sensory modality. Dr. Eike Budinger (Univ. Magdeburg, Germany) will talk about anatomy and postnatal development of multisensory connections in primary sensory cortices. In particular, he will focus on how thalamocortical and corticocortical systems may serve short latency integration processes in the primary sensory cortical areas, and how these connections normally develop. Dr. Huizhong Tao (Univ. Southern California) will present her finding that presentation of sound sharpens orientation selectivity of layer 2/3 neurons in the primary visual cortex, especially under low visual contrast. In addition, she will present evidence that this is achieved by direct projection from auditory cortex to layer 1 of primary visual cortex through inhibitory and disinhibitory circuits. Dr. Hey-Kyoung Lee (Johns Hopkins Univ., chair) will discuss how loss of a sensory modality allows two distinct forms of adaptation in the deprived and spared primary sensory cortices. In particular, she will present data that feedforward and intracortical synapses undergo distinct synaptic plasticity, which may influence cortical processing. Dr. Patrick Kanold (Univ. Maryland, co-chair) will talk about how intralaminar and interlaminar circuits in the auditory cortex refine after visual deprivation in a balanced fashion. He will present how such refinement allows for a more reliable processing of auditory stimuli.

77. Stress and cocaine: a thorny problem in the PFC-accumbens circuit

Chair: Jacqueline McGinty
Presenters: Jason Radley, Ben Siemsen, Shannon Gourley, Robert Wheeler

Stress can cause complex neuroadaptations that lead to seeking and/or taking of addictive substances. This panel will discuss interactions between stress and drug taking/seeking based on concomitant changes in the brain that are common to both conditions. Jason Radley (Univ Iowa) will present research findings based on 3D imaging and analysis of dendritic spine morphometry that chronic cocaine self-administration leads to prominent dendritic spine attrition in prelimbic cortical pyramidal neurons, working memory deficits, and protracted increases in adrenocortical activity. These studies will also highlight the contingency of cocaine exposure as a key factor in the induction of cocaine-related prefrontal structural and functional alterations. Ben Siemsen (Medical Univ SC) will discuss evidence that reduced dendritic spine density in layer II/III pyramidal neurons of the prelimbic cortex 2 hours after the end of cocaine self-administration positively correlates with profound ERK, CREB, Glun2A/B dephosphorylation and increased activation of the tyrosine phosphatase, STEP. These data suggest a transient hypofrontality during early withdrawal from cocaine. Shannon Gourley (Emory Univ) will address evidence that stress hormones and cocaine commonly regulate cellular structure within the orbitofrontal prefrontal cortex, resulting in failures in goal-directed decision-making and consequently, maladaptive habits. Her group has accordingly targeted molecular regulators of cytoskeletal signaling events to rescue goal-directed action selection strategies. Bob Wheeler (Marquette Univ) will discuss how aversion-induced reductions in ventral striatal dopamine signaling create a terminal environment in which cortical output is more likely to promote stress-induced behaviors, like drug seeking. Together these studies indicate that stress in response to cocaine self-administration drives drug-seeking and PFC-NAc neuroadaptations.

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Poster Abstracts

SUNDAY, JANUARY 24 • 3:30 PM–4:30 PM • PEAK 1–4

SU1. Generation of Ca2+-independent CaMKII activity by nitric oxide

Steven Coultrap, Vincent Zaegel, Ulli Bayer*

Ca2+/calmodulin-dependent protein kinase II (CaMKII) and nitric oxide (NO) have both been implicated as mediators of synaptic potentiation and depression, as well as cell death. The ability of CaMKII to generate Ca2+-independent (autonomous) activity plays an important role in both its physiological and pathological functions in the brain. This autonomous activity is traditionally induced by autophosphorylation of Thr-286 (in the α isoform) or Thr-287 (in the β isoform). Here we show that similar albeit lower level of autonomous activity can be induced by nitrosylation of neighboring cysteine residues (Cys-280/289). In addition to inducing activity, nitrosylation of these residues also interacts with phosphorylation-dependent CaMKII regulation CaMKII nitrosylation reduces subsequent T286 phosphorylation. Also, while T286-generated autonomoy promotes subsequent phosphorylation of the inhibitory sites T305/306, nitrosylation-generated autonomy does not. Thus, while nitrosylation causes a lower level of autonomous activity, it also prevents the T305/306 phosphorylation that uncouples autonomous CaMKII from further stimulation by Ca2+/CaM. This crosstalk between nitric oxide and CaMKII signaling likely plays a role in neurotoxicity as a selective inhibitor of CaMKII reduces neuronal cell death induced by either excitotoxic glutamate or by direct application of nitric oxide donors.

SU2. RGS14 binds and colocalizes with Rap2 to regulate PC12 cell neurite outgrowth

Katherine Squires, Feng-jue Shu, Christopher Vellano, Mary Rose Branch, John Hepler*

G protein coupled receptors direct many aspects of synaptic signaling and plasticity in the central nervous system, and their "off rate" is mediated by the regulators of G protein signaling (RGS). Some RGS proteins, such as RGS14, are multifunctional and bind additional signaling proteins. RGS14 is a brain protein whose expression is limited to the enigmatic CA2 area of the hippocampus. Under typical conditions, Shaffer collateral input to

the CA2 neurons does not undergo LTP like its neighbor CA1 neurons. However, a knockout of RGS14 rescues this suppression of LTP and enhances hippocampal-based learning and memory. The mechanisms by which RGS14 mediates suppression of LTP and learning is unknown, but several small G proteins related to LTP, H-Ras and Rap2A, are reported RGS14 binding partners. Our previous work has shown that active H-Ras-GTP, a well-characterized facilitator of LTP, complexes and colocalizes with RGS14, and that the RGS14:H-Ras-GTP complex stimulates neurite outgrowth in PC12 cells. Here we examine the functional effects of Rap2 interactions with RGS14. We find that active Rap2-GTP forms a stable complex with RGS14 and Gi1, and BRET analysis reveals that Rap2A:RGS14 complexes are regulated by Gi in live cells. ICC shows that RGS14 is recruited to the membrane by activated Rap2. Finally, neurite outgrowth in PC12 cells is inhibited by co-expression of RGS14 and Rap2, consistent with Rap2's characterized inhibition of spine growth and potentiation in hippocampal cells. While the definitive mechanism of RGS14-mediated suppression of synaptic plasticity and learning remains incomplete, here we describe evidence for the possible involvement of a specific RGS14:Rap2A signaling complex.

SU3. Behavioral phenotyping in ankyrin 3 knockout mice

Daniel Petrus, Marisa Moret*

Bipolar disorder (BD) is a mental illness characterized by alternating episodes of mania and depression. BD affects nearly 3% of the US adult population and is associated with a high rate of suicide. Genome-wide association studies have strongly implicated the Ankyrin 3 (ANK3) gene as a risk factor for BD in patient populations. Previous reports have observed altered behavior in ANK3 –/– mutant mice, but not in ANK3 +/– mutant mice. In the present study we used an automated apparatus to test ANK3 function in relation to behavior. We tested mice in the open field, light-dark box, and social interaction tests. Results show significantly altered exploratory locomotion and social interaction time between –/– ANK3 homozygotes and +/– heterozygotes in a bimodal pattern compared to WT mice. In all tests –/– ANK3 homozygotes exhibited a significant reduction in exploratory activity with less social engagement while +/– heterozygotes exhibited a significant increase in exploratory activity with increased social engagement. This would indicate a reduced level of anxiety in +/– heterozygotes compared to –/– ANK3 homozygotes and WT mice. The pathogenesis of BD is poorly understood and this study may shed light into the possible use of ANK3 mice in modeling mental illness.

SU4. Inhibition of POMC neuron activity by mu opioid receptors overshadows pre-synaptic disinhibition through GABAergic synapses

Philip Fox, Reagan Pennock, Shane Hentges*

Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC) are regulated by mu opioid receptors (MORs) which reside in either the somato-dendritic compartment of the POMC neuron (post-synaptic) or axon terminals of upstream neurons (pre-synaptic). Activation of pre-synaptic MORs predominantly inhibits the release of GABA onto POMC neurons, potentially increasing excitability through disinhibition, while activation of post-synaptic MORs directly inhibits neuronal activity. Furthermore, the dose-response of pre-synaptic MORs is left-shifted compared to post-synaptic MORs such that lower concentrations of MOR agonist selectively activate pre-synaptic MORs. In order to determine if there is a point at which pre-synaptic disinhibition predominates we tested the effect of a range of MOR agonist concentrations on POMC neuron activity. To measure POMC neuron activity non-invasively, we used intracellular Ca2+ as a surrogate for action potential firing by expressing the genetically encoded Ca2+ indicator GCamp6F in POMC neurons. The action of MOR agonists on POMC neuron excitability was predominated by direct post-synaptic inhibition, even at lower concentrations which favor pre-synaptic inhibition of GABA release. Direct inhibition of ionotropic GABAergic neurotransmission by blocking GABA-A receptors with bicuculline caused a modest increase (~50%) in POMC neuron activity in only a sub-set of neurons (15-20%). Blockade of glutamatergic transmission had no effect on POMC neuron activity. In conclusion, the predominant effect of MOR agonists on POMC neurons is to silence somatic excitability even at sub-maximal concentrations. GABA inputs onto POMC neurons modulate excitability in a subset of neurons while glutamatergic inputs are not explicitly required for baseline excitability.

SU5. Monosynatic inputs to ventral tegmental area glutamate neurons

Carlos Mejias-Aponte, Brenda Garicia Iglesias, David Barker, Steven Zhang, Marisela Morales*

Glutamate neurons are one of the three major cell types of the ventral tegmental area (VTA). These neurons express vesicular glutamate transporter 2 (VGluT2), a marker of glutamate neurotransmitting neurons. Like VTA dopamine and GABA, glutamate neurons send forebrain afferents to brain networks involved in psychiatry disorders including schizophrenia and addiction. To better understand the function of VTA glutamate neurons, we set

to investigate their afferents. Using a transgenic mouse line that expresses Cre under the regulation of the VGluT2 promoter, we targeted VGluT2-expressing VTA neurons for monosynaptic tract-tracing using the modified pseudorabies technique. Specifically, VGluT2::Cre mice were injected with adenoviral vectors into the VTA to selectively express an avian cognate receptor, TVA, a mammalian rabies glycoprotein (RG), and the fluorescent reporter mCherry in VTA VGluT2 neurons. Three weeks after, a rabies vector modified with an avian glycoprotein and the fluorescent reporter green fluorescent protein was injected into the VTA. The initial "starter" neurons from which afferents were identified from were delineated by co-expression of green fluorescent protein and mCherry. The neurons monosynaptically projecting to VTA VGluT2 neurons were delineated by expression of green fluorescent protein alone. Approximately one week after the rabies vector was delivered, brains were collected. Retrogradely-labeled neurons were mapped throughout the brain. Because of the ubiquitous expression of VGluT2 neurons in area surrounding the VTA, control injections were also made in a number of proximal regions including the suprammamillary, red nucleus, and interpeducular nucleus. Ongoing experiments are aimed to verify major inputs to VGluT2-VTA neurons using anterograde tracing.

SU6. Characterizing Fos-expressing neuronal ensembles in the nucleus accumbens after amphetamine sensitization in rats

Rebecca Fallon, F. Javier Rubio, Bruce Hope*

Our lab has previously shown that conditioned drug behaviors, such as sensitization in rats, are mediated by sparsely distributed neurons that express the protein Fos by activation of the cfos promoter. We call these Fos-expressing neurons, which act in concert to regulate behavior, neuronal ensembles. We have confirmed in Long Evans background rats what others have found, that rats will exhibit locomotor sensitization after an acute injection of amphetamine (but not saline) if they have previously had chronic exposure to amphetamine (but not saline). We have also confirmed that this induces an increase in Fos expression in the nucleus accumbens core and shell that is significantly higher than non-sensitized rats (shell: $p = 0.0027$, core: $p = 0.0011$). We are now determining proteins other than Fos that are expressed in the amphetamine sensitization ensemble in order to better understand function and development of this critical ensemble. Canonical work done in mice has indicated that D1R-expressing neurons are predominantly the ones Fos-expressing after glutamaterigic input activation. However, we hypothesize that D2R-expressing neurons in rats are also recruited to our sensitization ensemble, since our drug

exposure and conditioning are done in a novel environment. To prove this, we are looking at mRNA for cfos, D1R and D2R in amphetamine-sensitized animals using the novel technique, RNAscope. We expect to see expression of cfos in both D1R and D2R cell types. We also hypothesize the ensemble activated during sensitization is formed from the same neurons that were chronically activated during the repeated amphetamine exposure of previous conditioning. Because ΔFosB is a long lasting protein that accumulates with chronic activation, we are performing immunohistochemistry for both ΔFosB and Fos to look for co-localization. To dually confirm this co-localization, we are also doing FACS to select ΔFosB positive cells and perform qPCR for cfos mRNA. Together, these results will help determine cellular characteristics and development of neuronal ensembles, specifically those encoding amphetamine locomotor sensitization. These results may shed light on mechanisms of learning in conditioned drug behaviors and create potential targets for therapeutics.

SU7. Effect of cocaine self-administration pattern on reinstatement and corticostriatal activity

Aaron Garcia, Lindsay Yager, Susan Ferguson*

A continuous access to cocaine self-administration paradigm produces a susceptibility to reinstatement of cocaine seeking after an extinction period when a cocaine-associated cue is presented. However, there is evidence that the pattern of drug intake may strongly influence drug-taking even more so than total intake. An intermittent pattern of cocaine intake has previously been shown to increase motivation to take cocaine significantly more than short or long continuous access paradigms. Here, we compared cue-induced reinstatement of cocaine seeking after an intermittent or continuous access paradigm. We found that despite taking less cocaine, intermittent access animals had similar levels of reinstatement compared to continuous access animals. Additionally, intermittent access animals displayed a higher ratio of cocaine seeking during the first day of extinction. It is known that the corticostriatal circuitry is a critical part of the limbic system and underlies many important functions, including motivation, reward, and learning. Dysfunction in corticostriatal signaling has been heavily implicated in drug addiction. We, therefore, are currently examining reinstatement-induced Fos in different cortical populations after continuous or intermittent access self-administration. Additionally, we are examining changes in neuronal activity patterns in the dorsal striatum after intermittent or continuous access cocaine self-administration through the use of 2-photon imaging of GCaMP6.

SU8. Signaling prediction for reward size in rodent medial orbitofrontal cortex during Pavlovian unblocking

Nina Lopatina, Michael McDannald, Brian Sadacca, Geoffrey Schoenbaum*

The orbitofrontal cortex (OFC) has been broadly implicated in the ability to use the current value of expected outcomes to guide behavior. While value correlates have been prominently reported in lateral OFC (lOFC), they are more often associated with more medial areas. Further, recent studies in primates have suggested a dissociation in which the lOFC is involved in credit assignment and representation of reward identity and more medial areas are critical to representing value. We have recently used unblocking to test more specifically what information about outcomes is represented by OFC neurons. Consistent with the proposed dichotomy between the lateral and medial OFC (mOFC), we found relatively little linear value coding in the lOFC. Here we have repeated this experiment, recording in the mOFC, to test whether such value signals might be found there. The current study examined changes in mOFC neural activity using single-unit electrophysiological recording, measuring activity during a Pavlovian unblocking procedure that assesses excitatory and inhibitory cue learning driven by upshifts or downshifts in expected reward size. We have recorded hundreds of mOFC neurons during the task. We found that mOFC neurons acquired responses to these cues, however these responses did not signal value across cues. Cue-related activity is regulated by the unblocking paradigm used, with findings of differential firing to blocked, size-downshift and size-upshift cues in individual neurons. A more comprehensive analysis of these neural data will be presented.

SU9. A novel method for isolation and quantification of human peripheral cannabinoid receptors

Ariel Ketcherside, Christa McIntyre, Francesca Filbey*

9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis, binds to cannabinoid receptor 1 receptors (CB1R) in the brain. This is the primary mechanism that leads to a cascade of events resulting in the rewarding effects of cannabis. Thus, determining the relationship between CB1Rs and reward response to cannabis is important for identification of risk to cannabis use disorders (CUDs). To date, associations between CB1R expression and function and cannabis use disorders have only been available via PET imaging with a novel CB1 radioligand. We aimed to test whether CB1R expression and function can also be measured via peripheral human lymphocytes. To that end, we developed a protocol with which we isolate human CB1Rs and quantify receptor density in relation to overall protein concentration via enzyme-linked immunosorbant assay (ELISA). We collected

peripheral lymphocytes from participants and quantified both total protein concentration (via Pierce BCA Protein Assay), and CB1 protein (via ELISA Assay from MyBioSource, item #MBS2503052). We tested three different isolation buffers to determine the highest and most consistent protein yield. Normalized CB1:total protein ratios were calculated to determine concentration of CB1Rs in whole blood. This work shows that baseline levels of CB1Rs are sufficient for quantification via ELISA assay without amplification. Our method holds potential as an efficient, non-invasive tool for measuring CB1R signaling in vivo that could advance the determination of risk for CUDs.

SU11. Human postmortem brain collection and the study of PTSD

Michelle Mighdoll, Amy Deep-Soboslay, Rahul Bharadwaj, Joel Kleinman, Thomas Hyde*

The Lieber Institute for Brain Development (LIBD) began collecting postmortem human brains from the Maryland Office of Chief Medical Examiner in September 2012. The collection of postmortem human brains from large medical examiners' offices provides a unique resource for the rapid accrual of samples from normal controls and a diverse population of psychiatric disorders, encompassing all age, sex, and racial boundaries. Since inception, of 1,210 families contacted, the consent success rate (of reachable next-of-kins) is 71.5% (n=721). Of the cases collected, 65.6% are male (M) and 34.4% are female (F), with equal rates of donation (~56%). Our collection is comprised of cases across the lifespan, with the largest cohorts between 36-50 and 51-65 years of age. Additionally, of the referrals, while 75.99% of Caucasian (C) families consented, 60.47% of all African-American (AA) referrals also agreed to postmortem human brain donation, a rate that refutes the belief that African-Americans are unwilling to participate in biomedical research studies. All psychiatric and neurological diagnoses are confirmed by two board-certified psychiatrists according to DSM-V criteria. The LIBD has the largest collection in the world of post-mortem human brains with a history of Post-Traumatic Stress Disorder (PTSD) (n=55; 80% C, 20% AA; 63.6% M, 36.4% F; mean age = 45.7 yrs). Of these, n=18 (100% M) had a history of military combat, and n=37 (54% F, 46% M) PTSD patients had a history of domestic (sexual and/or physical) abuse. The military combat cohort and domestic abuse cohorts had similar rates of depression (66.7% and 54.1%, respectively). However, the comorbid incidence of Bipolar Disorder diagnoses was seen only in patients in the domestic cohort (n=16, or 43.2%). Additionally, while both the military combat and domestic cohorts had similar rates of alcohol and/or polysubstance abuse (~38%), 11 of the 16 patients with a history of Bipolar Disorder had a history of substance abuse.

SU12. TrkB regulates behavioral vulnerabilities to adolescent stress hormone exposure

Elizabeth Barfield, Kyle Gerber, Kelsey Zimmermann, Shannon Gourley*

In humans and rodents, stress regulates reward-related decision-making. For instance, prolonged stressor and corticosteroid exposure impair the ability of rodents to select actions based on their consequences. However, neurodevelopmental factors remain largely uncharacterized, despite evidence suggesting that adolescents may be particularly vulnerable to stressors. In this study, behavioral pharmacology, intracranial viral-mediated gene transfer, and instrumental conditioning techniques were used to test the hypothesis that adolescence is a period of vulnerability to the long-term influence of corticosterone (CORT) on goal-directed decision making and depression-like amotivation. Subchronic CORT exposure in early adolescence, but not in adulthood, resulted in a long-lasting bias towards habit-based response selection in instrumental contingency degradation, but not reinforcer devaluation, tests. This deficiency is reminiscent of hippocampal damage and, accordingly, adolescent CORT exposure up-regulated the expression of truncated receptor tyrosine kinase (trkB) in the ventral hippocampus and downstream amygdala. Viral-mediated over-expression of truncated trkB recapitulated behavioral deficiencies caused by CORT, including depression-like amotivation. Conversely, the trkB agonist 7,8-dihydroxyflavone (7,8-DHF) rescued CORT-induced decision-making deficits and had antidepressant-like consequences that were durable, detectable well after the treatment period. Interestingly, mice exposed to CORT during the late adolescent period were relatively CORT-resilient. These findings suggest that trkB activity within an amygdalo-hippocampal neurocircuit regulates goal-directed decision-making and reward-related motivation. This network may be particularly vulnerable to stress hormone exposure, especially in early adolescence, but CORT-induced behavioral deficiencies in adulthood can be blocked by trkB stimulation during adolescence.

SU13. Environmental experience rescues spatial discrimination and gene expression patterns in offspring following prenatal toll-like receptor 4 activation

Amanda Kentner, Erika Queiroz, Molly MacRae, Antoine Khoury*

Stemming from evidence that environmental enrichment (EE) can rescue the brain from early-life psychogenic stressors, we are interested in how the various components of enrichment (i.e. novelty, physical space, social engagement) may contribute to the reversal of the behavioral and neural disruptions that accompany prenatal inflammation. In the present study, standard housed female

Sprague-Dawley rats were administered either the inflammatory endotoxin lipopolysaccharide (LPS; 100ug/kg) or pyrogen-free saline (equivolume) on gestational day 15. On postnatal day 50, offspring were randomized into one of three conditions: EE (groups of 3-4 animals housed in a large multi-level cage with toys, tubes and ramps), Colony Nesting (CN; groups of 4 animals socially-housed in a larger style cage), or Standard Care (SC; animals pair-housed in standard cages). Six weeks later we scored their level of social engagement and performance in the object-in-place task. Afterwards we collected hippocampus and prefrontal cortex (n = 7-9) and evaluated these structures for excitatory amino acid transporter (EAAT) 2, brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (TrkB) gene expression (normalized to GAPDH) using qPCR methods. Overall, we show that gestational inflammation downregulates these genes critical to cell functioning and plasticity, which may underlie the pathogenesis of neurodevelopmental disorders such as schizophrenia and autism. Additionally, we observed disruptions in both social engagement and spatial discrimination. Importantly, behavioral and neurophysiological effects were reversed in an experience dependent manner. Given the evidence that behavioral and neural changes in offspring may be associated with infection during pregnancy, these data have compelling implications for the reversibility of immune activation early in life.

SU14. Effects of risperidone treatment in adolescence on adult neuroinflammation and DA receptors in a developmental model of schizophrenia

Moazam Cheema, Jasbeer Dhawan, Anat Biegon*

Maternal infection during pregnancy is an established environmental risk factor for developing schizophrenia in the offspring. Neurodevelopmental animal models of schizophrenia have provided strong support for the role of in utero exposure to maternal viral infection in causing neuroinflammation. Also it is well recognized that dopamine receptor activity in certain regions of the brain has a role in pathogenesis and treatment of this disease. We recently showed that schizophrenia-relevant behavioral and brain structural abnormalities emerging in adult offspring of dams treated with the viral mimic polyriboinosinic-polyribocytidilic acid (poly I:C) are prevented by administration of the atypical antipsychotic drug risperidone in peri-puberty. In the current study, we aimed to assess the efficacy of risperidone in downregulating dopamine receptor density in offspring of pregnant mice exposed to poly IC. In addition we studied the effects poly IC on mice not give risperidone. The dopamine receptor density was measured in all regions of the brain of female mice sacrificied at postnatal day 48, using quantitative 124 ul [3H] Raclopride autoradiography. [3H] Raclopride binding was significantly increased in the Amygdala, CA1,

CA3, dentate gyrus, cingulate and the frontal cortex of adolescent mice given Poly I:C compared to those given saline. These increases were not observed in Poly I:C offspring administered at peri puberty with Ris. We conclude that administration of dopamine does have a significant effect in decreasing the density of dopamine receptors in certain regions of the brain in mice exposed to maternal infection in utero. This suggests the possibility that anti-inflammatory agents may prove efficacious in future pharmacological interventions aimed at preventing the deleterious effects of in utero infections on brain neurochemistry.

SU15. Changes in synaptic plasticity and the development of an autistic phenotype following kainate induced early life seizure

Paul Bernard, Anna Castano, Timothy Benke*

Many individuals with autism spectrum disorder (ASD) have a history of early life seizures (ELS) and 30% of children with ASD and intellectual disability (ID) have epilepsy. Clinically the influence of ELS on causation and severity of ASD remains correlative. We probed the behavioral consequences of a single episode of kainic acid induced ELS (KA-ELS) on a Sprague Dawley genetic background. We find multiple behavioral changes consistent with an autistic phenotype in adult KA-ELS rats: abnormal social behavior, changes in repetitive behaviors in a social setting and restricted interest. We also detect changes in synaptic plasticity (reduced long term potentiation (LTP) and enhanced long term depression (LTD)) that may underlie these behavioral abnormalities. Using pharmacological intervention, we can rescue abnormal synaptic plasticity. Reduced LTP can be normalized using an mGluR antagonist (MTEP) and enhanced LTD can be normalized using a voltage gated calcium channel inhibitor (isradipine). This suggests that the ASD phenotype may be rescued using similar pharmacological intervention in vivo. Current ASD models are almost exclusively made in the mouse. Rats have a richer social repertoire, thus are preferable to model social behavior and communication. Therefore our rat model of KA-ELS will allow a more thorough analysis of social deficits in ASD.

SU16. PI3K-MTOR hyperactivity contributes to cognitive deficits following a single generalized seziure

Anne Anderson, Heather Born, Wai Ling Lee, Angela Carter*

Epilepsy is characterized by seizures and comorbidities that include deficits in cognition. Previous studies show that seizures induce learning and memory deficits and hyperactive phosphoinositide 3-kinase (PI3K) and mechanistic target of rapamycin (mTOR) signaling, yet whether hyperactivation of

PI3K-mTOR underlies behavioral deficits following a seizure remains unclear. We evaluated the effects of a single generalized seizure on PI3K-mTOR signaling, dendritic structure, and behavior and tested whether inhibition of PI3K would restore the behavioral deficits. Rats were treated with saline (control; CTL) or pentylenetetrazole (PTZ) to induce a generalized seizure. Hippocampus was harvested at 1, 3, and 24 hours and western blotting for phospho (P) AKT at threonine 308 and P-S6 at serine 240/244 was performed. Dendritic spines were assessed using Golgi staining. We tested contextual and associative short-term memory (STM) using the Fear Conditioning (FC) assay in CTL and PTZ animals treated with vehicle or the PI3K inhibitor, wortmannin (Wort). P-AKT and P-S6 levels were significantly elevated at 1- and 3-hours and back to baseline levels at 24-hours post PTZ relative to CTL ($p<0.01$). Analyses of spines revealed a significant increase in length-to-width ratio and a decrease in mushroom spines in PTZ compared to CTL ($p<0.05$). In the FC task, PTZ animals had significant deficits in contextual ($p<0.05$) and associative ($p<0.001$) STM relative to CTL. Wort restored the STM contextual deficits ($p>0.05$), and partially restored the STM associative impairments ($p<0.05$). Our findings reveal that a single generalized seizure is associated with signaling pathway alterations, changes in spine maturation, and deficits in short-term memory. Our studies also show that inhibition of PI3K signaling restores seizure-induced contextual memory deficits. Studies are underway to evaluate whether PI3K-mTOR dysregulation underlies the altered dendritic morphology in this model.

SU17. Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression

Olaf Paulson*, Anders Jorgensen, Peter Magnusson, Lars G. Hanson, Thomas Kirkegaard, Helene Benveniste, Hedok Lee, Claus Svarer, Jens D. Mikkelsen, Anders Fink-Jensen, Gitte Moos Knudsen, Tom G. Bolwig, Martin Balslev Jorgensen

Objective: To investigate the role of hippocampal plasticity in the antidepressant effect of electroconvulsive therapy (ECT). *Methods:* We used Magnetic Resonance (MR) Imaging, including Diffusion Tensor Imaging (DTI) and proton MR Spectroscopy (1H-MRS) to investigate hippocampal volume, diffusivity and metabolite changes in 19 patients receiving ECT for severe depression. Other regions of interest included the amygdala, dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and hypothalamus. Patients received a 3T MR scan before ECT (TP1), one week (TP2) and four weeks (TP3) after completion of the ECT series. *Results:* Hippocampal and amygdala volume increased significantly at TP2, and continued to be increased at TP3. DLPFC exhibited a transient volume reduction at TP2. DTI revealed a reduced

anisotropy and diffusivity of the hippocampus at TP2. We found no significant post-ECT changes in brain metabolite concentrations, and we were unable to identify a spectral signature at ≈1.30 ppm previously suggested to reflect neurogenesis induced by ECT. None of the brain imaging measures correlated to the clinical response. *Conclusions:* Our findings show that ECT causes a remodelling of brain structures involved in affective regulation, but due to their lack of correlation with the antidepressant effect, this remodelling does not appear to be directly underlying the antidepressant action of ECT.

SU18. Short general anaesthesia induces prolonged changes in gene expression in the mouse hippocampus

Tulen Pekny, Daniel Andersson, Ulrika Wilhelmsson, Marcela Pekna, Milos Pekny*

While essential for many medical procedures, general anaesthesia can negatively affect memory and cause persistent learning deficits. The long-term molecular changes in the CNS constitute an important aspect of general anaesthesia, but little is known about to what extent they are affected by anaesthesia duration. We evaluated the effects of short duration (20 min) general anaesthesia with isoflurane or avertin on the expression of selected genes in the mouse hippocampus 1 and 4 days after anaesthesia. Male mice were subjected to (i) 20 min of avertin anaesthesia, or (ii) 20 min of isoflurane anaesthesia, or (iii) no anaesthesia. 1 and 4 days after anaesthesia, gene expression in the hippocampus was determined with reverse transcription quantitative real-time PCR. We found that anaesthesia led to the upregulation of six genes: Hspd1 (heat shock protein 1), Plat (tissue plasminogen activator), a protein promoting blot clot breakdown and synaptic remodeling/plasticity, and Npr3 (natriuretic peptide receptor 3) were upregulated 1 day after anaesthesia, whereas Thbs4 (thrombospondin 4), a regulator of protective astrogenesis, was upregulated 4 days after anaesthesia. Syp (synaptophysin), a marker of synaptic remodeling, and Mgst1 (microsomal glutathione S-transferase 1), a xenobiotic detoxifier, were upregulated at both time points. Hspd1, Mgst1 and Syp expression was increased regardless of the anaesthetic used, Npr3 and Plat were increased only in mice exposed to avertin, and Thbs4 was upregulated only after isoflurane induced anaesthesia. Our finding that Hspd1 levels are elevated in the hippocampus 24 hours after 20 min long isoflurane anaesthesia indicates a persisting stress response in this part of the brain connected with learning and memory, at least for a full day after surgery. This study shows that some of the effects of short general anaesthesia on gene expression in the mouse hippocampus persist for at least 4 days.

SU19. Peripheral and central deficits contributing to manual function in patients with Type II Diabetes

*Stacey Gorniak**

Pathology induced by metabolic disorders, eg. Type II Diabetes (T2D), has recently been linked to both sensory and motor deficits of the hands in the absence of formal clinical diagnosis of peripheral neuropathy. Additional studies have demonstrated mild cognitive impairment (MCI) in T2D patients, which also plays a role in one's loss of ability to successfully perform basic manual self-care activities. In order to investigate the contribution of sensory and cognitive dysfunction on manual function, our lab has undertaken two specific projects to elucidate the effects of each system dysfunction on manual motor function. In the first project, the effects of impaired tactile function on manual function in patients with T2D was compared to age- and sex- match control subjects. Sensory and motor function of the hand was assessed in both groups prior to and after the administration of a series of median nerve blocks. Monofilament testing confirmed that tactile function in both WB and EB conditions in the control group were comparable to baseline tactile function in the T2D group. Timed clinical evaluations indicated that baseline function of the T2D group was similar to that of the control group under both anesthesia condition; whereas kinetic analyses revealed T2D-specific features of manual disability persisting in all tested conditions versus controls. In the second project, MCI, particularly in the domain of working memory was found in the T2D group versus controls. When T2D patients were asked to perform manual activities in conjunction with working memory tasks (dual-tasking), manual performance declined significantly versus controls while cognitive performance remained consistent. Overall, our data are the first to suggest (1) deficits beyond tactile dysfunction contributing to manual disability in T2D, and (2) attentional allocation shifts in T2D patients that contribute to manual motor errors as compared to controls.

SU20. Multiple Sclerosis patients show less flexible reallocation of cognitive resources during dual-task walking: a mobile brain/body imaging (MoBI) study

Elizabeth Chernyak, John J. Foxe, Brenda R. Malcolm, Sophie Molholm, John S. Butler, Pierfilippo De Sanctis*

Multiple sclerosis (MS) is characterized by motor and cognitive impairments, which are typically assessed as independent functions. Yet evidence supports significant motor-cognitive coupling in MS. One approach for studying motor-cognitive coupling is dual-task walking tests where individuals perform a task while walking. We employed an EEG-based Mobile Brain-Body Imaging

(MOBI) system, which combines foot-force sensor data with event-related potential (ERP) recordings to monitor gait, cognitive performance and brain activity. We predicted that MS patients have deficits in redistributing cortical resources across tasks. Ten MS patients (8 females, age = 31.1) and nine healthy controls (HC, 5 females, age = 27.1) were tested using behavioral and ERP measures associated with a Go/No-Go response inhibition task while participants sat still (single-task load) and walked on a treadmill (dual-task load) to assess the effect of motor load on cognition. Gait was measured with and without participants performing the inhibitory task, thereby assessing the effect of cognitive load on gait. We found improvement in accuracy during dual-task load in HC, but not in MS patients. We utilized the N2 and P3 components, two established measures that are evoked when participants withhold their response to No-Go stimuli and found changes in ERPs: HC showed a decrease in N2 amplitude and an earlier P3 peak during dual-task load, while MS participants showed small but emerging reduction during the N2 time period. Gait analysis showed that while the HC group took fewer, longer strides during dual-task load, there was minimal change in stride time in the MS group. Differences suggest that unlike HC, who reallocate cortical resources to optimize dual-task performance, MS patients are unable to modulate their cortical and gait activity to compensate for increased task load. Our preliminary results provide insight into the neural bases of impaired motor-cognitive coupling that add to our knowledge about mobility limitations in MS.

SU21. Nicotinic acetylcholine receptors in inflammation and immunity—multiple sclerosis

Ronald Lukas*, Qiang Liu, Linda Lucero, Alain Simard, Paul Whiteaker, Barbara Morley, Fu-Dong Shi

Acetylcholine (ACh) has been implicated in modulation of immune system as well as nervous system function. This reflects primordial roles of ACh in chemical signaling early in the evolution of life forms before its specialization as a neurotransmitter. Our earlier work defined nicotinic ACh receptor (nAChR) subunit gene expression patterns in mouse and human immune system cells and demonstrated nicotinic suppression of T cell development and differentiation. This suggested that nicotine could have immunosuppressive and anti-inflammatory effects. Further studies using experimental autoimmune encephalomyelitis (EAE) in mice as a model for multiple sclerosis (MS), coupled with exploitation of a range of nAChR subunit knock-out mice, suggests that different nAChR subtypes play disease exacerbating or protective roles in different stages in disease progression and recovery, building upon initial observations that nicotine protects against EAE.

Our studies have been extended to define nAChR subunit mRNA levels in many different immune cell types in the periphery or infiltrating into the brain, including T cells, B cells, dendritic cells, peripheral macrophages, and brain microglia, finding remarkably widespread expression that changes with disease stage and cell microenvironment. Results continue to support the hypotheses: (1) that peripheral immune cell nAChR containing #alpha#9 subunits (#alpha#9*-nAChR) play disease initiating/exacerbating roles as revealed by their attenuation in #alpha#9 subunit knockout mice or via nicotine's antagonism of #alpha#9*-nAChR, (2) that there are neuroprotective roles of #alpha#7-nAChR, probably expressed by brain cell types, and made particularly evident in #alpha#7/#alpha#9 double knock out mice, and (3) that #beta#2*-nAChR are involved in recovery from EAE, which is absent in #beta#2 subunit knock out mice. Adoptive transfer studies support these hypotheses, and additional nAChR subunits and subtypes also could play roles. Importantly, nAChR gene expression profiles change with disease stage and for a given immune cell type depending on whether it is in the periphery or has entered the central nervous system. Taken together, our results suggest that modulation of disease-exacerbating or disease-ameliorating inflammatory and/or immune processes is possible through therapeutic approaches targeting nicotinic signaling. nAChR expression also could be used a s abiomarker for disease stage. There are exciting possibilities that improved treatment of hyperimmune and inflammatory disorders such as MS, lupus and arthritis, and even stroke, brain cancer or neurodegenerative diseases, could result from nAChR modulation.

SU22. Attenuation of reactive gliosis slows down progression of amyotrophic lateral sclerosis (ALS) in mice

Roy Pekny, Ulrika Wilhelmson, Carina Sihlbom, Peter Smith, Harald Jockusch, Marcela Pekna, Jörg Bartsch, Milos Pekny*

While essential for many medical procedures, general anaesthesia can negatively affect memory and cause persistent learning deficits. The long-term molecular changes in the CNS constitute an important aspect of general anaesthesia, but little is known about to what extent they are affected by anaesthesia duration. We evaluated the effects of short duration (20 min) general anaesthesia with isoflurane or avertin on the expression of selected genes in the mouse hippocampus 1 and 4 days after anaesthesia. Male mice were subjected to (i) 20 min of avertin anaesthesia, or (ii) 20 min of isoflurane anaesthesia, or (iii) no anaesthesia. 1 and 4 days after anaesthesia, gene expression in the hippocampus was determined with reverse transcription quantitative real-time PCR. We found that anaesthesia led to the upregulation of six genes: Hspd1 (heat shock protein 1), Plat (tissue plasminogen activator), a protein promoting blot clot breakdown and synaptic remodeling/plasticity, and Npr3

(natriuretic peptide receptor 3) were upregulated 1 day after anaesthesia, whereas Thbs4 (thrombospondin 4), a regulator of protective astrogenesis, was upregulated 4 days after anaesthesia. Syp (synaptophysin), a marker of synaptic remodeling, and Mgst1 (microsomal glutathione S-transferase 1), a xenobiotic detoxifier, were upregulated at both time points. Hspd1, Mgst1 and Syp expression was increased regardless of the anaesthetic used, Npr3 and Plat were increased only in mice exposed to avertin, and Thbs4 was upregulated only after isoflurane induced anaesthesia. Our finding that Hspd1 levels are elevated in the hippocampus 24 hours after 20 min long isoflurane anaesthesia indicates a persisting stress response in this part of the brain connected with learning and memory, at least for a full day after surgery. This study shows that some of the effects of short general anaesthesia on gene expression in the mouse hippocampus persist for at least 4 days.

SU23. JZP-110: A dopamine-norepinephrine reuptake inhibitor (DNRI) with robust wake-promoting effects and low abuse potential

Lawrence Carter, Michelle Baladi, Jed Black*

Excessive sleepiness, a clinical hallmark of narcolepsy, is present in all patients and is often the first presenting symptom at onset. Although there are several FDA-approved medications to treat symptoms of narcolepsy, current treatments for excessive sleepiness have limitations. Here, we describe the development of JZP-110, a phenylalanine-derived, second-generation wake-promoting agent that is a dopamine-norepinephrine reuptake inhibitor (DNRI). Radioligand binding studies have shown that JZP-110 is a low potency reuptake inhibitor at dopamine (IC50=2.9 μM) and norepinephrine (IC50=4.4 μM) transporters. Clinically, a Phase 2b study showed that 12 weeks of once daily treatment with JZP-110 significantly increased the ability of patients with narcolepsy to stay awake on each of the five trials of the Maintenance of Wakefulness Test across 9 hours throughout the day with 93% percent of patients reporting improvement ($p<0.0001$ compared to placebo). However, in contrast to other drugs that have robust wake-promoting effects such as d-amphetamine, JZP-110 did not promote norepinephrine release in rat brain synaptosomes, did not produce rebound hypersomnia in three mice strains, and did not produce significant conditioned place preference in rats. Furthermore, and in contrast to cocaine, JZP-110 did not maintain self-administration in rats. Together, these data suggest that JZP-110 has a distinct mechanism of action with limited abuse potential. The most common adverse events versus placebo in the Phase 2b study were insomnia (22.7% vs 8.2%), headache (15.9% vs 10.2%), nausea (13.6% vs 6.1%), decreased appetite (13.6% vs 0%), diarrhea (11.4% vs 6.1%), and anxiety (11.4% vs 0%). In summary, these observations suggest that once

daily dosing with JZP-110 might have therapeutic potential for the treatment of excessive sleepiness and impaired wakefulness in narcolepsy. Phase 3 studies of JZP-110 in patients with narcolepsy or obstructive sleep apnea are ongoing.

SU24. Improving therapeutic efficacy on Alzheimer's pathology using transcranial MRI-guided focused ultrasound

Kelly Markham-Coultes, Sonam Dubey, Danielle Weber-Adrian, Jessica F. Jordão, Alison Burgess, Tiffany Scarcelli, Emmanuel Thévenot, Sebastian Kügler, Kevin D. Foust, Brian K. Kaspar, JoAnne McLaurin, Meaghan O'Reilly, Kullervo Hynynen, Isabelle Aubert*

Improve efficacy of immunotherapy and non-invasive gene delivery to the brain in a mouse model of Alzheimer's disease using transcranial MRI-guided focused ultrasound (MRIgFUS). We used a transgenic mouse model of amyloidosis and non-transgenic mice. Animals were anesthetized and secured in the FUS system. The cortex and hippocampus were located by MRI and targeted with the ultrasound. MRI images were capture to detect the increase in permeability of the blood-brain barrier due to the interaction of FUS with intravenous phospholipid microspheres. Therapeutics (i.e. antibodies) and reporter genes carried by adeno-associated viruses (AAVs) were injected intravenously, with and without MRIgFUS treatments. Outcome measures included the quantification of antibodies and AAVs in the brain, amyloid-beta pathology, neurogenesis, and behaviour. MRIgFUS immunotherapy significantly reduced amyloid pathology, increased neurogenesis, and improved cognitive function. Our studies also demonstrated that MRIgFUS alone contributed to these effects. We found that MRIgFUS increases microglia and astrocytic activation, which contributed to the internalization of amyloid beta. Delivery of AAV1/2, AAV6, AAV9 was localized to MRIgFUS targeted areas. Strategies utilizing specific neuronal promoters resulted in the expression of reporter genes in the brain and prevented peripheral expression. The delivery of immunotherapeutics and their efficacy was increased by MRIgFUS. Brain plasticity and cognitive functions were enhanced. Gene delivery was improved using MRIgFUS which could fulfill the goal of delivering therapeutic transgenes to diseased brain areas in a non-invasive manner.

SU25. The presence and identity of a companion affects neural responses to group separation in rhesus macaques (Macaca mulatta)

Tamara Weinstein, Simon Cherry, Karen Bales*

Numerous studies identify social support as critical in protecting against the harmful mental and physical health consequences of acute and chronic

stressors, yet it is unclear which types of social relationships are most beneficial or which neurobiological mechanisms are involved. We examined neural responses to separation from the natal group in six 2-year-old rhesus macaques (Macaca mulatta) using positron emission tomography (PET). Prior to separation, we conducted 15 ten-minute observations per subject to assess affiliative peer preferences (friendships). During separation, subjects were either housed alone, with grated access to a familiar (but not preferred) peer from the natal group, or with grated access to a friend. Subjects experienced each housing condition in a counterbalanced order. Twenty four hours after separation, subjects were injected with 1 mCi/kg [F-18]-fluorodeoxyglucose (FDG), videotaped for a 30-minute conscious uptake period, then anesthetized and scanned using a microPET P4 primate scanner. PET data were co-registered with structural magnetic resonance images. We found greater FDG uptake in the nucleus accumbens in the "familiar peer" condition compared to the "alone" condition (GLM Repeated Measures, $p = 0.02$). In addition, nucleus accumbens activity significantly correlated with the total time the familiar peer spent in proximity to the grate during conscious uptake, as well as with the duration that the subject and familiar peer simultaneously spent in proximity to the grate (both Spearman's rho = 0.83, $p = 0.04$). Interactions between the subject and friend did not predict nucleus accumbens activity. The nucleus accumbens contains a high density of dopaminergic neurons and responds particularly to unanticipated reward. Our data suggest that interacting with the familiar peer may have been unexpectedly rewarding as compared to interacting with the friend, whose social support in a stressful context might have been anticipated.

MO1. The 2.2-angstrom crystal structure of carboxy-terminal region of ataxin-3

*Vladimir Zhemkova, Anna Kulminskayaa, Ilya Bezprozvannya, Meewhi Kim**

An expansion of polyglutamine sequence in ataxin-3 protein causes spinocerebellar ataxia type 3, an inherited neurodegenerative disorder. The crystal structure of the polyglutamine-containing carboxy-terminal fragment of human ataxin-3 was solved at 2.2-Å resolution. The Atxn3 carboxy-terminal fragment including fourteen glutamine residues adopts both random coil and α-helical conformations in the crystal structure. The polyglutamine sequence in α-helical structure is stabilized by intra-helical hydrogen bonds mediated by glutamine side chains. The intra-helical hydrogen-bond interactions between glutamine side chains along the axis of the polyQ α-helix stabilize the secondary structure. Analysis of this structure furthers our understanding of the polyQ-structural characteristics that likely underlie the pathogenesis of polyQ-expansion disorders.

MO2. The role of CSPGs in neuronal differentiation of stem cells from the adult zebrafish brainstem

*Maia Valls, Beatriz Lopez, Rayshell Sands, Martin Oudega, Jeffery Plunkett**

In the mammalian central nervous system (CNS), neurons fail to regenerate their axon after injury due at least in part to the presence of growth-inhibitory molecules such as chondroitin sulfate proteoglycans (CSPGs). However, in adult zebrafish (Danio rerio) certain CNS neuron populations regenerate their axon after an injury in the presence of CSPGs. To investigate the axonal growth response of zebrafish brainstem neurons in the presence of CSPGs, we developed and characterized a unique primary culture system. This heterotypic culture contains neurons, glia, and stem/progenitor cells. Our preliminary in vitro data showed the presence of distinct populations of stem cell-derived neural progenitor cell populations that can differentiate into mature neurons and extend processes into CSPG-rich terrains. In the present study, we investigated a potential role for CSPGs in the differentiation of adult zebrafish brainstem-derived stem cells into neurons. We hypothesized that CSPGs promote the differentiation of stem cells into neurons to enable CNS repair. Using our unique culture system, we examined whether specific concentrations of CSPGs combined with laminin as a growth-promoting substrate play a role in the degree of neuronal differentiation seen after 7 days in culture. Cellular/morphological analysis of CSPG/laminin substrate cultures revealed a more prominent neuronal-like differentiation pattern when compared to a laminin alone substrate condition. Future studies will need to investigate these cellular populations using immunocytochemical and molecular in situ techniques and attempt to gain a better understanding of the roles of CSPGs and stem cells in CNS regeneration as seen in teleost fishes.

MO3. Late mTOR inhibition suppresses established epilepsy in the NS-Pten KO mouse model of cortical dysplasia

Angus Wilfong, Anne Anderson, Lena Nguyen*

Hyperactivation of the phosphatidylinositol 3-kinase (PI3K)–mechanistic target of rapamycin (mTOR) pathway has been demonstrated in humans and animal models of cortical dysplasia (CD) with epilepsy. mTOR inhibition early in epileptogenesis suppresses epileptiform activity (EA) in the neuron subset-specific Pten knockout (NS-Pten KO) mouse model of CD, however, the effects of mTOR inhibition after epilepsy is fully established is unknown. Here, we characterized the progression of epilepsy and mTOR dysregulation with age and evaluated the effects of late mTOR inhibition on EA in NS-Pten KO mice with well-established epilepsy. Video-electroencephalography (VEEG) recordings and western blotting were used to evaluate the progression of EA and mTOR

dysregulation, respectively, in NS-Pten KO and WT mice between postnatal weeks 2 and 9. Antibodies against p-S6 (S240/244) and p-AKT (S473) were used as markers for mTORC1 and mTORC2 activation, respectively. NS-Pten KO and WT mice were treated with rapamycin (10 mg/kg, 5 days/week) starting at postnatal weeks 9 and monitored with VEEG for EA. Western blotting was performed to evaluate the effects of rapamycin on mTORC1 and mTORC2 signaling. Epilepsy worsened with age in NS-Pten KO mice ($p<0.001$) with parallel increases in mTOR dysregulation ($p<0.05$). Rapamycin treatment significantly suppressed EA ($p<0.001$) and increased survival ($p<0.05$) in severely epileptic NS-Pten KO mice compared to untreated controls. At the molecular level, rapamycin treatment suppressed mTORC1 and mTORC2 activation ($p<0.05$).Late mTOR inhibition suppresses severe and established epilepsy in NS-Pten KO mice. These findings reveal a wide window for successful therapeutic interventions with mTOR inhibition in the NS-Pten KO mouse model and further support mTOR inhibition as an effective treatment for late-stage epilepsy associated with CD. Studies are underway to evaluate the effects the dual PI3K/mTOR inhibitor NVP-BEZ235 on epilepsy in NS-Pten KO mice.

MO4. MTOR signaling in oligodendrocyte differentiation during developmental myelination and remyelination

Teresa Wood, Lauren McLane, Stacey Wahl, Isis Ornelas, Aminat Saliu, Angeliki Evangelou, Luipa Khandker*

The pathogenesis of Multiple Sclerosis (MS) includes demyelination, oligodendrocyte death, axonal transection and neuronal degeneration. Some MS lesions spontaneously remyelinate in early stages of the disease, and attempts at remyelination by newly generated oligodendrocytes occur even in chronic inactive lesions. Thus, many aspects of the repair process remain intact even at late stages of the disease. Unfortunately, the majority of MS lesions do not repair. Therefore, stimulation of endogenous remyelination is an important goal for MS patients. The focus of our studies is on how oligodendrocyte differentiation and myelination is regulated during development and following a demyelinating event. We have shown that the mTOR signaling pathway is critical for oligodendrocyte progenitor differentiation and developmental myelination both in vitro and in vivo [1, 2]. The tuberous-sclerosis complex (TSC) is an important intermediary in the PI3K/Akt/mTOR pathway downstream of Akt and upstream of mTOR. Most often thought of as an upstream inhibitor of mTORC1, more recent studies suggest that TSC activates the second mTOR signaling complex, mTORC2. While TSC/mTOR signaling is a clear regulator of developmental myelination, it has yet to be studied in remyelination. Our current studies are focused on the function of TSC/mTOR signaling in remyelination. Utilizing conditional KO (cKO) mice that express

floxed alleles for either TSC or mTOR along with an inducible Cre recombinase transgene specific to oligodendroglia, our studies indicate that oligodendrocyte-specific deletion of either mTOR or TSC results in decreased remyelination efficiency after a focal, demyelinated lesion in the spinal cord. Currently we are analyzing lesions in the cKO lines using two different inducible Cre recombinase transgenic lines, the NG2-CreERT line that enables us to study the function of TSC/mTOR signaling in the differentiation of oligodendrocyte progenitors, and the PLP-CreERT line that allows us to investigate TSC/mTOR signaling during remyelination independent of differentiation.

MO5. Behavioural assessment of mice with mosaic expression of ATRX in the CNS

Renee Tamming, Jennifer Li, Yan Jiang, Marco Prado, Frank Beier, Nathalie Berube*

ATRX mutations are a common cause of intellectual disability in children. The gene encodes a chromatin remodelling protein involved in the activation and repression of many genes. In this study we examined the effects of a mosaic pattern of ATRX expression on neurobehaviours. Atrx conditional heterozygosity resulted in stunted growth and decreased levels of circulating Igf-1. Mutant mice also displayed hindlimb clasping, suggestive of neurological impairments. We thus tested Atrx mutant mice in various neurobehabioural tests. The findings indicate that loss of ATRX expression leads to decreased anxiety in the elevated plus maze and impaired working memory in the novel object recognition task. Mutant mice also exhibited severe impairments in hippocampal-dependent learning and memory in the contextual fear conditioning and Morris water maze paradigms. However, they also performed poorly in the cued version of the Morris water maze and showed signs of decreased motivation or apathy, highlighting the complexity of the defects that possibly confound learning and memory assessments. These results have important implications for our understanding of ATRX function in brain function and the behavioural outcomes of its dysregulation in the CNS.

MO6. Borders of primary sensory areas reflect natural variation in parenting received, and exogenous exposure to oxytocin, in prairie voles

*Adele Seelke, Shi-Min Yuan, Allison Perkeybile, Leah Krubitzer, Karen Bales**

Experiences during the early postnatal period, whether through parental care or perinatal exposure to exogenous hormones, significantly impact adult social behavior in prairie voles (Microtus ochrogaster), socially monogamous rodents. However, it is unknown what, if any, effect these early experiences have on brain

organization. We examined whether natural variation in parenting or exogenous exposure to oxytocin resulted in changes in the area occupied by the primary (S1) and second (S2) somatosensory cortical areas in voles. We characterized offspring as coming from either the top quartile ("High contact", or HC) or bottom quartile ("Low contact", or LC) of parental care received. In a second group, we exposed PND0 voles to an i.p. injection of either saline, oxytocin at a dose shown to cause long-term facilitation of social behavior (OT; 3 ug in males and 6 ug in females), or oxytocin antagonist (OTA, 0.3 ug), and took brains at 60 days. Cortices were flattened and sectioned tangential to the pial surface, then stained for myelin. Borders of sensory regions were identified, and the proportion of the cortical sheet occupied by each was calculated, as was the overall proportion that was myelinated. Differential parenting resulted in changes to cortical boundaries, with LC females having significantly lower proportion of myelinated cortex than all other groups, as well as a lower proportion of cortex devoted to M1 than in HC females. Early administration of OT or OTA resulted in changes to cortical boundaries that differed from those observed in HC and LC voles. Treatment with OTA produced males with a smaller somatosensory areas (S1 and S2 combined). Females treated with OT had a smaller S1, and a larger V1, than females treated with saline or OTA. These results show that variation in natural experience, as well as a single pharmacological experience with OT or OTA, can significantly impact the size of cortical fields determined by architectonic analysis.

MO7. A specialized pro-resolution mediator approach to cognitive performance in the Ts65Dn mouse model of down syndrome

Eric Hamlett, Xiuzhe Wang, Aurélie Ledreux, Rebecca Derex, Laura Columbo, Marianne Schultzberg, Ann-Charlotte Granholm*

Alzheimer's disease occurs in individuals with Down syndrome with high incidence. Neuropathological alterations of DS-related AD (DS-AD) begin at age of thirty and progress to near uniformity by the age of 60. DS-AD encompasses classical AD hallmarks including: amyloid-beta (Aβ) plaques, neurofibrillary tangles, neurodegeneration in the basal forebrain, locus coeruleus, and hippocampus; all exacerbated by chronic inflammation including microglial activation and elevated proinflammatory cytokines. The mechanisms of inflammatory imbalance in the brain remain elusive. Inflammation is known to be counter-regulated by resolution processes which are initiated by specialized pro-resolving mediators (SPMs). SPMs play an important role in every tissue and a singular SPM, when administered at higher doses, can decrease inflammation in the periphery. Resolution processes are biologically active in the brain but the relationship to chronic inflammation

involved in AD and DS-AD is unknown. Whether SPM supplementation can rescue resolution failure in the brain is also still unknown. This poster debuts early studies to determine the therapeutic potential of a potent SPM, Resolvin E1, in the well characterized DS mouse model (Ts65Dn) which develops neuropathology and cognitive impairments very early. This poster provides a first glimpse of resolution components in post mortem brains from individuals with DS-AD. Mouse pharmacological treatments. Chronic resolvin E1 (RvE1) (10ng/gram weight/day) or vehicle (10% EtOH, 90% saline) was delivered by subcutaneous Alzet mini-osmotic pumps for a 30 day period starting at 8 months of age, when neuropathology and cognitive impairments are readily measurable in the Ts65Dn model relative to Normosomic controls. Mouse behavior methods. After 1 month of treatment (9 months of age), open field, novel object recognition (NOR) and water radial-arm maze (WRAM) tasks were employed for each mouse to assess locomotion, short-term vs long-term novel object discrimination and cue-based memory performance. Immunohistochemistry. Human Brian Sections: Beilchowsky's silver stain was employed to differentiate neuropathological senile plaques and neurofibrillary tangles in post mortem brain sections from individuals with Down syndrome and clinically validated Alzheimer's disease (a gift from UCI MIND center). Two resolution receptors, ChemR23 and LxA4, were stained following standard procedures with diaminobenzidine (DAB) colorimetric reagents. Mouse: The microglia marker, CD45, was stained following standard procedures with DAB in fixed hippocampal cross-sections from Normosomic and Ts65Dn mice. ELISA. Proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12) were quantified with multiplex ELISA kits (Eve technologies). ChemR23 and LxA4 resolution receptors are expressed in glia and neuronal cells in the brain and are more highly expressed in pathological situations as seen in post mortem AD and DS-AD brain sections. Chronic RvE1 treatment enhances memory in both NOR and WRAM tasks while normalizing hyperactivity. Chronic RvE1 treatment reduces peripheral inflammatory cytokines and microglial activation in Ts65Dn mice. Resolution receptors perturbations are correlated with pathological events in post mortem DS-AD brains as seen previously in post mortem AD brains. This suggests a potential involvement of resolution processes with neuropathology. The positive results from SPM (RvE1) supplementation in Ts65Dn mice suggest a potentially safe and transferable therapy that could benefit the entire spectrum of AD. Down syndrome (DS) is the most prevalent intellectual disability in the world and no other population has such a prevalence of Alzheimer's disease (AD). Therapeutic potential studies that target AD in the DS population is significant to the general population where idiopathic AD affects over 5 million US citizens, making it the 6th leading cause of death.

MO8. Early maternal deprivation in the rat alters cortical structure and function in adulthood

Sarine Janetsian, Maureen Timm, Aqilah McCane, Anthony Baucum II, Brian O'Donnell, Christopher Lapish*

Early life trauma is a risk factor for a number of neuropsychiatric disorders, including schizophrenia (SZ). Since SZ is a complex condition with a multifactorial etiology, it is difficult to model the breadth of this condition in a single animal model. Considering this, it is necessary to develop rodent models with clearly defined subsets of pathologies observed in the human condition and their developmental trajectory. The current study assessed how an early traumatic event alters cognition and brain function, similar to those observed in SZ, to better understand what neural systems might be compromised following these events. On postnatal day (PD) 9, male rat pups were maternally deprived (MD) for 24-hours or were left undisturbed. In Experiment 1, recognition memory was tested in adulthood using the novel object recognition task. Then, tissue was extracted and catechol-o-methyl transferase (COMT) and glutamic acid decarboxylase (GAD67) expression were quantified in the prefrontal cortex (PFC), striatum, and temporal cortex (TC). In Experiment 2, electrophysiological recordings were obtained from the PFC, vertex, and TC during a sensory gating paradigm to assess the effects of MD. Root mean squared (RMS) voltage signal and a gating ratio were quantified. Compared to shams, MD animals had impaired recognition memory, lower COMT expression in the PFC and TC, and lower GAD67 expression in the TC. In Experiment 2, MD animals exhibited an increase in RMS voltage in all three recording sites compared to shams. Lastly, MD animals exhibited a blunted gating response during the paired-click paradigm compared to shams, which was most pronounced in the TC. These data suggest that neurodevelopmental perturbation was associated with long-lasting alterations in cognition and brain function in adulthood. As such, this model may provide a useful tool to further explore the neural basis of early life trauma that may result in mental psychiatric disorders, including SZ.

MO9. Chemogenetic inactivation of the rat medial prefrontal cortex attenuates methamphetamine- and mating-induced neuronal activity, but not behavior

Lindsey Bishop, Lique Coolen*

The medial prefrontal cortex (mPFC) is involved in inhibitory control of behavior, and dysfunction of mPFC has been implicated in compulsive behavior. We showed that concurrent Methamphetamine (Meth) and mating experience (Meth/sex) causes compulsive sex and drug seeking behavior.

Moreover, Meth/sex experience activated and altered CAMKII-expressing pyramidal neurons in the mPFC. The current study examines effects of inactivation of CaMKII neurons in the mPFC on mating, Meth-induced behavior, and mating- or Meth-induced neural activation. Male Sprague Dawley rats received bilateral injections of AAV5-CaMKII-HM4D(Gi)-mCherry into the dorsal mPFC at least 3 weeks prior to behavioral testing. In the first experiment, sexually experienced animals received either CNO (1 mg/kg, s.c.) or vehicle 30 minutes prior to receiving either Meth (1 mg/kg s.c.) or saline, and locomotor activity was determined. Subsequently, males received a receptive female (sex) or roamed freely (no sex) for 10 minutes before perfusion. Brain sections were immunoprocessed for Meth-induced cFos and sex-induced pERK, and mCherry expression in CAMKII cells was verified. CNO did not affect mating or Meth-induced locomotion. CNO attenuated both Meth and sex-induced neural activity in the mPFC and target area nucleus accumbens. In a separate experiment, animals with dorsal mPFC CaMKII-HM4D(Gi) intravenously self-administered Meth for 5 daily sessions and received either concurrent or non-concurrent sex. CNO (1 mg/kg) or vehicle were administered 30 minutes prior to each session. CNO did not affect the acquisition of Meth self-administration. Preliminary findings show that concurrent Meth/sex vehicle treated animals displayed compulsive drug seeking behavior, while concurrent CNO treated animals did not. These results indicate that DREADD can be used to further test our hypothesis that neuronal ensembles in mPFC mediate development of compulsive behavior following Meth/sex experience.

MO10. A novel mouse model of resistance to drugs to treat alcohol binge drinking

*John Crabbe**

Abusive alcohol drinking is characterized by ingesting large amounts chronically as well as tending to drink in binges, defined by the NIAAA as a pattern leading to blood ethanol concentrations (BECs) > 0.8 mg/ml (i.e., exceeding the legal limit for driving) during a period of approximately 2 hr. High Drinking in the Dark mice were created by selective breeding for high BECs attained after a short period of binge-like drinking during limited access to alcohol during their circadian dark period. Two separate HDID lines reach average BECs > 1.6 mg/ml. Most attempts to screen compounds for efficacy to reduce drinking have employed some version of two-bottle preference drinking. Such studies have identified many candidate drugs, but nearly all have failed in the clinic, i.e., they have been found to be false-positives. HDID mice appear to be very resistant to therapeutic reductions in their drinking, failing to respond to many drugs including acamprosate and naltrexone. They recently responded to the PDE-4

inhibitor rolipram, which had been nominated by a genomics-bioinformatics-driven screen. They also respond to the newer drug, apremilast. We believe they may represent a very selective model for screening novel compounds.

MO11. Presynaptic inhibition of identified excitatory inputs to dorsomedial striatum

William Birdsong, Bart Jongbloets, Tianyi Mao, John Williams*

The striatum/ nucleus accumbens (NAc) receives excitatory glutamtergic inputs from various brain regions including cortex, thalamus, hippocampus and amygdala. Opioid dependent inhibition of glutamate inputs to the striatum/ NAc using electrical stimulation is small and variable. This variability may result from the heterogeneous expression of opioids among the array of afferent inputs. Projection mapping has shown evidence for glutamatergic projections to the dorsomedial striatum from prefrontal and anterior cingulate cortex as well as medial thalamus. Additionally, several nuclei in the medial thalamus express a high density of mu-opioid receptors, MOPr. Therefore, it was hypothesized that specific thalamo-striatal projections would be more sensitive to modulation by opioid receptor agonists than cortico-striatal afferents. The current project uses whole cell voltage clamp recordings in mouse dorsomedial striatum coupled with viral mediated expression of channelrhodopsin in subregions of thalamus or cortex. Optical stimulation of thalamo-striatal and cortico-striatal afferents as well as bulk electrical stimulation of striatal inputs were used to compare the opioid sensitivity of thalamic and cortical glutamatergic inputs onto striatal medium spiny neurons. The results suggest that cortico-striatal and bulk glutamate inputs are relatively insensitive to inhibition by MOPr activation while thalamo-striatal projections are strongly inhibited by MOPr agonists. Furthermore, cells can receive both cortical and thalamic input with only thalamic input being opioid sensitive. Thus, opioid treatment may alter the balance of glutamatergic input from thalamus and cortex to the striatum. This work was supported by the National Institutes of Health National Institute on Drug Abuse [DA08163].

MO12. Corticotropin-releasing factor (CRF) impairs prefrontal cortex-dependent cognitive processes

Sofiya Hupalo, Craig Berridge*

The prefrontal cortex (PFC) regulates cognitive processes critical for flexible, goal-directed behavior. Dysregulated PFC-dependent cognition is associated with multiple psychopathologies, including ADHD. Although it is well known that corticotropin-releasing factor (CRF) and CRF receptors are present in the PFC, the cognitive actions of CRF signaling in the PFC remain unknown. To

address this, we first examined the effects of intracerebroventricular (ICV) and intra-PFC CRF infusions on performance in a spatial working memory task in rats. ICV and intra-PFC CRF elicited a robust and dose-dependent impairment in performance. Subsequent studies investigated whether endogenous CRF signaling modulates working memory using the non-selective CRFR1/2 antagonist, D-Phe-CRF. Both ICV and intra-PFC infusions of D-Phe-CRF dose-dependently improved working memory. To better assess the clinical potential of CRF antagonists, we also observed that systemic administration of the CRFR1 receptor antagonist, NBI 35965, similarly improved working memory performance. Given all FDA approved treatments for ADHD improve working memory in rodents, monkeys and humans, these observations suggest that CRF antagonists may be effective in treating ADHD and other PFC cognitive disorders. Additional studies examined whether CRF modulates PFC-dependent cognition more broadly using an operant task of sustained attention. ICV CRF dose-dependently impaired performance in this task. However, CRF had no effect in sustained attention when infused intra-PFC. Collectively, these observations indicate that CRF signaling in the PFC differentially modulates distinct PFC-dependent processes. Ongoing studies investigate whether CRF antagonism improves sustained attention similarly to working memory. In summary, this research provides novel insight into the neurobiology of both the PFC and CRF and suggests that CRF may be an appropriate target for treating PFC dysfunction.

MO13. Alterations in hypoglossal neuron activity in a mouse model of DiGeorge/22q11.2 Deletion Syndrome

David Mendelowitz, Xin Wang, Anthony-Samuel LaMantia*

Pediatric dysphagia—feeding and swallowing difficulties that begin at birth—is one of the most common, yet least understood complication in children with developmental disorders. Pediatric dysphagia is a major complication of a common human genetic developmental disorder, DiGeorge/22q11.2 Deletion Syndrome (22q11DS). Infant mice carrying a parallel deletion to 22q11DS patients have feeding and swallowing difficulties. Hypoglossal motorneurons, that are located in the dorsal brainstem, generate activity to tongue muscles essential for feeding and swallowing. In this study we examine if the electrophysiological properties of brainstem hypoglossal neurons is altered in 22q11DS mice. Our preliminary results, using patch clamp electrophysiological approaches, indicate hypoglossal neurons in 22q11DS mice are hyper-excitable (compared to wild type control animals) and this is likely due, at least in part, to diminished potassium channel activity at the resting membrane potential in these neurons.

MO14. To study the effect of electroconvulsive therapy on visuospatial memory in rats

Navya Lakkappa, Praveen Thaggikuppe Krishnamurthy*

The clinical use of Electroconvulsive therapy (ECT) is limited due to its cognitive side effects, particularly retrograde and anterograde amnesia. In a clinical setup, the assessment of cognitive side effects of ECT on visuospatial memory is difficult due to ethical and procedural reasons. It is therefore, important to develop an appropriate animal model to study the same. In the present study, an effort has been made to develop a rat model to assess the effect of ECT on visuospatial memory using Barnes maze. The retrograde amnesia experiment was conducted by pretraining the animals with 2 days of habituation and 3 days of acquisition followed by Electroconvulsive shock (ECS) treatment (dose 10mC and 30mC). The ECS treatments were divided into 3, 5 & 7 sessions, followed by re-exposure to the maze to assess amnesia. The anterograde amnesia experiment was conducted with pre-treatment of 7 ECS sittings (dose 10mC and 30mC) followed by exposure to Barnes maze to assess new learning. The animals during the habituation and acquisition period showed a significant improvement in learning as evident from the decrease in latency and number of errors, indicating the model is appropriate for assessing the visuospatial memory. The results of retrograde amnesia study showed no significant effect of ECT on memory, indicating no effect of ECT on the retrograde memory. The results of anterograde amnesia study showed ECT has a dose dependent and significant ($p<0.001$) impairment effect on new learning. In conclusion, the rats treated with various doses of ECT showed no effect on retrograde memory, but showed a significant impairment on anterograde learning.

MO15. Why biperiden is a better model for memory impairments in dementia than scopolamine

Arjan Blokland, Inge Klinkenberg, Anke Sambeth*

Since the early studies of Deutsch (1971) scopolamine has been used as a drug that impairs memory performance in man. The notion that scopolamine could be used as a pharmacological model of age-associated memory impairment and dementia further strengthened by the cholinergic hypothesis of Bartus et al (1982). At present, scopolamine is still considered to be the best model for this cholinergic deficit. However, it has been argued that scopolamine has various side effects and that it is non-selective for peripheral and central muscarinic receptors. It has been shown that the muscarinic type 1 (M1) receptor is more specifically located in cortical and hippocampal structures and that the expression in the body is limited. Therefore, it has been suggested that blocking

the M1 receptor could be regarded as a better model for age-associated and dementia related memory deficits. We conducted different studies in animals and man to examine the effects of the selective M1 antagonist biperiden. In animals it was found that biperiden selectively impaired short-term memory performance, and not food motivation or attentional functions. In contrast, scopolamine had effects on motor responding and attention, and had a non-specific effect in a short-term memory task. In man, biperiden impaired the performance in a verbal word learning task, and in other memory tasks (spatial memory task, continuous recognition task). Although not compared directly with scopolamine, biperiden seemed to have fewer side effects. On basis of these data, it is claimed that biperiden should be preferably be used as a model for memory impairment in animals and man.

MO16. Postnatal Arc/Arg3.1 ablation causes profound impairments in long-term memory consolidation

Ora Ohana, Xiaoyan Gao, Sergio Castro-Gomez, Jasper Grendel, Sabine Graf, Dietmar Kuhl*

Arc/Arg3.1 expression is rapidly up-regulated by acquisition of experience and by synaptic plasticity-inducing stimuli. We previously generated conventional Arc/Arg3.1 Knockout mice (constitutive KO) which constitutively lack the Arc/Arg3.1 gene. These mice show a profound impairment in the consolidation of synaptic plasticity in the hippocampus. While synaptic transmission and short-term memory was unaffected, the KO-animals have completely lost the ability to form explicit and implicit long-term memories. Because Arc/Arg3.1 expression starts early in development, Arc/Arg3.1 bears the potential to impact on brain development and thereby cause a later disturbance of long-term memory consolidation. To address this possibility we generated Arc/Arg3.1 loxP-flanked mice (Arc/Arg3.1f/f; conditional KO) and bred those with various CaMKIIα-Cre carrying mouse lines to obtain KO mice (late KO) in which Arc/Arg3.1 is ablated in principal neurons of the forebrain during late development. For comparison we also generated KO mice (early KO) by crossing Arc/Arg3.1f/f mice with a CMV-Cre mouse resulting in Arc/Arg3.1 ablation during early embryogenesis in all cells including germ cells. Behavioral assessment confirms a profound impairment in the consolidation of explicit and implicit long-term memories in the early KO mice, recapitulating our previous findings in the constitutive KO. Similarly, we observed a loss of long-term memory consolidation in the late KO mice, demonstrating that the requirement for Arc/Arg3.1 in memory consolidation is independent of any possible additional role in developmental processes.

MO17. Nrf2-ARE activator carnosic acid decreases mitochondrial dysfunction, oxidative damage and neuronal cytoskeletal degradation following traumatic brain injury in mice

Edward Hall, Darren Miller, Indrapal Singh, Juan Wang*

The importance of free radical-induced oxidative damage after traumatic brain injury (TBI) has been well documented. Despite multiple clinical trials with radical-scavenging antioxidants that are neuroprotective in TBI models, none is approved for acute TBI patients. As an alternative antioxidant target, Nrf2 is a transcription factor that activates expression of antioxidant and cytoprotective genes by binding to antioxidant response elements (ARE) within DNA. Previous research has shown that neuronal mitochondria are susceptible to oxidative damage post-TBI, and thus the current study investigates whether Nrf2-ARE activation protects mitochondrial function when activated post-TBI. It was hypothesized that administration of carnosic acid (CA) would reduce oxidative damage biomarkers in brain tissue and also preserve cortical mitochondrial respiratory function post-TBI. A mouse controlled cortical impact (CCI) model was employed with a 1.0mm cortical deformation injury. Administration of CA at 15 minutes post-TBI reduced cortical lipid peroxidation, protein nitration, and cytoskeletal breakdown markers in a dose-dependent manner at 48 hours post-injury. Moreover, CA preserved mitochondrial respiratory function compared to vehicle animals. This was accompanied by decreased oxidative damage to mitochondrial proteins, suggesting the mechanistic connection of the two effects. Lastly, delaying the initial administration of CA up to 8 hours post-TBI was still capable of reducing cytoskeletal breakdown, thereby demonstrating a clinically relevant therapeutic window for this approach. Finally, CA was shown to improve the motor and cognitive function in terms of improved Neurological Severity Scores (NNS) and Novel Object Recognition (NOR), respectively at 7 days post-TBI. Similarly, transgenic Nrf2 over-expression was found to decrease post-TBI brain oxidative damage and to improve NOR at 7 days. This study demonstrates that pharmacological and genetic Nrf2-ARE induction is capable of neuroprotective efficacy when administered after TBI.

MO18. Diminished amygdala activation and behavioral threat response following traumatic brain injury

Christopher Palmer, Hannah Metheney, Jaclynn Elkind, Akiva Cohen*

Each year, approximately 3.8 million people suffer mild to moderate traumatic brain injuries (mTBI) that result in an array of neuropsychological symptoms and disorders. Despite these alarming statistics, the neurological bases of these

persistent, debilitating neuropsychological symptoms are currently poorly understood. In this study we examined the effects of mTBI on the amygdala, a brain structure known to be critically involved in the processing of emotional stimuli. Seven days after lateral fluid percussion injury (LFPI), mice underwent a series of physiological and behavioral experiments to assess amygdala function. Brain injured mice exhibited a decreased threat response in a cued fear conditioning paradigm, congruent with a decrease in amygdala excitability determined with basolateral amygdala (BLA) field excitatory post synaptic potentials together with voltage sensitive dye imaging (VSD). Furthermore, beyond exposing a general decrease in the excitability the primary input of the amygdala, the lateral amygdala (LA), VSD also revealed a decrease in the relative strength or activation of internuclear amygdala circuit projections after LFPI. Thus, not only does activation of the LA require increased stimulation, but the proportion of this activation that is propagated to the primary output of the amygdala, the central amygdala, is also diminished following LFPI. Intracellular recordings revealed no changes in the intrinsic properties of BLA pyramidal neurons after LFPI. This data suggests that mild to moderate TBI has prominent effects on amygdala function and provides a potential neurological substrate for many of the neuropsychological symptoms suffered by TBI patients.

MO19. Cerebrospinal fluid from HD subjects seeds aggregation of mutant huntingtin

Steven Potkin, Zhiqun Tan, Wei Dai, Jane Paulson, Katya Potkin, Leslie Thompson, Charles Glabe, Wah Chiu*

Huntington's disease (HD) is a dominant neurodegenerative disease resulting in progressive motor, cognitive and psychiatric impairment and ultimately death. HD is caused by an abnormal CAG trinucleotide repeat expansion within exon 1 of the HD gene producing a mutant Huntingtin protein (mHTT) containing an expanded polyglutamine (poly(Q)n, n≥ 36) tract. While expansion length is on average inversely related to age-of-onset of clinical motor symptoms, individual age of symptom onset remains unpredictable. We report that cerebrospinal fluid from BACHD transgenic rats and from human Huntington's subjects effectively seeds mutant Huntingtin aggregation in a cell model and its cell lysate. Our studies demonstrate that seeding is mutant Huntingtin template-specific and may reflect an underlying prion-like protein propagation mechanism. Light and cryo-electron microscopy show that synthetic seeds nucleate and enhance mutant Huntingtin aggregation. This seeding assay distinguishes living Huntington's subjects from healthy and non-Huntington dementia controls without overlap. Seeding measures from expansion-gene-positive subjects without clinical symptoms range from HD to control values.

Ultimately this seeding property in Huntington's patient cerebrospinal fluid may form the basis of a molecular biomarker assay to monitor HD and evaluate therapies that target mutant Huntingtin protein.

MO20. Real-time striatal measurements of oxidative stress and dopamine in the dyskinetic rat during chronic L-Dopa treatment for Parkinson's disease

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

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the preferential loss of dopaminergic neurons stemming from the substantia nigra pars compacta and innervating the dorsal striatum. The substantial decreases in striatal dopamine (DA) result in devastating hypokinetic movements and motor disturbances. Increased generation of reactive oxygen species, such as hydrogen peroxide (H2O2), is also thought to contribute to Parkinsonian symptoms. However, the precise role of H2O2 in the initiation, progression, and maintenance of the disease remains unclear, as reactive oxygen species are difficult to monitor in brain tissue. Further, several lines of evidence suggest that the standard treatment strategy of dopaminergic replacement therapy via administration of Levodopa (L-DOPA; L-3,4 dihydroxyphenylalanine) may serve to increase oxidative stress and potentiate cell death. We aim to investigate how striatal H2O2 and DA dynamics underlie behavioral changes that result from chronic L-DOPA administration in a rodent model of PD (unilateral 6-OHDA lesion) using fast-scan cyclic voltammetry, an electrochemical technique that affords precise spatial and temporal resolution, as well as selective detection of these neurochemicals. Specifically, carbon-fiber microelectrodes are used to simultaneously quantify rapid H2O2 and DA fluctuations at single recording sites in the dorsal striatum over several weeks of L-DOPA administration. The chemical fluctuations are correlated with behavioral abnormalities that develop over the course of treatment. These studies will aid in our understanding of how oxidative stress modulates nigrostriatal DA signaling, and will demonstrate how these signals correspond with the development of dyskinetic movements in the treatment of PD.

MO21. The circadian variation of sleep and alertness is advanced in women

Diane B. Boivin, Ari Shechter, Philippe Boudreau, Esmot Ara Begum*

From the expression of sex steriod receptors on the suprachiasmatic nuclei, the master circadian clock, to circulating hormones, many sex-based differences exist that influence the circadian system and could lead to sex difference in the regulation of sleep. We studied 16 healthy men and 11 healthy women in time

isolation with an 8-h sleep period followed by a 72-h ultradian sleep-wake cycle procedure (USW). During the USW procedure, participants maintained a semi-recumbent posture and were served iso-caloric snacks (1x/2 h). They alternated between 60-min wake episodes (<10 lux) and 60-min nap episodes (<0.03 lux). Sleep was recorded using polysomnography (PSG) during the baseline sleep period and naps. Core body temperature (CBT) was recorded continuously. Data were aligned based on the time since lights on and the circadian variation of measures was compared between sexes. Although there were no significant sex differences in habitual bed- and wake times, the CBT acrophase (time of peak) was 66 minutes advanced in women compared to men. By aligning our results with the time of CBT minimum, we observed a significant, although smaller advance in the circadian variation of sleep in women. The average phase angle (wake time – CBT minimum) for women was not significantly longer than men. A significant circadian rhythm was observed for all PSG parameters. Throughout the USW procedure, women presented more stage 2 sleep and REM sleep, whereas they had less stage 1 sleep and slow wave sleep compared to men. The acrophase (timing of peak values) of all sleep parameters was observed between 1.7 to 2.3 hours earlier in women compared to men. These observations have implications for understanding the increased prevalence of insomnia and subjective sleep complaints reported in women. Current findings are particularly relevant for helping to explain sleep maintenance insomnia and early morning awakenings in women.

MO22. Human brain collection core: a valuable free resource to study brain disorders

Jonathan Sirovatka, Brent Harris, Harker Rhodes, Robin Kramer, Jose Apud, Stefano Marenco, Barbara Lipska*

The mission of Human Brain Collection Core (HBCC) within the NIMH is to conduct and support postmortem research on the brain with the goal of reducing the burden of mental illness. HBCC is a national resource of human brain tissues, providing unique opportunities in mental health research. The tissues are obtained under protocols approved by the Combined Neuroscience Institutional Review Board and only with the permission of next-of-kin. There is no cost to the next-of-kin or the decedent's family. Importantly, there is no cost to the investigators who are approved to obtain tissue samples for their studies. The NIH promotes the sharing of resources and data as a way to speed the translation of findings into knowledge, and endorses projects that improve health, while protecting the privacy of research participants. The HBCC collects postmortem human brain tissue specimens that have been extensively characterized. The use of an individualized, 3-dimensionally printed cutting box ensures consistent and parallel pathologic sections. As a non-renewable

resource, the human brain collection requires oversight to ensure that specimens are distributed equitably and fairly to investigators. Requests for access to samples from the collection are emailed to hbccmail@mail.nih.gov. We will show that brain samples from HBCC have been successfully utilized for whole genome and RNAseq, and Cis regulatory epigenome mapping from the fluorescence-activated cell sorted neuronal and non-neuronal populations using chromatin immunoprecipitation with massively parallel DNA sequencing, Chipseq. Comprehensive identification of active gene regulatory elements are conducted using an Assay for Transposase-Accessible Chromatin with high throughput sequencing (ATAC-seq) for mapping chromatin accessibility genome-wide. Mapping of bioactive lipids and RNA expression by RNA-sequencing in migraine headaches using trigeminal ganglia, blood, blood vessels and dural tissues have also been conducted.

MO23. The changing face of acute neurology: experience from two decades of the Cambridge Neurology Emergency Clinic

Sybil Stacpoole, Stephen Sawcer, Axinte Laura*

Acute neurological presentations are a common problem, accounting for around 17% of GP consultations, 10% of A&E visits and around 20% of the medical take. There is an increasing appreciation of the need to reconfigure neurological services to meet this need, but the challenge is to provide a service for those who most need it with an under-resourced specialty. The Royal College of Physicians 2012 Consultant Physician Survey reported that there were 716 neurology consultants in the UK, resulting in 1 per 90,000 population, significantly lower than the recommended RCP minimum of 1 consultant per 70,000, every day of the week. One solution to the evident need is providing rapid access ambulatory pathways. Here we report on the Cambridge experience of nearly two decades provision of an emergency neurology clinic at Addenbrooke's Hospital. We show how the service has evolved and the changing patterns of presentation, management and outcomes of the patients seen. Annualised attendance data demonstrates increasing demand, whilst the proportion of patients presenting with headaches (now 40%) has escalated dramatically. By contrast, the number of patients referred with problems related to established chronic neurological diseases has fallen considerably, no doubt related to the development of specialist nurses and clinics.

MO24. An immersive 3D brain simulation that future health professionals explore via the Oculus Rift™ virtual reality headset

*Bradley Tanner**

Students of medicine and neuroanatomy attempt to create an internalized 3D map of brain structures and their connections. The rich data and visualizations created via the NIH BRAIN Initiative and the component Human Connectome Project offer a potential aid to students. Tractographic analysis of the data obtained via MRI Diffusion tensor imaging (DTI), diffusion functional MRI (DfMRI) and diffusion spectrum imaging (DSI) may help students visualize neuronal pathways. Yet students still struggle to visualize brain neuroanatomy using 2D displayed images from tractography, diagrams, and standard radiological scans; the potential value of DTI-based images is not fully achieved. Students need an educational tool to "step inside" the brain as one might walk through a house. In that brain they need clear educational objectives, context clues, and challenges that enhance learning. This project is using tractography data from DTI to build a 3D model of the brain that learners will experience in an immersive 3D virtual environment using Unity 3D and the Oculus Rift™ VR platform. Oculus enables a near perfect representation of reality in terms of low lag and a full field of view. It evokes strong engagement; users perceive themselves inside a real-world 3D environment. Initial work focused on describing the user experience, overcoming technological hurdles associated with Oculus, assessing and decreasing risk of simulation sickness, and investigating a methodology to convert tractographic data to a Unity-based 3D virtual environment. A planned study compares the immersive Oculus 3D experience with a 2D version of the same content to assess impact on: neuroanatomical knowledge, confidence in the ability to acquire more knowledge, and interest in learning more about brain-related illnesses. We will also measure attitudes related to: the scientific basis of disorders effected by brain functioning, and the value of medical intervention. Process outcomes include measures of realism, simulation sickness side effects, and satisfaction.

MO25. Gene X smoking interactions in the ventromedial PFC: alpha 5 nicotinic cholinergic receptor gene variation and smoking effects on adolescent grey matter

Hugh Garavan, Bader Chaarani, Scott Mackey, Phil Spechler, Stephen Higgins, Alexandra Potter, Robert Althoff, Elliot Stein*

The rs16969968 single nucleotide polymorphism (SNP) of the alpha 5 nicotinic receptor has A/G as minor/major alleles. The risk allele A has been previously associated with nicotine dependence. However, the neural mechanism, should one exist, associating this SNP to smoking behavior is still unknown. Here, we investigate structural and functional brain correlates of smoking, the rs16969968 genotype effect and the smoking*genotype interaction in a large sample of 14 years old adolescents. Voxel-based morphometry (VBM) and the Monetary Incentive Delay (MID) fMRI reward task were used to determine the brain structural and functional correlates of nicotine in 1,737 adolescents on whom whole-genome genotyping and behavioral data were acquired. A nicotine score was calculated from the European School Survey Project on Alcohol and Drugs questionnaire, scoring as follows (Score (Lifetime occurrences)): 0(0), 1(1-2), 2(3-5), 3(6-9), 4(10-19), 5(20-39), 6(≥40 cigarettes). An association analysis was performed to assess the relationship between genotype and nicotine exposure. Clusters identified from the whole-brain VBM analysis were used to calculate the mean activity from the MID task (both reward anticipation and reward outcome) and for an ROI-level ANOVA to test the smoking*genotype interaction on grey matter volume (GMV). In these analyses subjects were grouped by genotype (AA; GA; GG) and by smoking status as smokers (scores:1-6) or non-smokers (score=0). Age, sex, handedness, scanner site, puberty status, total GMV, socioeconomic status and IQ were included as nuisance covariates. Nicotine exposure was significantly associated with a higher frequency of the risk genotype in the 1,737 adolescents ($p=0.03$). The between-group VBM comparison between 389 non-smokers and 93 average and advanced smokers (scores 3-6) yielded significantly less GMV in smokers in the ventromedial prefrontal cortex (vmPFC) following a $p<0.05$ cluster-wise correction. The VBM regression that included 816 subjects (non-smokers and smokers with low, average and high nicotine exposure levels (scores:1-6)), showed a significant negative linear correlation between GMV and nicotine exposure in the same vmPFC region. There was also a nicotine*genotype interaction on the vmPFC volume ($p <0.03$), with no main effect for genotype ($p>0.05$). The vmPFC volume decrease in smokers was largest in the carriers of the nicotine-related high-risk genotype (AA). Further, there was a similar nicotine*genotype interaction on reward anticipation and outcome in the MID task where, similar to the GMV effects, activation was reduced in smokers with the largest effect in the AA carriers. This gene*environment interaction

in the vmPFC, a brain region known to be involved in value calculations and decision making processes, suggests a possible neurobiological mechanism that underlies both a genetic predisposition towards smoking and the detrimental effects of smoking. The linear relationship between cigarette use and vmPFC volume suggests effects at very low nicotine exposure levels. The reward-related hypoactivity in the smokers with the high-risk genotype suggests a genetic predisposition combining with nicotine exposure to produce a reward-blunted phenotype which, in turn, may increase the reinforcing effects of nicotine. These observations further support the need for strong regulatory protections of adolescents from cigarette smoking.

TU1. Throughout life, multisensory connections of primary sensory cortices develop within five phases

Julia Henschke, Patrick Kanold, Frank Ohl, Goldschmidt Jürgen, Eike Budinger*

Multisensory integration does not only recruit higher-level association cortex, but also primary sensory cortices like A1(auditory), S1(somatosensory), and V1(visual). In the adult, the underlying anatomical pathways, which might preferentially serve short-latency integration processes, include direct thalamocortical and corticocortical connections across the senses. So far, it is unknown how these connections develop over the individual's life span. Using a rodent model, the Mongolian gerbil, we show that multisensory connections form, constitute, but also alter within five developmental phases. Neuronal tracer injections into A1, S1, and V1 at several postnatal time points covering the onset of senses, weaning, adolescence, adulthood, and aging, revealed an initial competition between the developing senses (competition phase), characterized by an overproduction of multisensory connections, but a subsequent elimination of exuberant and a structural consolidation of remaining and new connections during the critical and sensitive phase. At adult stages (stable phase), many multisensory connections exist; however, most of them disappear during aging (degradation phase). Immunohistochemical markers for neurogenesis, cell apoptosis, axonal plasticity, myelinization, and calcium-binding proteins show that during normal development, thalamic and cortical projection neurons are not newborn and do not die; instead major axonal reorganization processes take place, which are mediated by non-lemniscal thalamic nuclei and the primary sensory cortices themselves. This knowledge about mechanisms underlying normal development and concomitant changes provides the fundament for understanding further plastic processes, e.g., caused by experience, learning, and sensory deprivation.

TU2. Characterization of neuregulin 3 subclass expression across cortical development, in affective disorders, and genetic regulation by risk variation

Clare Paterson, Yanhong Wang, Daniel Weinberger, Thomas Hyde, Joel Kleinman, Amanda Law*

Neuregulin 3 (NRG3) has been implicated in a wide range of neurodevelopmental and neuropsychiatric disorders. While studies have demonstrated altered gene expression and genetic regulation of NRG3 transcripts in schizophrenia, little is known regarding the normal expression of NRG3 transcripts across brain development, or whether expression changes are evident in additional neuropsychiatric disorders. Therefore, using RT-qPCR we aimed to study the expression profiles of NRG3 subclasses (Class I-IV) across normal human cortical development in postmortem dorsolateral prefrontal cortex samples (n=286 unaffected control individuals, aged gestational week 14 to 85 years old). Additionally, we assessed the cortical expression levels of NRG3 Class I-IV in affective disorders (bipolar disorder, n=34 and major depressive disorder, n=71) compared to age matched control individuals, and examined the impact of NRG3 risk variants, rs10748842 and rs6584400, on gene expression. NRG3 subclasses displayed non-overlapping expression profiles across the lifespan, whereby expression of Classes I, II and IV were significantly affected by developmental stage (p=6.19x10-6, p=0.002 and p=6.45x10-5, respectively), being predominantly expressed during fetal and early postnatal stages. Affective disorder diagnosis impacted NRG3 expression in a subclass and diagnosis specific manner, with cortical levels of NRG3 Class I and II significantly increased in BPD and NRG3 Class I and III significantly increased in MDD. rs10748842 and rs6584400 risk genotype predicted elevated NRG3 Class II and III expression in BPD and MDD. Our findings provide support for NRG3's importance in neurodevelopment, and demonstrate novel evidence that NRG3 subclasses are differentially affected by developmental stage, affective disorder diagnosis and genetic regulation. These observations suggest that NRG3 transcripts are not redundant, but instead have specific temporal, diagnostic and tissue type selective functions.

TU3. Microglia establish region specific phenotypes in the basal ganglia and exhibit variable responses to normal aging

Lindsay De Biase, Zach Fusfeld, Kornel Schuebel, Kam-Wing Jair, Haiying Zhang, Qing-Rong Liu, Raffaello Cimbro, Isobel Hawes, Sissi Palma-Ribeiro, Hui Shen, Zheng-Xiong Xi, David Goldman, Antonello Bonci*

Microglia promote brain homeostasis and respond to diverse CNS insults. Recent studies show that microglia also influence synaptic transmission

through release of inflammatory and trophic signaling factors and phagocytosis of synapses. Microglia are generally assumed to be equivalent throughout the CNS, but this assumption has not been rigorously tested. To accurately define how microglia influence neuronal function, it will be critical to determine the nature and extent of regional microglial heterogeneity. We quantified anatomical, electrophysiological, and molecular properties of microglia in the basal ganglia (BG), a collection of brain nuclei that regulate goal-directed behaviors and are pathologically altered during addiction and neurodegeneration. Microglial density and morphology varied significantly across the nucleus accumbens (NAc), ventral tegmental area (VTA), substantia nigra pars compacta (SNc), and pars reticulata (SNr). Intracellular lysosome content was elevated in SNr microglia, suggesting that microglial phagocytotic activity varies across BG nuclei. Electrophysiological recordings revealed that 65% of SNr microglia but only 9% of VTA and SNc microglia exhibited delayed rectifier potassium currents, which have been linked to altered microglial functional states. Whole transcriptome RNA sequencing of microglia isolated from distinct BG nuclei revealed broad similarities in gene expression as well as region-specific gene expression signatures, with VTA microglia differing most prominently from other groups. During normal aging, microglial density increased by up to 80% in the VTA and SNc, but increased only moderately in the NAc and SNr and morphological abnormalities were more frequent in midbrain BG microglia. Together these findings challenge the idea that microglia throughout the CNS are functionally equivalent and raise important questions about the impact of this heterogeneity on neuronal function and susceptibility to neurodegeneration.

TU4. VTA dopamine activation regulates neuroplasticity and sensitized psychostimulant reward following sexual experience in male rats

Lauren Beloate, Lique Coolen*

Experience with and subsequent removal of the natural reward sex, leads to alterations in the mesolimbic pathway, including increased expression of the transcription factor, deltaFosB. These changes regulate sex experience-induced psychostimulant reward sensitization, as evidenced by an increased conditioned place preference (CPP) for a low dose of d-Amphetamine (Amph). Sexual behavior activates VTA dopamine neurons via activation of mu opioid receptors on inhibitory GBA interneurons and results in dopamine release in nucleus accumbens (NAc). Antagonism of D1 dopamine receptors in the NAc during mating blocks sex experience-induced deltaFosB expression and Amph CPP, suggesting that mating-induced VTA dopamine activation regulates sex experience-induced neuroplasticity and sensitized Amph reward. In the current study, we test this hypothesis using inhibitory designer receptor exclusively

activated by designer drugs (DREADD) specifically in VTA dopamine cells. rAAV5/hSvn-DIO-hm4D-mCherry was injected bilaterally into VTA of TH-Cre transgenic adult male rats. Three weeks later, males received either saline or CNO injections (i.p.) prior to each of 5 consecutive days of sexual experience or handling. Following an abstinence period of 7 days, all males were tested for Amph CPP. The next day, males were again injected with saline or CNO prior to mating or handling and perfused one hour later for analysis of CNO effects on mating-induced deltaFosB and cFos. Results showed that CNO during sex experience did not affect mating behavior, but prevented sex-induced deltaFosB expression in the NAc and medial prefrontal cortex (mPFC) and cross-sensitization of Amph CPP. Moreover, CNO blocked mating-induced cFos expression in VTA dopamine cells without affecting cFos in NAc or mPFC. In conclusion, the current study provides direct evidence that VTA dopamine cell activation during sexual experience regulates increased Amph-CPP and deltaFosB expression in the NAc and mPFC.

TU5. Estrous cycle modulates inhibition of dorsal vagal motor neurons

Carie Boychuk, Katalin Halmos, Bret Smith*

Neurons in the dorsal motor nucleus of the vagus (DMV) comprise the preganglionic parasympathetic motor output to much of the viscera and critically contribute to autonomic regulation of energy homeostasis. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter mediating both tonic (extrasynaptic) and phasic (synaptic) inhibition to the DMV. A small body of evidence suggests that GABAA receptor activity exhibits sexually dimorphic regulation. This regulation is estrous cycle-dependent and occurs even in brain regions with no direct role in reproduction. Therefore, it is possible that DMV neurons may express estrous cycle-dependent modulation of GABAergic inhibition. Since females demonstrate changes in autonomic function and energy homeostasis - both normally and after disease- differently from males, modulation of GABAergic inhibition may account for some of these sex differences. This study investigated the effect of sex and estrous cycle on both tonic and phasic modalities of GABAA receptor-mediated inhibition in the DMV using whole-cell patch-clamp recordings in FVB mice. Since estrous cycle modulation of GABAergic inhibition is typically through regulation of specific GABAA receptor subunits, subunit-specific modulation is also investigated. Results of subunit-specific changes in GABAA receptor regulation from whole-cell patch-clamp experiments can be further assessed using quantitative RT-PCR to determine if changes are transcriptionally-regulated.

Taken together, these experiments confirm that a non-reproductive brain region, the DMV, can be modulated by differences in sex hormones. Results suggest that plasticity of GABAA receptor-mediated signaling related to changes in receptor subunit composition accompanies fluctuations in sex hormones across the estrous cycle. These altered GABAA receptor currents in female mice could contribute to male-female differences in autonomic and metabolic dysfunction in disease.

TU6. GIRK channels in VTA DA neurons regulate sensitivity to cocaine-related behaviors

Nora McCall, Lydia Kotecki, Nicole Victoria, Nicholas Carlblom, Kevin Wickman*

Dopamine (DA) neurons of the ventral tegmental area (VTA) are an important neural substrate for natural rewards and drugs of abuse within the mesocorticolimbic system. In vivo exposure to drugs of abuse, such as cocaine, triggers an increase in DA neuron excitability, and thus DA neurotransmission, in the mesocorticolimbic DA system. A better understanding of the molecular changes that occur following exposure to drugs of abuse will increase our ability to develop novel pharmacotherapies for addiction. Our lab recently demonstrated that a single injection of cocaine in mice transiently suppresses G protein-gated inwardly rectifying K+ (GIRK)-dependent signaling in VTA DA neurons, an adaptation that requires the activation of D2/3 DA receptors (D2/3R) and involves GIRK channel internalization. The present work focuses on GIRK channels in VTA DA neurons and their relevance to the behavioral effects of cocaine. We hypothesize that reducing inhibitory G-protein signaling mediated by GIRK channels in DA neurons will result in increased sensitivity to cocaine. To study the contribution of GIRK channels in VTA DA neurons to behaviors triggered by cocaine, we used a conditional knockout mouse line in which Girk2 was selectively ablated in DA neurons (DATCre:Girk2flox/flox mice, GIRK2DAKO). Our preliminary data demonstrate that DA neurons of GIRK2DAKO mice have significantly blunted D2/3R- and GABABR-mediated somatodendritic currents. The reduced inhibitory function corresponds with enhanced locomotor responses to both acute and repeated cocaine exposure. Further studies will examine the role of GIRK channels in a drug-seeking behavioral task, conditioned place preference. Together, this work suggests GIRK channel activity in VTA DA neurons regulates the sensitivity of the mesocorticolimbic system to cocaine.

TU7. The lateral habenula receives an unexpected glutamatergic input from the lateral preoptic area

David Barker, David Root, Steven Zhang, Jorge Miranda-Barrientos, Huiling Wang, Marisela Morales*

The Lateral Habenula (LHb) has been identified as a brain region that plays important roles in drug abuse, psychiatric illnesses and motivated behavior. Convergent evidence has established that the LHb receives a major input from the Lateral Preoptic Area (LPO). Although the nature of this LPO-LHb pathway hasn't bee determined, it has been prosed to be inhibitory, presumably from LPO GABAergic neurons. Here, we characterized the anatomical and functional network between the LPO and the LHb. To identify specific LPO neurons targeting the LHb, the retrograde tracer fluorogold was injected into the LHb (1% via iontophoresis). Next, we established the phenotype of the fluorogold-tagged neurons by in situ hybridization detection of transcripts encoding either glutamic acid decarboxylase 65/67 mRNA (GAD, a marker of GABAergic neurons) or vesicular glutamate transporter 2 mRNA (VGluT2, a marker of glutamate neurons). Surprisingly, we found that within the total population of fluorogold-positive neurons only 15.9 ± 3.2% expressed GAD mRNA, and as many as 74.7 ± 3.2% expressed VGluT2 mRNA. These neuroanatomical findings indicate that the major projection from the LPO to the LHb is from excitatory glutamatergic neurons rather that from inhibitory GABAergic neurons, as has been previously proposed. Based on our current understanding of the habenula, this suggests that the LPO-LHb glutamatergic pathway may be important for numerous psychopathologies including depression or the aversive effects of psychostimulants. Future work will focus on the participation of the LPO-LHb glutamatergic pathway in ongoing behavior in order to specifically investigate its participation in psychiatric illness.

TU8. Ca2+-dependent and -independent inhibition of GABA release onto POMC neurons by presynaptic inhibitory GPCRs

Reagan Pennock, Shane Hentges*

GABA release onto proopiomelanocortin (POMC) neurons of the arcuate nucleus of the hypothalamus occurs through action potential (AP)-dependent synchronous release, as well as AP-independent spontaneous release. Both AP-dependent and -independent release are robustly inhibited by Gαi/o-coupled G-protein coupled receptors (GPCRs) located on GABAergic terminals presynaptic to POMC neurons, but it is currently unknown whether inhibition of both types of release occurs through a common mechanism.

GPCR-mediated inhibition of GABA release onto POMC neurons by the mu opioid receptor (MOR) and GABAB receptor (GABABR) was examined under various conditions that altered Ca2+ influx into presynaptic terminals. Both receptors maintained their ability to inhibit GABA release onto POMC neurons in the absence of external Ca2+, as well as in the presence of unregulated Ca2+ influx into presynaptic terminals. Thus, inhibition of AP-independent GABA release onto POMC neurons occurs through a Ca2+-independent mechanism, possibly through direct actions at the release machinery. To examine the Ca2+-dependence of MOR- and GABABR-mediated inhibition of AP-dependent GABA release, Ca2+ was replaced with Sr2+ in the external recording solution. Previous studies have shown that evoking transmitter release with Sr2+ can occlude GPCR-mediated inhibition of release that acts directly on the release machinery. Both MOR- and GABABR-mediated inhibition of evoked release was maintained in the presence of Sr2+, demonstrating that inhibition of evoked release by both the MOR and GABABR occurs through a Ca2+-dependent mechanism. Further experiments performed in the presence of selective Ca2+ channel blockers demonstrated that evoked GABA release onto POMC neurons was dependent on Ca2+ influx through both P/Q- and N-type voltage dependent Ca2+ channels, and that influx through both type of channel was strongly inhibited by activation of the MOR or GABABR.

TU9. Optogenetic assessment of dynamic input integration in the ventral striatum

Julie Brooks, Patricio O'Donnell*

Medium spiny neurons (MSN) serve as a site of convergence for multiple brain regions involved in goal-directed behavior, including the prefrontal cortex (PFC) and hippocampus (HP). These inputs are believed to differentially influence striatal circuitry in an activity dependent manner. Electrophysiological recordings from anesthetized rats showed robust PFC stimulation leads to a reduction in ongoing HP-evoked MSN responses, partially, through the recruitment of local inhibitory mechanisms within the ventral striatum (VS). These data indicate that burst-like cortical activity is capable of attenuating less salient excitatory input within the striatum. Here, we explored the mechanisms involved in cortical suppression of competing excitatory synaptic inputs on MSNs. Whole-cell recordings were performed from rats receiving bilateral hippocampal injections of channelrhodopsin (ChR2). Input interactions were assed in MSNs through electrical stimulation of PFC fiber tracts and light stimulation of HP inputs expressing ChR2. We have demonstrated that optogenetically evoked HP EPSPs are greatly attenuated after a short latency following burst-like corticostriatal stimulation. Bath application of picrotoxin, but not saclofen, reduced the magnitude of suppression suggesting

inhibitory GABA-A, but not GABA-B, receptor activation is likely to play a role. As the reduction is not complete, we assessed the role of two signaling molecules known to modulate striatal neurotransmission in a retrograde manner. We found that bath application of the cannabinoid receptor antagonist AM251 enhanced cortical suppression of optically evoked HP responses suggesting a GABAergic locus of action for AM251. Similar experiments are being conducted using the kappa antagonist nor-BNI. These data further substantiate the assertion that robust PFC activation gates weaker, competing excitatory inputs in the VS through the recruitment of multiple local synaptic mechanisms.

TU10. Reversal of morphine-induced cell-type specific synaptic plasticity in the nucleus accumbens shell blocks reinstatement

Matthew Hearing*, Jakub Jedynak, Anna Ingebretson, Stephanie Ebner, Anders Asp, Erin Larson, Mark Thomas

Unlike psychostimulants, little is known of opiate-induced synaptic plasticity at excitatory synapses in the nucleus accumbens (NAc) and its relevance to drug-seeking. Medium spiny neurons (MSNs), the principal NAc cell-type, typically express either the dopamine receptor 1 (D1-MSNs) or dopamine receptor 2 (D2-MSNs), the presence of which determines cell physiology and contribution to drug-related behaviors. BAC transgenic mice expressing fluorescent proteins under the control of D1R or D2R promoters were used to identify opiate-induced plasticity in NAc shell MSN glutamate signaling following 10-14 d withdrawal from repeated morphine. Both AMPAR/NMDAR (A/N) ratios and AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs) were increased in D1R-, while the latter was reduced in D2-MSNs. Assessment of curren-voltage relationships and use the selective antagonist, Naspm, showed an increased presence of GluA2-lacking AMPAR following morphine. Furthermore, paired-pulse stimulation showed significant increases and decreases in release probability at D1- and D2-MSNs respectively. We next explored whether reversal of this plasticity is able to prevent drug-associated behavior using a conditioned place preference model. Repeated administration of the antibiotic, ceftriaxone, which up-regulates glutamate transporter GLT-1 expression, during withdrawal reversed increases in D1-MSNs AMPAR signaling, enhanced signaling in D2-MSNs, and blocked reinstatement of place preference. Furthermore, optogenetically-induced depotentation of morphine synaptic strength of infralimbic cortex-shell synapses blocked reinstatement of place preference. These data identify novel cell-type and pathway-specific alterations in synaptic strength and transmission

that are distinct and overlapping in locus and timeline from those produced by psychostimulants, and implicates the NAc shell as a key site for plasticity involved in the conditioned rewarding effects of morphine.

TU11. Methylphenidate enhances early sensory signal processing in the rat visual thalamus through noradrenergic signaling

Rachel Navarra, Andrew Gargiulo, Brian Clark, Barry Waterhouse*

Abnormal processing of sensory information is a feature of many neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD). The psychostimulant methylphenidate (MPH) is used clinically to treat ADHD as well as off-label as a performance enhancing drug (PED) by healthy individuals. MPH enhances catecholamine transmission via blockade of norepinephrine (NE) and dopamine (DA) reuptake transporters. However, it is not clear how MPH impacts neural circuits responsible for sensory signal processing. To investigate the effects of MPH acting on sensory circuits, we recorded neuronal responses to light cues within the dorsal lateral geniculate nucleus (dLGN; thalamic relay for visual information) while rats performed a visual signal detection task. MPH increases both speed and strength of responses to visual stimuli within dLGN, suggesting that enhanced sensory signal transmission may be a significant component of the action of PEDs. Although MPH administration did not affect accuracy of signal detection in rats highly trained in this task, it did improve the speed of making correct responses. Further, we immunostained sections through the dLGN and demonstrated that all catecholaminergic axons were noradrenergic, not dopaminergic. This work suggests that MPH, acting via noradrenergic mechanisms, can substantially impact early stage sensory signal processing, an effect that could positively influence responses to salient stimuli in ADHD patients and healthy individuals seeking performance enhancement.

TU12. β-Arrestin D2-receptor biased ligand, UNC9994, increases the excitability of prefrontal fast-spiking interneurons

Steven Gee, Patricio O'Donnell*

Activation of dopamine 2 receptors (D2Rs) not only leads to downstream effects through canonical, G-protein mediated signaling, but also through non-canonical β-arrestin-dependent signaling. Indeed, all clinically effective antipsychotics interact with D2Rs and signal through both canonical and non-canonical pathways. Parsing apart the effects of these signaling pathways in prefrontal and striatal circuits may shine light on the mechanisms of current

antipsychotics and lead to the development of more effective ones. Here, we examined the effects of second-generation antipsychotic, aripiprazole, and β-arrestin biased D2R ligand UNC9994, on fast spiking interneurons (FSIs) in the prefrontal cortex. We performed whole-cell recordings from GFP-labeled FSIs in acute slices from GAD1-eGFP mice. We injected depolarizing current steps in current-clamp mode and recorded the number of action potentials generated. Aripiprazole elicited an increase in excitability in prefrontal FSIs, consistent with agonist-like activity previously reported with the D2R agonist, quinpirole. Interestingly, we found that UNC994 elicited a more robust increase in FSI excitability than the increase observed with aripiprazole. This effect was absent in FSIs recorded from β-arrestin2 KO mice, suggesting signaling through β-arrestin. Parvalbumin-positive FSIs in the prefrontal cortex are thought to be dysfunctional in schizophrenia and enhancing their activity may reverse the cognitive deficits observed in this disorder. Thus, enhancing the activity of prefrontal FSIs by β-arrestin signaling offers an opportunity for novel antipsychotic drugs that also improve negative symptoms and cognitive deficits associated with schizophrenia.

TU13. DAPK1 functions in NMDA receptor dependent synaptic long-term depression

Dayton Goodell, Vincent Zaegel, Steven Coultrap, Ulli Bayer*

Death associated protein kinase 1 (DAPK1) is a Ca2+/calmodulin (CaM) regulated serine/threonine protein kinase that acts as a ubiquitous mediator of cell death, playing a key role in signaling pathways leading to apoptosis, autophagy, and necrosis. DAPK1 is expressed highly in the developing brain, and its expression remains high in the cortex and hippocampus into adulthood. During acute neuronal insult, pathological increases in intracellular Ca2+ influx through NMDA type glutamate receptors (NMDARs) result in the calcineurin dependent activation of DAPK1 through dephosphorylation of S308 within the autoregulatory CaM binding domain of DAPK1. However, a role for DAPK1 outside of pathological signaling has not been examined previously. Here, we reveal a novel role for DAPK1 in the long-term depression (LTD) of synaptic strength in the hippocampus. Using slice biochemistry we show that DAPK1 is transiently activated in the CA1 in response to LTD stimuli, noted by a reduction in the autoinhibitory phosphorylation of S308 of DAPK1. Live imaging of over-expressed DAPK1 in hippocampal neuronal culture demonstrates that DAPK1 localizes to excitatory spines, and is trafficked differentially in response to different plasticity inducing stimuli. While DAPK1

remains primarily synaptic in response to LTD stimuli, it rapidly leaves excitatory synapses during long-term potentiation (LTP) like stimuli. Finally, genetic or pharmacological inhibition of DAPK1 demonstrates a necessity for DAPK1 in the normal expression of electrophysiological NMDAR dependent LTD in the CA1. Together, these results demonstrate a novel role for DAPK1 in physiological synaptic plasticity, separate from its known pathological roles.

TU14. NMDA efficiently evokes dendritic release of neuropeptides: a quantitative real time assessment

Soledad Pitra, Javier Stern*

Neuroendocrine neurons of the hypothalamic paraventricular nucleus (PVN) are known to dendritically release neuropeptides, such as vasopressin (VP), that mediate communication between functionally distinct neuronal populations of this brain region. Still, the fundamental mechanisms regulating neuropeptide dendritic release remain unknown, due to the lack of highly sensitive tools that enable its quantitative measure. To overcome this, Chinese hamster ovarian cells were engineered to express the VP V1a receptor and the genetically-encoded Ca2+ indicator RGeco (CHOVP). These cells were plated onto hypothalamic slices containing eGFP-VP neurons in the PVN. Exogenously applied VP evoked dose-dependent increases in CHOVP [Ca2+] i (maximum sensitivity= 10 nM; $p<0.0001$, 1-way ANOVA); CHOVP [Ca2+] i responses were directly proportional to the stimulus duration ($p=0.01$, 1-way ANOVA), and inversely related to the distance to the VP source ($p=0.003$, 1-way ANOVA). Neuropeptide dendritic release from the entire VP neuronal population following an osmotic challenge (+10 mOsm) induced a gradual increase in CHOVP [Ca2+]i (106.5±19.1 F/F0*s, n=7). To determine if CHOVP detected dendritic VP release from a single neuron, we patched and stimulated eGFP-VP neurons. Repetitive burst firing evoked by direct current injection (5 pulses, 500 ms, 5 Hz, 102.1±14 action potentials) increased CHOVP [Ca2+]i (22.7±5.8 F/F0*s, n=21) with a mean delay of 64.1±13.1 s. Despite evoking less action potentials (67.3±26.3), focal application of NMDA (50 μM) induced a significantly larger CHOVP [Ca2+]i (64.1±14.3 F/F0*s, n=23) with a shorter delay (14.6±2.8 s) ($p<0.02$ in both cases). Changes in CHOVP [Ca2+]i were blocked by a V1a-R antagonist. Our results validate a novel approach for real time detection of neuropeptide dendritic release in an in vitro preparation, and support NMDA receptor-driven firing to more efficiently trigger dendritic release of neuropeptides than action potential firing alone.

TU15. Observing and controlling projection-defined medial prefrontal cortex subpopulations in reward and aversion

Caitlin Vander Weele, Romy Wichmann, Eyal Kimchi, Isabella Espinel, Ehsan Izadmehr, Schut Evelien, Craig Wildes, Kay Tye*

The medial prefrontal cortex (mPFC) has been implicated in high order cognitive functions and coordinates the execution of motivated behaviors though its projections to downstream targets. However, how mPFC neurons that project to different downstream targets represent and coordinate motivated behaviors is unclear. Our goal is to understand how mPFC neuronal subpopulations encode stimulus valence and where this information is communicated downstream to instigate adaptive behavioral responses, such as approach or avoidance. Using in vivo freely-moving calcium imaging enabled by a genetically-encodable calcium indicator (GCaMP6m), we explored the real-time neural dynamics in the mPFC during exposure to innately appetitive and aversive olfactory stimuli. We have found that the mPFC neurons have diverse response profiles. Approximately 50% of neurons (n = 273) responded similarly, perhaps encoding general salience. ~26% showed selective responding to only one of the stimuli. Another subset of mPFC neurons (~19%) showed opposing responses, characterized by increased activity to one stimulus and decreased activity to the other. mPFC neurons encoding positive or negative valence likely have distinct downstream targets. The dorsal periaqueductal gray (dPAG) is has been linked to aversive behaviors and we have found that optogenetic activation of mPFC terminals in the dPAG produces avoidance and anxiety-related behaviors. Further, stimulation of this pathway evokes defensive in the marble burying assay, suggesting that stimulation of the mPFC:dPAG circuit triggers active avoidance behaviors. These effects were not observed in control animals. The paraventricular nucleus of the thalamus (PVT) has been implicated in reward, and receives dense input from the mPFC. To selectively manipulate mPFC neurons terminating in PVT, we used an anterogradely traveling viral vector carrying ChR2 in a double inverted open reading frame in the mPFC and a retrogradely traveling viral vector carrying cre-recombinase in the PVT. In animals expressing ChR2 only in neurons originating in the mPFC and terminating in the PVT, we show that activation of the PVT-projecting mPFC neurons is positively reinforcing; an effect not observed in controls. Together, these data suggest that the mPFC controls avoidance and approach behaviors through its projections to the dPAG and PVT, respectively. Our results advance us towards a circuit-level explanation for how the mPFC can exert control over valence-defined motivated behaviors.

TU16. Synthetic activation of infralimbic cortex inhibits cocaine seeking via efferents to the nucleus accumbens shell

Jamie Peters, Isabel F. Augur, Andrew R. Wyckoff, Gary Aston-Jones, Peter W. Kalivas*

Traditional brain-site pharmacology and disconnection studies have suggested that the projection from infralimbic medial prefrontal cortex to the nucleus accumbens shell inhibits cocaine seeking. However, due to the decussation of this pathway, such methodologies fall short of proving a direct connection between the infralimbic cortex and accumbens shell mediates this effect. Furthermore, brain-site specific pharmacology is not amenable to clinical applications. Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) can be artificially expressed in a brain region of interest using viral-mediated gene transfer, and thereafter activated by systemic administration of the synthetic ligand Clozapine-N-oxide (CNO), underscoring the translational potential of such an approach. We expressed the Gq-DREADD in infralimbic cortex under control of a synapsin promoter and examined its therapeutic potential in a preclinical model of cocaine seeking. Acute synthetic activation of infralimbic cortex with CNO inhibited cue-induced reinstatement. To restrict expression of the Gq-DREADD to nucleus accumbens projecting infralimbic neurons, we used a combinatorial viral approach coupling a Cre-dependent Gq-DREADD in infralimbic cortex with the retrograde-traveling canine adenovirus (CAV-Cre) in accumbens shell. Acute synthetic activation of infralimbic-shell projecting neurons with CNO similarly inhibited cue-induced reinstatement. Synthetic activation of this same neuronal population (in the same animals) did not alter food seeking. These data strongly suggest that a direct projection from infralimbic cortex to nucleus accumbens shell exerts inhibitory control over cocaine seeking (consistent with Ma et al. 2014). As viral-mediated gene transfer therapies move closer to the clinic, this DREADD-approach offers therapeutic potential for the treatment of cocaine addiction.

TU17. Regulation of goal-directed action selection by cocaine, MDMA, and orbitofrontal BDNF-TrkB

Elizabeth Pitts, Kristie Garza, Shannon Gourley*

Cocaine dependence is characterized by compulsive drug use and maladaptive decision-making. Adolescents are particularly vulnerable to the effects of cocaine; for example, cocaine exposure during adolescence increases the risk of developing lifelong addictions. Previous studies have shown that subchronic cocaine exposure during adolescence, but not adulthood, results in a bias

towards stimulus-driven habits in mice, and this bias persists into adulthood. Changes in Brain-derived Neurotrophic Factor (BDNF) in the orbitofrontal prefrontal cortex (oPFC) could underlie, in part, this habit bias, while strategies that stimulate cortical BDNF systems could be protective. Here we utilized viral-mediated gene transfer to decrease the expression of Bdnf and, in separate mice, interfere with the activity of its high-affinity receptor tyrosine kinase receptor B (trkB) selectively in the oPFC. Both manipulations induced habit-like behavior in an instrumental contingency degradation task. Next, we hypothesized that stimulating BDNF expression in the oPFC could block habits by enhancing response-outcome learning and memory. We report that 3,4-methylenedioxymethamphetamine (MDMA) increases BDNF levels in the oPFC, but not the amygdala or dorsal striatum, and also "breaks" habits resulting from adolescent cocaine exposure, as well as oPFC-selective Bdnf knockdown. MDMA was delivered immediately following instrumental contingency degradation, suggesting that it enhances the consolidation of new response-outcome learning and memory. Finally, 7,8-dihydroxyflavone (7,8-DHF), a trkB agonist, also reverses cocaine-induced habits, further suggesting that BDNF-trkB systems are a point of intervention in combatting maladaptive decision making following repeated cocaine exposure.

TU18. Subanesthetic ketamine reduces the incentive-motivational value of reward cues in sign-tracking individuals: implications for addiction treatment

*Christopher Fitzpatrick, Jonathan Morrow**

The attribution of incentive-motivational value to reward-related cues contributes to cue-induced craving and relapse in addicted patients. Recently, it was demonstrated that subanesthetic ketamine increases motivation to quit and decreases cue-induced craving in cocaine-dependent individuals. Although the biopsychological mechanism of this effect in addicted patients is currently unknown, one possibility is that subanesthetic ketamine decreases the incentive-motivational value of reward-related cues. In order to address this, we used a Pavlovian conditioned approach (PCA) procedure to identify rats that are more (sign-trackers; STs) or less (goal-trackers; GTs) likely to attribute incentive-motivational value to reward-related cues. This model is useful because STs are more vulnerable to cue-induced reinstatement of drug-seeking behavior and seek drug-related cues despite adverse consequences. We tested the effect of subanesthetic ketamine (32 mg/kg) on the expression of PCA behavior (Experiment 1) and the conditioned reinforcing properties

of reward-related cues (Experiment 2) in STs and GTs. In Experiment 1, subanesthetic ketamine decreased sign-tracking behavior in STs but did not affect PCA behavior in GTs. In Experiment 2, subanesthetic ketamine did not affect conditioned reinforcement. Rather, when the cue was presented, ketamine decreased conditioned approach in STs but not GTs. These results suggest that subanesthetic ketamine may decrease the incentive-motivational value of reward-related cues, a mechanism that could be exploited for therapeutic benefit in addiction treatment.

TU19. An evaluative conditioning approach to alter behavioral and neuronal responses to visual food cues

Kristina Legget, Jason Tregellas*

Implicit (automatic) attitudes towards food are associated with self-reported food choices and consumption. As such, altering neuronal and behavioral food cue responses by changing automatic associations may be a viable weight loss strategy. This study investigated effects of an evaluative conditioning approach, in which high-calorie food cues were implicitly primed with negatively-valenced images, and low-calorie food cues with positively-valenced images. These images were presented immediately before food images, but not consciously perceived. We hypothesized that this bottom-up conditioning approach would alter food cue perception by modifying affective food associations. Measures of "desire to eat" the foods were assessed before and after (a) "active" implicit priming (IP; N=22), or (b) a control intervention (N=20). There was a significant main effect of calorie ($p<0.001$) and a significant calorie-by-group interaction ($p=0.025$), with significantly greater high-calorie rating decline in active compared to control IP ($p=0.036$). Effects persisted 3-5 days post-intervention ($p=0.007$), and extended to high-calorie foods not included in the intervention ($p=0.008$), suggesting effect generalization. An additional 6 subjects completed fMRI (a) while viewing food cues before and after the IP intervention, and (b) during IP, to identify potential neuronal mechanisms. IP engaged a similar network to that previously shown to be altered in obese-prone individuals in response to energy intake. Furthermore, IP decreased neuronal response of this network to high- vs. low-calorie food cues, specifically in insula/inferior prefrontal cortex, $p<0.05$. The negative images were selected to elicit disgust, which would be expected to elicit an insula response. Indeed, results support insula activation during IP, suggesting that the intervention is affecting the hypothesized biological target. IP may represent a potential novel intervention for treatment and prevention of obesity.

TU20. The role of Akt3 in neurocognitive dysfunction: linking GWAS and function in schizophrenia

Kristy Howell, Amanda Law*

Genome Wide Association studies (GWAS) have identified risk loci in and around the AKT3 gene. AKT3 plays a role in attainment of normal brain size, but the neural mechanisms and its potential role in schizophrenia are unknown. The focus of this project was to examine a novel mouse model deficient in Akt3 on the C57BL6 background to determine its role in neurodevelopment and behavior. Adult wildtype (Akt3+/+), heterozygous (Akt3+/–), and knockout (Akt3–/–) mice were phenotyped to evaluate the role of Akt3 on development. We assessed sensorimotor gating, anxiety, learning and memory, cognitive deficits and social cognition in both male and female mice. Normal sensorimotor gating, fear conditioning and extinction and sociability were observed with no anxiety phenotype detected in male mice. However, we determined a significant deficit in the temporal order object recognition (TOOR) task with an allelic dose dependent response in Akt3 male mice. As the TOOR task involves multiple brain regions including the perirhinal cortex, hippocampus and frontal cortex, we investigated further to disentangle which region is impacted by Akt3 deficiency. As no deficits were observed in Novel Object or Object Location tasks, which are perirhinal cortex- and hippocampal-mediated respectively, we conclude that Akt3 plays a specific role in prefrontal cortical (mPFC) mediated cognitive function. Preliminary female behavior results will be presented alongside the male behavior. Molecular studies to examine the impact of Akt3 deficiency on the AKT pathway and its downstream targets are underway. Our studies suggest Akt3 plays distinct roles in neurodevelopment and behavior as it relates to specific domains of learning and memory, providing Akt3 as a novel potential pharmacological target for cognitive dysfunction in schizophrenia.

TU21. Movement modulates phase-locking between neuronal discharge in human STN and cortical oscillations

Witold J. Lipski, Tom A. Wozny, Ahmad Alhourani, Efstathios Kondylis, Michael J. Randazzo, Robert S. Turner, Donald J. Crammond, R. Mark Richardson*

Deficits in the initiation and control of movement account for many symptoms in Parkinson's disease (PD), including akinesia, bradykinesia, freezing, rigidity and tremor. The underlying etiology in PD involves the degeneration of the dopaminergic nigrostriatal pathway, which results in increased activity in the subthalamic nucleus (STN). This pathological hyperactivity of STN, in turn, suppresses thalamocortical activity via the indirect pathway, and is thought to result in hypoactive movement deficits such as akinesia, bradykinesia,

rigidity, and freezing for which deep brain stimulation (DBS) of the STN is an effective therapy. Recent findings implicate the interactions between sensorimotor cortex and the STN in the pathophysiology of PD, which may contribute to the generation of aberrant cortical-basal ganglia activity that disrupt movement control. However, the physiology and functional significance of these interactions is not understood. In order to elucidate the role of cortico-subthalamic interactions in movement control, we recorded single neuron (spike) activity in the STN simultaneously with ECoG activity from sensorimotor cortex of PD patients undergoing STN DBS electrode implantation. Nine subjects performed a bimanual grip force reaction time task intra-operatively during data recording. Neuronal spike firing in the STN was found to be phase-synchronized with oscillations in sensorimotor cortex within theta-alpha (4-11) and low beta (12-24) and high beta (25-40) frequency bands. Furthermore, the magnitude of synchronization was dynamically modulated during movement, and this modulation was distinct within each frequency band examined. This suggests that synchronization of STN neurons to LFP oscillations within these frequency bands subserves different functions.

TU22. Preventing calcium dysregulation and synaptic loss in Huntington's disease: an evaluation of sigma-1 receptor agonists in corticostriatal co-cultures from YAC128 mice

Daniel Ryskamp, Jun Wu, Lili Wu, Ilya Bezprozvanny*

In Huntington's disease (HD), mutant Huntingtin (mHtt) causes early corticostriatal synaptic dysfunction and eventual neurodegeneration of striatal medium spiny neurons (MSNs). There are no disease-modifying treatments for HD, but ongoing clinical trials with Pridopidine show promise for improving motor symptoms. Also, Pridopidine is neuroprotective in R6/2 HD mice. Yet, the target of Pridodipine and its mechanism of action are unclear. As recent binding studies identified Sigma-1 receptor (S1R) as a high affinity receptor for Pridopidine, we evaluated the relevance of S1R as a therapeutic target. S1R is an endoplasmic reticulum (ER)-resident transmembrane protein and changes in its expression or genetic sequence are associated with neurodegenerative phenotypes. S1R activity is regulated by ER Ca2+ homeostasis, which is perturbed in HD, making it likely for S1R activity to also be abnormal. Consistent with this we observed compensatory upregulation of S1R protein in striatal samples from aged YAC128 HD mice and HD patients. We used corticostriatal co-cultures to examine mechanisms of age-dependent dendritic spine loss in MSNs from YAC128 mice. The commercially available S1R agonist 3-PPP, which has a very similar chemical structure to Pridopidine and an identical affinity to S1R, completely prevented MSN spine loss in YAC128 co-cultures (100 nM for 16 hours on DIV21). This rescue was blocked by

knockout of neuronal S1R using lenti-viruses to express Cas9/gRNA targeting mouse S1R. Expression of human S1R restored protection by 3-PPP. We previously found that mHtt sensitizes the ER Ca2+ channel InsP3R1, resulting in depletion of ER Ca2+ and elevation of store-operated Ca2+ entry in MSNs to synaptotoxic levels. We now report that 3-PPP normalizes YAC128 MSN Ca2+ homeostasis by suppressing InsP3R1 hyperactivity. S1R knockout prevented replenishing of ER Ca2+ by 3-PPP. This reveals a potential mechanism of action for S1R agonists and highlights S1R as a target for HD.

TU23. Alzheimer-associated Aβ oligomers impact the central nervous system to induce peripheral metabolic deregulation

Natalia Lyra e Silva*, Julia Clarke, Claudia Figueiredo, Rudimar Frozza, Jose Ledo, Danielle Beckman, Renata Frazão, Rodrigo Medeiros, Frank LaFerla, Jose Carvalheira, Mario Saad, Douglas Munoz, Licio Velloso, Sergio Ferreira, Fernanda De Felice

Alzheimer's disease (AD) is associated with peripheral metabolic disorders. Clinical/epidemiological data indicate increased risk of diabetes in AD patients. Here, we show that intracerebroventricular infusion of AD-associated Aβ oligomers (AβOs) in mice triggered peripheral glucose intolerance, a phenomenon further verified in two transgenic mouse models of AD. Systemically injected AβOs failed to induce glucose intolerance, suggesting AβOs target brain regions involved in peripheral metabolic control. Accordingly, we show that AβOs affected hypothalamic neurons in culture, inducing eukaryotic translation initiation factor 2α phosphorylation (eIF2α-P). AβOs further induced eIF2α-P and activated pro-inflammatory IKKβ/NF-κB signaling in the hypothalamus of mice and macaques. AβOs failed to trigger peripheral glucose intolerance in tumor necrosis factor-α (TNF-α) receptor 1 knockout mice. Pharmacological inhibition of brain inflammation and endoplasmic reticulum stress prevented glucose intolerance in mice, indicating that AβOs act via a central route to affect peripheral glucose homeostasis. While the hypothalamus has been largely ignored in the AD field, our findings indicate that AβOs affect this brain region and reveal novel shared molecular mechanisms between hypothalamic dysfunction in metabolic disorders and AD.

TU24. Differential mechanisms of action of monoacylglycerol lipase inhibition on blood-brain-barrier integrity following inflammatory or ischemic insults

Justin Piro, Georgette Suidan, Sharron O'Neill, YeQing Pi, Marrissa Ilardi, Edward Guilmette, Andrew Cameron, Robert Bell, Tarek Samad*

Acute neurological insults caused by infection, ischemia or traumatic events are often associated with breakdown of the blood brain barrier (BBB) followed by infiltration of peripheral cells and proteins. Extravasation of these peripheral components into the brain parenchyma results in inflammation, oxidative stress, edema, excitotoxicity and neurodegeneration. Preserving or rescuing BBB integrity and function represents a drug discovery area of high therapeutic potential. Elevated levels of arachidonic acid, and downstream arachidonates, are known to induce BBB dysfunction. Moreover, cannabinoid agonists were shown to protect BBB function in vitro and in vivo. The most abundant endocannabinoid in the brain, 2-arachidonyl glycerol (2-AG), is tightly regulated by the enzymatic activity of serine hydrolases. Monoacylglycerol lipase (MAGL) hydrolyzes 2-AG, terminating its signaling at cannabinoid receptors. We and others have recently shown that arachidonic acid pool produced by MAGL hydrolysis of 2-AG is used to fuel arachidonate production in the brain. Pharmacological inhibition of MAGL leads to simultaneous enhancement of cannabinoid receptor signaling and arachidonic acid lowering in the brain. We hypothesized that selective and brain penetrant MAGL inhibitors can rescue BBB function following insult. Here we show that MAGL mRNA is abundantly expressed in human cerebral endothelial cells and pericytes, both components of the neurovascular unit. Furthermore, the protein levels of MAGL are increased in cerebral endothelial cells following addition of TNFα suggesting a direct role for MAGL activity in BBB biology. We tested the ability of a MAGL inhibitor to prevent or reverse BBB damage following an inflammatory or ischemic insult in vivo. Utilizing a systemic inflammation model (LPS) or an ischemia model (Rose Bengal) to induce BBB breakdown, we demonstrate that inhibition of MAGL is sufficient to improve BBB integrity. In order to dissect out the mechanism by which MAGL inhibition exerts its protective properties, we co-administered CB1 and CB2 antagonists. Interestingly, simultaneous antagonism of CB1/2 revealed two different mechanisms of action. In the inflammatory LPS model, CB1/2 antagonists had no effect on the efficacy of MAGL inhibitors at protecting the BBB. However, blocking CB1/2 signaling altered MAGL inhibitor efficacy in the ischemic Rose Bengal model. These results suggest that MAGL inhibition exerts its effects on

BBB function through two distinct modes of action depending on the nature of the initial insult, by lowering arachidonic acid (inflammation driven pathology) or enhancing cannabinoid signaling (ischemia driven pathology). The current findings suggest that MAGL inhibition is a promising strategy to reduce neurovascular dysfunction associated with systemic infection or ischemic stroke.

TU25. Effects of controlled cortical impact brain injury on cell loss and neurogenesis in the mouse dentate gyrus

Jeffery Boychuk, Corwin Butler, Bret Smith*

Hippocampal circuits containing dentate granule cell (DGCs) are altered after brain insult, but the status of these circuits following focal brain injury is not fully understood. In this study we examined changes in the dentate gyrus contralateral and ipsilateral to controlled cortical impact (CCI) brain injury. Histological analysis was performed using Fluoro-Jade B (FJB), Nissl, and doublecortin (DCX) markers to test for CCI-induced changes in degenerating DGCs, DGC layer thickness, and adult-born DGCs, respectively. Coronal sections of hippocampus were sampled along the septotemporal hippocampal axis of male CD-1 mice. The hippocampus located contralateral to CCI did not significantly differ from sham-injury for any outcome tested. At 72 hours post-injury, the dentate gyrus and hilus ipsilateral to CCI exhibited a significantly greater density of FJB-positive cells than in the hemisphere contralateral to CCI. The thickness of the DGC layer was then measured to test whether this degeneration resulted in a net change in DGC layer area. At 14 days post-injury, no significant difference was detected in the thickness of the DGC layer ipsilateral to CCI compared to sham-injury or contralateral to CCI. The density of DCX-positive cells in the dentate gyrus was then measured in order to test whether CCI affected adult neurogenesis. At 14 days post-injury, the dentate gyrus ipsilateral to CCI exhibited a significantly greater density of DCX-positive cells relative to sham-injury or contralateral to CCI. These results suggest that adult-born DGCs may provide endogenous cell replacement following focal brain injury, but questions remain regarding newborn DGC survival and integration into hippocampal networks. Ongoing studies are using viral vector approaches to identify integration of adult-born DGCs of CCI and sham-injured mice into hippocampal circuitry.

WE1. Neuronal Pentraxin 1 is essential for neuronal activity dependent mitochondrial dynamics

*Joana Figueiró-Silva, Petar Podlesniy, Ramon Trullas**

Neurons regulate the length of their mitochondria in an activity dependent manner by altering the equilibrium between mitochondrial fission and fusion. We have investigated the role of Neuronal Pentraxin 1 (NP1), a neuronal activity dependent pro-apoptotic protein, in mitochondrial fragmentation evoked by potassium depolarization or by Amyloid beta (Ab) oligomers in cultured cortical neurons. Both treatments reduce mitochondrial length through different pathways; fragmentation caused by Ab, but not that evoked by potassium depolarization, depends on NMDA receptor activation. In contrast, fragmentation evoked by both treatments is mediated by DRP1. Deletion of NP1 inhibits mitochondrial fragmentation evoked either by potassium depolarization or oligomeric Ab and prevents the translocation of DRP1 from cytosol to mitochondria. These results suggest that mitochondrial fragmentation evoked by potassium depolarization or by Amyloid beta (Ab) oligomers is through facilitation of Drp1 dependent mitochondrial fission evoked by NP1. Supported by grants SAF2014-56644-R and CIBERNED-PI2013/08-03.

WE2. Sirtuin3 regulates mitochondrial fusion by optic atrophy 1 deacetylation

Kimberly Kleinschmidt, Bradley Kincaid, Austin Kennedy, Wenjun Song, Jin Chen, Michael Kalizeswski, Blaise Bossy, Eric Verdin, Ella Bossy-Wetzel*

Mitochondrial dysfunction is implicated in neurodegeneration. Mitochondria are highly dynamic and divide and fuse. Excessive division without fusion causes fragmented mitochondria, ATP depletion, oxidative stress, synaptic loss, and neuronal cell death. Optic atrophy 1 (OPA1) is required for mitochondrial fusion. Inherited OPA1 mutations trigger retinal ganglion cell death and optic nerve degeneration. While OPA1 mutations predispose to genetic forms of optic nerve degeneration, it is unknown whether OPA1 becomes inactivated in aging and sporadic disorders. Sirtuins are NAD+-dependent protein deacetylases stimulating energy metabolism and cell survival. Sirtuin-3 (SIRT3) is present in mitochondria. SIRT3 is activated by mild metabolic stress. As a result, mitochondrial enzymes become activated. The role of SIRT3 in the retina remains unknown. Both SIRT3 and OPA1 localize to the mitochondrial cristae and their deletions show similar defects suggesting a functional link. The purpose of this study was to test whether SIRT3 regulates OPA1. We show here that OPA1 is acetylated at a specific lysine residue close to the GTPase

domain and a hot spot for pathogenic OPA1 mutations linked to optic nerve degeneration. Purified SIRT3 deacetylates OPA1 and stimulates its GTPase activity and mitochondrial fusion. SIRT3 deletion in mice causes chronic OPA1 hyperacetylation in the retina and mitochondrial fragmentation in vivo. SIRT3 activation during fasting causes OPA1 deacetylation in vivo. By contrast, a SIRT3 decrease during high-fat diet feeding results in OPA1 hyperacetylation. SIRT3 reduction in aged mice causes OPA1 hyperacetylation. Deacetylated OPA1 has enhanced GTPase activity, promotes mitochondrial fusion and inhibits cell death. Collectively, we discovered a novel SIRT3-mediated OPA1 activation and the erosion of this protective pathway in aging.

WE3. Regulation of the actin interacting protein drebrin by mutations in HspB1

*Marina Mata, XianKui Sun, David Fink**

Heat shock protein B1 (HspB1) is an ATP-independent molecular chaperone with a conserved α-crystalline domain in the C-termini region. A number of mutations in HspB1 have been identified in families with Charcot Marie Tooth type IIF (CMT-IIF) disease or with distal hereditary motor neuropathy II (dHMN II). Mutations outside the crystalline domain (P39L, G84L, P128S, P182L) associate with dHMN, while mutations S135F, R136W and R127W associate mainly with a AD CMT-IIF phenotype. Wild type (wt) HspB1 reduces RhoA activation by translational inhibition of PDZ-RhoGEF, a RhoA specific GEF. Decreased expression of PDZ-RhoGEF by HspB1 was accomplished by enhancing expression of specific microRNAs (miR20a and miR128) that inhibit the translation of PDZ-RhoGEF and resulted in an increased neurite growth response. The regulatory effect of HspB1 on RhoA activity is blocked by mutation in S135F of HspB1 but not by R136W and R127W. This suggested either that these HspB1 mutations alter independent cellular mechanisms or that their effects may converge downstream of RhoA GTPase signaling to cause similar disease phenotype. We constructed lentiviral vectors carrying full length human HspB1 cDNA of wt or mutant S135F, R136W or R127W. Cortical neurons derived from SD rat pups E15 were transfected to expressed wt or mutant HspB1transgene to determine their effect on actin cytoskeleton. The studies showed S135F, R16W and R127W mutations cause HspB1 to partition more readily with the cytoskeletal fraction and enhance the binding of HspB1 to F-actin leading to the loss of Drebrin, an F-actin side-binding protein, from the F-actin domain. These findings highlight the diverse mechanisms by which HspB1 functions as an important regulatory protein of the actin cytoskeleton, and have implications for understanding the pathogenesis of neuropathy.

WE5. Knocking down targets in the CNS: antisense oligonucleotide distribution and pharmacodynamics in the rat CNS

Fredrik Kamme, Berit Powers, Curt Mazur, Daniel Norris, Eric Swayze*

Antisense oligonucleotides (ASOs) knock down target proteins by hybridizing to the cognate RNA and triggering RNAseH-mediated scission and subsequent RNA degradation. For clinical CNS indications, ASOs are delivered into the CSF via a bolus intrathecal injection. We imaged ASOs semi-quantitatively using an antibody specific for ASOs, fluorescent detection and high throughput laser-based scanning in order to characterize ASO distribution to various brain structures and the spinal cord in the rat after a lumbar intrathecal bolus dose.. Target knock down was quantified by qRT-PCR and immunofluorescent staining against the target protein and the same laser-based scanning. Doses ranged from 10 ug to 700 ug and time points stretched from 15 minutes up to 112 days post dosing. Finally, ASO tissue concentrations were measured by ELISA. Early after dosing, imaging for ASO showed 1st order diffusion of the ASO from the CSF space into the brain parenchyma. This was followed, at 6–8 h after dosing by a rapid redistribution of the ASO from what is likely the interstitial space and into cell bodies. After 24 hours, ASO distribution changes are subtle through the end of the observation period, at 16 weeks. Certain structures, such as leptomeninges, showed different kinetics and affinity of ASO binding than cells in the brain parenchyma. Maximum mRNA knock down was achieved 7 days after treatment, and >50% mRNA reduction was maintained for 8 weeks. Staining for the target protein also showed sustained effect with maximum reduction in the cortex at 7 days and later in deeper brain structures. We show broad distribution of an ASO, delivered by an intrathecal dose, into brain and spinal cord, including deep brain structures. Target mRNA and protein knock down is efficient and sustained. ASO technology is a versatile and powerful platform for research that can be readily translated into clinical applications.

WE6. The desensitization of midbrain dopamine D2 receptors

Brooks Robinson, John Williams*

In this study, the desensitization of dopamine D2 receptors is examined using electrophysiology and two-photon imaging of live substantia nigra (SN) dopamine neurons with labeled D2 receptors. We show that D2 receptors are clustered into specific "puncta" on the soma and dendrites of midbrain dopamine neurons. Additionally, we find that upon extended

agonist exposure, D2 receptors desensitize, however they do not internalize or translocate. The dopamine D2 receptor is a 7 transmembrane G protein-coupled receptor (GPCR). GPCRs are primarily thought to be activated by the volume transmission of certain neurotransmitters and therefore, by necessity, to be evenly and widely distributed across cell membranes. Canonically, desensitization of GPCRs occurs through the activation of GRKs (G protein receptor kinases), which phosphorylate intracellular domains of the receptors. Adaptor proteins known as arrestins then come and bind the active phosphorylated receptors. Among other actions, arrestins cause rapid receptor internalization and a reduction in signaling. A clear example of these typical GPCR properties is the μ-opioid receptor (a similar class GPCR to the D2), which has been shown to evenly coat the membrane of expressing neurons. Upon prolonged agonism, the μ-opioid receptor activates and desensitizes with corresponding receptor internalization. The results from this study indicate that D2 receptors are likely both activated and desensitized in a manner that is atypical for GPCRs.

WE7. Diametric changes in cue-elicited phasic dopamine release mediate drug-taking and drug-seeking

Lauren Burgeno, Nicole Murray, Ingo Willuhn, Paul Phillips*

Altered dopamine transmission is implicated in most contemporary theories of drug abuse, however the timing and directionality of these changes remain a matter of debate. While many studies demonstrate dopamine in the nucleus accumbens core(NAcc) plays an important role in producing drug satiety and regulating drug intake, other work suggests NAcc dopamine mediates craving and promotes cue-driven drug-seeking. How might cue-elicited dopamine transmission within the NAcc serve both as a satiety signal and to produce craving? Drug cues serve different purposes in different situations. During drug-taking, cues confirm the success of drug-seeking actions and indicate drug delivery is imminent, signaling that drug-seeking can be terminated. In contrast, during drug-seeking paradigms, the same cues presented unexpectedly during abstinence signal that drug may be available nearby, thereby promoting the initation of drug-seeking. Consistent with the satiety theory, recent work from our laboratory demonstrates a causal link between decreases in cue-elicited NAcc dopamine during drug taking and the escalation of cocaine intake. In order for NAcc dopamine transmission to be able to both decrease drug-taking and promote drug-seeking, we hypothesized that there must be a divergence in cue-elicited dopamine release during drug-seeking. We tested the prediction that dopamine responses elicited by unexpected presentation of drug-paired cues would increase over the course of drug-use, opposite that observed when

cues are presented contingently during drug-taking. We measured phasic dopamine release in the NAcc using fast-scan cyclic voltammetry during unexpected cue presentations throughout short and long-access cocaine self-administration. As predicted, we find that changes in cue-elicited phasic dopamine transmission during drug-taking and drug-seeking oppose one another, and therefore might contribute to different, but equally important, core symptoms of substance use disorders.

WE8. C-Fos expression in the striatal circuitry following reinstatement in differentially reared rats

Margaret Gill*, Zachary Orban, Catherine John, Kevin Evenson, Olivia Lopez, Dax Jantz, Kyle Olesen

Drug addiction is a multi-factorial disorder, and the environmental factors during childhood have a large impact on susceptibility to addiction during adolescence. Rearing rats in enriched (EC) or impoverished (IC) conditions post weaning causes neurological and behavioral changes that impact future drug taking behavior. In particular, a protective effect develops during rearing as EC rats self-administer less psychostimulant than IC rats at low unit doses. Additionally, previous research shows attenuated c-fos expression in the nucleus accumbens of EC compared to IC rats following an acute amphetamine administration. The current study looked to quantify the neurobiological changes in EC and IC rats to determine the origins of this protective effect. Rats were reared in either an enriched condition (EC) or impoverished condition (IC), and trained to self-administer cocaine utilizing a standard 2-hr self-administration model. Following extinction, rats underwent cue-induced or cocaine-primed reinstatement, after which, rats were immediately perfused. Immunohistochemistry was utilized to quantify c-fos positive neurons in the dorsolateral striatum and nucleus accumbens. Experiments revealed a main effect of rearing condition as well as a main effect for cue vs cocaine primed reinstatement. Multiple comparisons show greater cocaine-seeking behavior in IC rats compared to EC rats during cue-induced reinstatement. Analysis of c-fos expression in the dorsolateral striatum revealed a main effect for reinstatement test, showing greater c-fos expression following cocaine-primed compared to cue-induced reinstatement in IC rats. These results suggest that the habit circuitry of the dorsolateral striatum is indirectly impacted by differential rearing as differences in reinstatement test were only observed in IC rats.

WE10. Extrasynaptic NMDA receptor signaling under astrocyte control contributes to central neuropeptide regulation of hypothalamic neuronal activity and sympathetic control

Javier Stern, Sook Jin Son, Vinicia Biancardi, Hong Zheng, NM Sharma, Kaushi Patel*

Extrasynaptic signaling by ambient levels of neurotransmitters has emerged as a non-conventional intercellular communication modality. We recently showed in the hypothalamic paraventricular nucleus (PVN), activation of extrasynaptic NMDA receptors (NMDARs) by extracellular glutamate tonically stimulates neuronal activity. Moreover, we showed that the strength of this excitatory modality is dictated by astrocyte glutamate transporters (GLT1). Still, whether extrasynaptic glutamate transmission can be modulated in a physiological relevant manner is unknown. Angiotensin II (AngII) is a brain neuropeptide that acting within the PVN regulates sympathetic outflow to the circulation. Recent studies support an interaction between ANGII and glutamate in regulating sympathetic outflow from the PVN. However, the precise mechanisms underlying the interaction between these two signals remains unknown. Here we tested the hypothesis that ANGII stimulates PVN neuronal activity by inhibiting astrocyte GLT1 activity, resulting in a build up of extracellular glutamate and activation of extrasynaptic NMDARs. Patch-clamp recordings from presympathetic PVN neurons showed that bath-applied ANGII (0.5 μM) induced an NMDAR-mediated inward current (~20 pA, $p< 0.01$, n=7) that increased firing activity (430%, $p< 0.01$, n=13). ANGII effects were occluded by previous exposure to the GLT1 blocker dihydrokainate (DHK, 300 μM, $p> 0.1$, n=6). Moreover, we found that ANGII inhibited GLT1-mediated transporter currents (~45%, $p< 0.05$, n=7) in patched PVN astrocytes. Finally, we report that microinjections of ANGII directly into the PVN increased renal sympathetic nerve activity, an effect that was also blunted by DHK. Taken together, our studies support that extrasynaptic NMDAR signaling is amenable to modulation by the neuropeptide ANGII, and that this constitutes a critical mechanism underlying ANGII effects on hypothalamic neuronal activity and sympathetic outflow.

WE11. Contingent exposure to a high-fat diet alters reward circuitry and increases "craving-like" behaviors over a period of abstinence

Paige Dingess, Rebecca Darling, Travis Brown*

Sensory cues indicative of palatable food reward have been shown to induce a motivational craving state, which may trigger and underlie unhealthy eating

behaviors. Craving has been shown to increase in intensity progressively over time to rewards such as cocaine and sucrose, a phenomenon known as the "incubation of craving" effect. Craving behavior can be measured in rats as an enhancement in lever responding for contingent cues (light and tone) previously associated with the presentation of a reward. Our laboratory has observed an incubation of craving effect in response to a high-fat (HF) pellet reward following 10 days of 2 h training sessions. However, this effect was also observed in our standard chow (SC) controls. Literature suggests a difference in neuroadaptations following 6 h extended-access compared to 2 h access. Therefore, we repeated our experiments with a 6 h training protocol in which rats learned to self-administer either HF or SC pellets during 10 days of 6 h access and were subsequently tested for their motivation to seek the food-associated cues in the absence of the reward at two time points, 1 day (Test 1) and 30 days (Test 2) post training. Our results indicate that lever pressing for HF cues increases from Test 1 to Test 2 (44.3 ± 4.9 vs. 79.3 ± 10.4, $p<0.05$, $n=15$) and therefore elicits an incubation of craving. Lever pressing for cues paired with SC was significantly less than lever pressing for cues paired with HF but the relative magnitude of incubation was comparable between the two dietary conditions (24.0 ± 2.9 vs. 58.6 ± 5.2, $p<0.05$, $n= 16$). Current ongoing experiments are being conducted to evaluate whether there are differences in structural and synaptic plasticity within the reward circuit, such as changes in AMPA:NMDA ratio and dendritic spine density, that may parallel the changes observed in craving behavior. We conclude that extended-exposure to cues paired with HF undergo an incubation of craving effect, which may contribute to maladaptive food seeking behaviors.

WE12. The effects of AgRP neuron stimulation on food intake during appetite suppression

Alison Smith, Matthew Carter*

Proper regulation of food intake depends on a balance between activity in orexigenic and anorexigenic brain regions. Within the hypothalamus, neurons that express agouti-related protein (AgRP) are known to promote hunger and food-seeking behavior. Optogenetic stimulation of AgRP neurons increases food intake, however, the effect of this stimulation during conditions of appetite suppression is unknown. Here, we tested the hypothesis that stimulation of AgRP neurons would be sufficient to increase food intake during pharmacologically-induced appetite suppression. We injected mice intraperitoneally (i.p.) with amylin, cholecystokinin (CCK), and lithium chloride (LiCl), then optogenetically stimulated AgRP neurons. As expected, AgRP neuron stimulation evoked a significant increase in food intake following i.p. injection of saline. The administration of amylin or CCK blocked this

increase in food intake, while the administration of LiCl attenuated but did not entirely eliminate the food intake response. These results indicate that AgRP neurons are not sufficient to increase food intake during pharmacological conditions that suppress appetite, suggesting that anorexigenic brain systems override hunger signals in the brain.

WE13. The presence or absence of QTc prolongation in buprenorphine-naloxone among youth with opioid dependence

George Woody, Sabrina Poole, Anna Pecoraro, Geetha Subramaniam, Victoria Vetter*

To evaluate buprenorphine-naloxone effects on the QTc in youth with opioid dependence. Buprenorphine is a partial opioid agonist that is an effective treatment for opioid dependence. Compared to methadone it has a lower risk of QTc prolongation in adults but is less well studied in youth. Secondary analysis of ECG data from 95 subjects who participated in a multi-site trial for youth with opioid dependence. Subjects were randomized to a 2-week (DETOX), or a 12-week course of buprenorphine-naloxone (BUP). 12-lead ECGs were done at baseline, weeks 4 and 12, and QTc intervals were hand measured and calculated using Bazett's formula. Increases > 60 milliseconds (ms) were considered clinically significant, and readings > 450 ms (males) and 470 ms (females) indicated a prolonged QTc. Mean QTc intervals were higher for BUP than DETOX participants at baseline, week 4, and week 12 ($p = 0.045$), and females had longer mean QTc intervals than males ($p < 0.0005$). Variations in QTc intervals were observed in some, however none were above 500 ms, the level at which risk for TdP becomes more significant. In this randomized trial, the mean QTc at baseline, before randomization, was higher in BUP than DETOX patients. Minimal changes in the QTc were seen at 4 and 12-weeks in a few patients in both groups. There was no evidence that buprenorphine-naloxone alone increased the QTc to a level that increased the risk for TdP.

WE14. Neuropathic pain alters reward and affect via kappa opioid receptor (KOR) upregulation

Shiwei Liu, Christopher Cook, Eric Thai, Sarah Pickens, Anna Taylor, Vicki Tea, F. Ivy Carroll, Frances Leslie, Christopher Evans, Catherine Cahill*

The kappa opioid receptor (KOR) is crucial for the regulation of mood and reward pathways in the brain. Activation of this receptor with endogenous ligand dynorphin or KOR agonists can lead to dysphoria in humans. It is hypothesized that chronic neuropathic pain leads to a decreased dopaminergic tone within the mesocorticolimbic pathway, which could induce depression,

insomnia, anxiety, demotivation, and anhedonia. In this study, we aimed to determine the role of KOR signaling on the negative affective component of neuropathic pain. We produced neuropathic pain (NP) in adult C57/BL6 male mice by implanting a polyethylene cuff around their left sciatic nerve. Using qRT-PCR analysis, we found that NP mice exhibited significant increases in dynorphin and KOR gene expression in the prefrontal cortex (PFC), nucleus accumbens (NAc), and amygdala when compared to sham counterparts. Furthermore, we observed increased KOR protein availability and activation in NP mice via phosphorylated KOR immunoblotting of brain tissue punches and agonist-stimulated [35S]GTPγS autoradiography of coronal brain slices, suggesting a link between KOR and the resulting decrease in dopamine levels within these regions. To understand the functional consequences of the increase in KOR expression and activity, we tested the effects of KOR antagonist on pain induced affective like behaviors. NP mice also displayed negative affect symptoms such as increased anxiety in the light-dark test and increased depression in the forced swim test when compared to sham surgery mice. When NP mice were given the KOR-specific antagonist, JDTic, these symptoms were attenuated. These results demonsrate that neuropathic pain increases the expression and activation of KOR, which subsequently leads to decreased dopamine release in brain regions important for reward and affect. This mechanism contributes to negative affect in chronic pain, and that inhibiting KOR activity can reduce the symptoms, thereby suggesting a novel therapeutic to treat chronic pain.

WE15. Mechanisms of tolerance to the antinociceptive effects of Δ9-THC in the formalin test of inflammatory pain

*Matthew Yuill, Michael Zee, Josee Guindon, Daniel Morgan**

The use of cannabinoids in pain management is of significant interest due to the analgesic efficacy of Δ9-THC as well as the increasing prevalence of prescription opiate abuse among the general population. Δ9-THC produces potent antinociceptive effects but, like opiates, is subject to tolerance. The objective of this study was to examine the time-course of tolerance for Δ9-THC using a model of pathological pain. The effect of Δ9-THC in pathological pain was assessed in male wild-type and cannabinoid receptor 1 (CB1) desensitization-resistant S426A/S430A mutant mice using the formalin test for inflammatory pain. Intraplantar formalin injection (10 µl at 2.5 %) produces a biphasic nociceptive response composed of acute and inflammatory pain phases. Experimental groups were subjected to the formalin test after receiving daily injections of Δ9-THC (6 mg/kg) for periods of time ranging from zero to twelve days. As expected, wild-type mice tested after one day of Δ9-THC exposure showed robust antinociception that was absent by day eight due to

tolerance. Interestingly, we find that tolerance to the antinociceptive effects of Δ9-THC is attenuated in S426A/S430A mutants for the inflammatory pain phase but not for the acute pain phase. Additionally, we examined the effect of c-jun N-terminal kinase (JNK) inhibitor SP600125 on the time-course of Δ9-THC tolerance. Pre-treatment with SP6 (3 mg/kg) attenuates tolerance for the Δ9-THC antinociceptive effects of Δ9-THC in both the acute and inflammatory pain phases. These results are consistent with previous studies showing the rapid onset of tolerance to the antinociceptive effects of Δ9-THC in the tail-flick and hotplate tests. This study reinforces the validity of the formalin test as a tool for assessing cannabinoid tolerance in clinically relevant, pathological pain model relevant to assess cannabinoid tolerance in mice models. Furthermore, it suggests that Δ9-THC tolerance in the acute and inflammatory pain phases may be mediated by different signaling mechanisms.

WE16. Novel anti-inflammatory TNF-alpha synthesis inhibitors derived from the backbone of thalidomide

Nigel Greig*, David Tweedie, Weiming Luo, Susanna Rosi, Debomoy Lahiri, Kumar Sambamurti, Chaim Pick

Clinical and preclinical studies indicate that basal inflammatory status increases as a function of normal aging, and progressive development of a mild pro-inflammatory state closely associates with the major degenerative diseases of the elderly (Holmes et al., Neurol 73:768-74, 2009; Heneka et al., Lancet Neurol 14:388-405, 2015). In line with this, levels of brain pro-inflammatory cytokines are elevated with age in rodents and humans, and several regulatory molecules and anti-inflammatory cytokines reduced (Deleidi et al., Front Neurosci 9:172, 2015). Microglia, as a source of these pro- and anti-inflammatory molecules, are thereby implicated as the major culprit of this neuroinflammation. We hypothesize that correcting the overproduction of pro-inflammatory cytokines by microglia may mitigate a broad number of neurodegenerative disorders prevalent in the elderly, and, in particular Alzheimer's disease (AD). However, finding an appropriate drug target to safely and effectively achieve this has proved difficult, and accounts for the numerous failures of clinical trials of anti-inflammatory agents in AD and other disorders. TNF-α, a key pro-inflammatory cytokine, is synthesized and released by microglial during their activated M1 phase. Once released and if not appropriately time-dependently reduced by transition of microglia to a M2 phase, dysregulated TNF-α generation can initiate a self-propagating cycle of unchecked inflammation (Frankola et al., CNS Neurol Disord Drug Targets 10:391-403, 2011). Pharmacological interruption of this cycle may be of significant benefit for disorders with a neuroinflammatory component. The drug 'thalidomide' can lower TNF-α protein levels post-transcriptionally by accelerating degradation of its mRNA.

However, it is not a particularly potent TNF-α synthesis inhibitor in vivo and is associated with sedation and serious teratogenic adverse effects at clinical doses (Calabrese & Fleischer, Am J Med 108:487-95, 2000). Our generation of more potent, well-tolerated analogs is providing pharmacological probes to understand the role of TNF-α in disease processes and drug candidates to treat them.

WE17. Whole-brain mapping of neuronal activity in the learned helplessness model of depression

Yongsoo Kim, Zinaida Perova, Martine Mirrione, Kith Pradhan, Fritz Henn, Stephen Shea, Pavel Osten, Bo Li*

Some individuals are resilient, whereas others succumb to despair in repeated stressful situations. The neurobiological mechanisms underlying such divergent behavioral responses remain unclear. Here, we employed an automated method for mapping neuronal activity in search of signatures of stress responses in the entire brain. We used serial two-photon tomography to detect expression of c-FosGFP—a marker of neuronal activation—in c-fosGFP transgenic mice subjected to the learned helplessness (LH) procedure, which has been widely used to induce depression-like phenotypes in laboratory animals. We found that mice showing "helpless" behavior had brain-wide reduction in the level of neuronal activation compared with mice showing "resilient" behavior, with the exception of a small number of brain areas including the locus coeruleus, in which helpless mice had stronger activation than resilient ones. Moreover, compared with resilient mice, helpless mice had increased similarity among individuals in brain activity, showing a stereotypic brain-wide activation pattern. This latter effect was also observed in rats subjected to the LH procedure, using 2-deoxy-2[18F]fluoro-D-glucose positron emission tomography to assess neural activity. Our findings reveal distinct brain activity markings that correlate with adaptive and maladaptive behavioral responses to stress, and provide a framework for further studies investigating the contribution of specific brain regions to divergent stress responses.

WE18. AgRP neurons disrupt sleep/wake architecture and cause deficits in rapid eye movement (REM) sleep

Kelsey Loy, Nitsan Goldstein, Matt Carter*

Sleep quality is important for an animal's health and cognition. Fragmentation of normal sleep/wake states causes impairments in physiological parameters and learning and memory. A factor that may impact sleep/wake architecture is the degree to which an animal is hungry or motivated to seek food. Neurons in the hypothalamus that express agouti-related protein (AgRP) are well known to

sense the nutritional needs of the body and positively regulate food intake. We tested the hypothesis that stimulating AgRP neurons would cause maladaptive changes in sleep architecture using optogenetics and electroencephalographic recordings in mice. We found that AgRP neuron stimulation before sleep onset decreased rapid eye movement (REM) sleep and increased non-REM (NREM) sleep. AgRP neuron stimulation during sleep decreased REM sleep, increased wakefulness, and increased transitions between sleep and wake states. These results demonstrate that activation of brain hunger pathways either before or during sleep disrupts transitions into REM sleep and causes abnormal sleep/wake architecture. Therefore, brain hunger pathways are capable of negatively regulating sleep quality, even in the absence of an actual nutritional deficit.

WE19. Sleep disorder impact on efficacy of prolonged exposure therapy for PTSD

Christopher Reist, Andrea Gory, Michael Hollifield*

There is growing evidence indicating that sleep disturbance may be a primary contributor to the maintenance of PTSD and impede the utility of existing therapeutic interventions (Krakow, 2015). There is likely a bi-directional effect between PTSD and sleep disturbances, where they make each other worse and impede treatment for PTSD. One mechanism by which PTSD treatment may be hindered in the context of sleep disturbances is through disruption of memory consolidation and generalization of extinction memory. Substantial evidence exists to support the idea that good sleep is important for extinction generalization and will facilitate improved treatment outcomes in PTSD patients. Conversely poor sleep may interfere with exposure based treatments for PTSD. This retrospective review examined the hypothesis that the presence of sleep disturbance would impact the outcome of a course of prolonged exposure therapy (PE) for PTSD in treatment-seeking combat Veterans. Eighteen male subjects with PTSD who completed PE in the Program for Traumatic Stress at the VA Long Beach Healthcare System were identified. Six of the 18 subjects (mean age 55.8 ±11.6 years) had a sleep disturbance, five of which were documented by sleep polysomnography (4 had at least moderate sleep apnea, 1 had very poor sleep efficiency with frequent awakenings). A sixth subject had a well-documented history of sleep disturbance by his wife as well as primary care providers. Twelve subjects (mean age 46.7 ±18.7 years) had no evidence in the medical record of sleep disorder or were successfully treated with CPAP. Baseline severity of PTSD on PCL scores was similar between groups (64.75 ± 8.56; 70.501± 6.83 (sleep disordered group), ns). All subjects in the sleep disordered group received a minimum of 10 sessions and the mean number of sessions was comparable between both groups. Post treatment PCL scores were significantly reduced in those without a sleep disorder (–28.25; 43% reduction) but not those with a sleep disorder (–7.17; 10% reduction)

($t = 5.52$, $p < .001$). With the exception of one subject in the group without a sleep disorder, all post-treatment PCL scores were below 50 (one subject had a score of 50). In contrast, in the sleep disordered group, no post treatment PCL scores were below 50. In mental health settings, a PCL score of over 50 is generally indicative of the presence of PTSD. These observations are the first to our knowledge to support the idea that efficacy of prolonged exposure therapy is impacted by sleep quality. The subjects with poor sleep had a striking lack of response to exposure therapy, despite receiving at least 10 exposure sessions. If these findings are replicated, particularly in a prospective study, treatment algorithms may need to incorporate the presence or absence of sleep disorders as a factor in treatment choice.

WE20. Salivary biomarkers for Huntington's disease

*Alaina Aikin, Bill Webb, Gary Siuzdak, Jody Corey-Bloom, Elizabeth Thomas**

Peripheral biomarkers are greatly needed in the field of neurodegenerative disorders in order to anticipate onset of disease symptoms, to monitor disease progression, and to track potential therapeutic effects. Huntington's disease (HD) is a fatal, inherited neurodegenerative disorder caused by a CAG repeat expansion in the gene encoding the huntingtin protein (Htt). Pathogenesis is associated with expression of the mutant Htt protein in the CNS; however, HD is also associated with abnormalities in peripheral tissues. The Htt protein is the most significant molecular target for disease modifying therapies, and several therapeutic approaches that target its production, processing, and/or turnover are under development or approaching clinical trials in patients. Measurement of Htt has broad potential as a biomarker. Since non-invasive methods to quantify Htt in the CNS do not exist, measuring Htt in peripheral cells represents an essential step in biomarker discovery for HD. In the current study, we have measured Htt protein levels in saliva from HD gene "positive" individuals (N=29) and age- and sex-matched normal controls (N=42) using ELISA and Western blot methods. Full-length soluble Htt protein levels detected by Western blot analysis were decreased in saliva samples from HD patients compared to normal controls. In contrast, ELISA using antibodies recognizing amino acids 802-940 of human Htt protein revealed significant increases in Htt expression in saliva from HD individuals compared to normal controls. Further, salivary Htt levels were higher in symptomatic HD patients compared to pre-symptomatic or transitional patients. No correlations were detected between Htt expression and age or sex in all subjects. Additionally, we sought to identify differentially produced salivary metabolites from HD patients that might be used to characterize this disease. Saliva samples were analyzed from N=24 HD patients and N=25 matched normal controls using the XCMS Online metabolomic technology platform, coupled to liquid chromatography tandem mass spectrometry. These findings will be discussed. Measurements

of salivary proteins and metabolites offer significant promise as relevant, non-invasive disease biomarkers for HD, and their use could be immediately implemented into both translational and clinical research use.

WE21. A novel LRRK2 radioligand demonstrates increased active LRRK2 in sporadic Parkinson's disease brain

*Weisong Shan, Anastasia Henry, Harry Samaroo, Charles Adler, Geidy Serrano, Thomas Beach, Ashley Winslow, Paul Galatsis, Warren Hirst**

Genetic mutations in leucine-rich repeat kinase 2 (LRRK2) have been linked to autosomal dominant Parkinson's disease (PD). The most prevalent mutation, G2019S, results in increased LRRK2 kinase activity, hypothesized to contribute to the etiology of PD. However, to date, there is no direct evidence of increased LRRK2 kinase activity in patient brains from either G2019S mutation carriers or patients with sporadic disease.

Using a novel radiolabeled LRRK2 kinase inhibitor, [3H]PF-06454589, we have measured the LRRK2 protein levels in post-mortem brain (superior temporal gyrus) samples (n = 22 for sporadic PD and n = 18 for control). There is a significant 2.6 fold increase in the high-affinity LRRK2 binding site in the Parkinson's disease brain homogenates (control = 9.6 ± 1.1 fmol/mg protein; PD = 25.3 ± 3.6 fmol/mg protein; P = 0.0005). There is also a significant change in the binding affinity of the radioligand: control KD = 11.6 ± 1.5 nM; PD KD = 32.9 ± 3.9 nM; P = 0.0001. We believe that this increase in affinity is related to a conformational change in LRRK2, potentially reflecting a more active "G2019S-like" conformation, as a similar increase in KD is observed in transgenic mice which express the G2019S LRRK2 compared to mice expressing wild-type LRRK2: KD = 7.7 ± 1.0 nM and KD = 19.6 ± 1.7 nM; P = 0.0001, respectively, as well as in G2019S patient post-mortem brains (KD = 23.2 ± 4.6 nM, n = 7). We also measured the radioligand binding in lung and kidney samples, from a sub-set of the subjects, and there is not a significant difference in the Bmax or KD between the sporadic PD and control groups, demonstrating a brain (and disease) specific change in these measured parameters. Overall, these data show that in sporadic Parkinson's disease there is an increase in the levels and active conformation of LRRK2, providing key data to increase our confidence in rationale for inhibiting LRRK2, not only in mutation carriers, but also in the sporadic PD population.

WE22. Anterior cingulate cortex and cognitive aging: mechanisms

*Jose Pardo**

The anterior cingulate cortex (ACC) is a critical nexus for declining glucose metabolism during healthy aging. The decline in glucose metabolism correlates with age-associated decline in cognitive function particularly executive functions. Healthy elders from the ADNI database were examined for changes in brain metabolism, amyloid, and vascular disease risk (Hachinski, "Hach") that correlated with age. Data included FDG and amyloid PET both normalized to the cerebellum. The significance of voxel-wise, whole-brain, Z-scores was adjusted ($p < 0.05$) dividing by resels. Several comparisons are shown in the figure showing voxel-wise correlations with age: a) 46 healthy normals (18-90 y) reported in Pardo et al 2008 (Neuroimage 35:1231); b) 210 ADNI normal (age 56-90 years); c) 103 ADNI normal (56-90 y) Hach = 0; d) 107 ADNI normal (63-89 y) Hach = 1-3. For the ACC region, the correlation of metabolism with age was $r = -0.49$ ($p < 10\text{-}6$), while for amyloid the correlation with age was $r = +0.01$ ($p = 0.88$). The robust decline in metabolism of the ACC with age was replicated in the ADNI dataset and occurred even in those without major vascular risk factors. ACC metabolism decreased at a much greater rate than did amyloid deposition. These findings suggest the need to consider alternative pathophysiological mechanisms for aging-associated ACC dysfunction.

WE23. Acute effects of kainic acid induced early life seizures

Heather Caballes, Paul Bernard, Tim Benke*

Neonatal seizures are associated with long term disabilities including epilepsy and cognitive deficits. Using a neonatal seizure rat model that does not develop epilepsy, but develops a phenotype consistent with other models of intellectual disability (ID) and autism spectrum disorders (ASD), we sought to isolate the acute effects of a single episode of early life seizure on hippocampal CA1 synaptic development and plasticity. In the adult rat, we have previously shown chronic changes in glutamatergic synapses, loss of long term potentiation (LTP) and enhanced long term depression (LTD), ~50 days following kainic acid (KA) induced early life seizure (KA-ELS) in post-natal (P) 7 day old male Sprague-Dawley rats. In the present work, we examined the electrophysiological properties and expression levels of glutamate receptors in the acute period, 2 and 7 days, post KA-ELS. Our results show for the first time enhanced LTP 7 days after KA-ELS, but no change 2 days post KA-ELS. Additionally, we report that ionotropic α-amino-3-hydroxy-5-methyl-isoxazole-propionic acid type

glutamate receptor (AMPAR) desensitization is decreased in the same time frame, with no changes in AMPAR expression, phosphorylation, or membrane insertion. Inappropriate enhancement of the synaptic connections in the acute period after the seizure could alter the normal patterning of synaptic development in the hippocampus during this critical period and contribute to learning deficits. Thus, this study demonstrates a novel mechanism by which KA-ELS alters early network properties that potentially lead to adverse outcomes.

WE24. Assessment of skiing-related concussion and mild traumatic brain injury using multivariate signatures from combined portable telemetric EEG and cognitive testing data

*Adam Simon, Keith Tatsukawa, Janet Van Gelder, Jasmine Weavers, Hashem Ashrafiuon, David Devilbiss**

Concussion is a common mild traumatic brain injury (mTBI) affecting approximately 1.7 million Americans each year. Estimates may be as high as 3.8 million when cases not seen by emergency department physicians are included. Current concussion assessment tools include symptom checklists and cognitive/behavioral tests. In addition, electroencephalographic (EEG) measures of cortical activity have begun to be used to assess concussion-related changes in neurological function. However, many of these tests are limited in their diagnostic reliability or require transportation of the patient to a electrodiagnostic clinic. The present study evaluated single channel EEG recorded during resting state (Eyes Open or Eyes Closed) and a neuro-ophthalmologic task in control (n = 45) and mTBI subjects (n = 26) injured at ski resorts. Preliminary analysis revealed univariate features and multivariate classifiers demonstrating good diagnostic accuracy (up to 85% sensitivity and 60% specificity). Together, this evidence indicates that low-channel telemetric EEG combined with a brief (5 minute) cognitive test battery can provide a portable, rapid approach to assess injury following concussion. Moreover, these data demonstrate that multivariate models of combined EEG and performance measures on concussion assessment tools can enhance diagnostic accuracy. Nonetheless, further work is needed to validate current findings and concussion-related signatures.

WE25. Validity of the chronic social defeat stress model on sex differences in glutamate homeostasis

Akiko Shimamoto, Virginie Rappeneau, Amanda Blaker, Jeff Petro, Bryan Yamamoto*

Chronic social defeat stress (CSDS) is an animal model that produces some cardinal features of human depression, including anhedonia-like behavior. This behavioral deficit may be caused by disruption in glutamate homeostasis that is normally regulated by the tripartite synapse (pre- and post-synapses and glia cells) in brain areas associated with mood and motivation. Astrocytes, the major glial cells in the brain, remove extracellular glutamate via glutamate transporters (GLTs). Since the function and distribution of astrocytes are known to be sexually dimorphic, a disruption in glutamate homeostasis after CSDS may be sex-dependent. To test this hypothesis, no-net-flux in vivo microdialysis was used to measure extracellular glutamate and its astrocytic product glutamine, in the nucleus accumbens (NAc) of both male and female adult Long-Evans rats exposed to CSDS for 21 days. CSDS disrupted the glutamate-glutamine cycle more in females than in males, and reduced the number of astrocytic glial fibrillary acidic protein (GFAP) positive cells in the NAc of females compared to males. In prefrontal cortex (PFC), a major glutamatergic efferent target of the NAc, CSDS significantly reduced the number of GFAP positive cells and the protein levels of GLT-1 exclusively in females. Next, we analyzed behavioral signatures and patterns of defeated males and females that occurred during each direct confrontations. During the 1st week of CSDS, while males showed increased escape behavior, females showed increased self-grooming and immobile behavior. By the 3rd week of CSDS, the behavioral signatures observed during the 1st week were diminished and instead, males showed increased defensive postures and females showed increased walking behavior and genital contacts. Taken together, CSDS induces sex-dependent disruption in glutamate homeostasis in the NAc and glial glutamate uptake in the PFC, possibly due to differential behavioral outcomes of CSDS.

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