F·S·T®
Fine Science Tools
FINE SURGICAL INSTRUMENTS FOR RESEARCH™
Incredible discoveries with Fine Science Tools
SHIPPING GLOBALLY SINCE 1974
REQUEST A CATALOG AT FINESCIENCE.COM OR CALL 1-800-521-2109

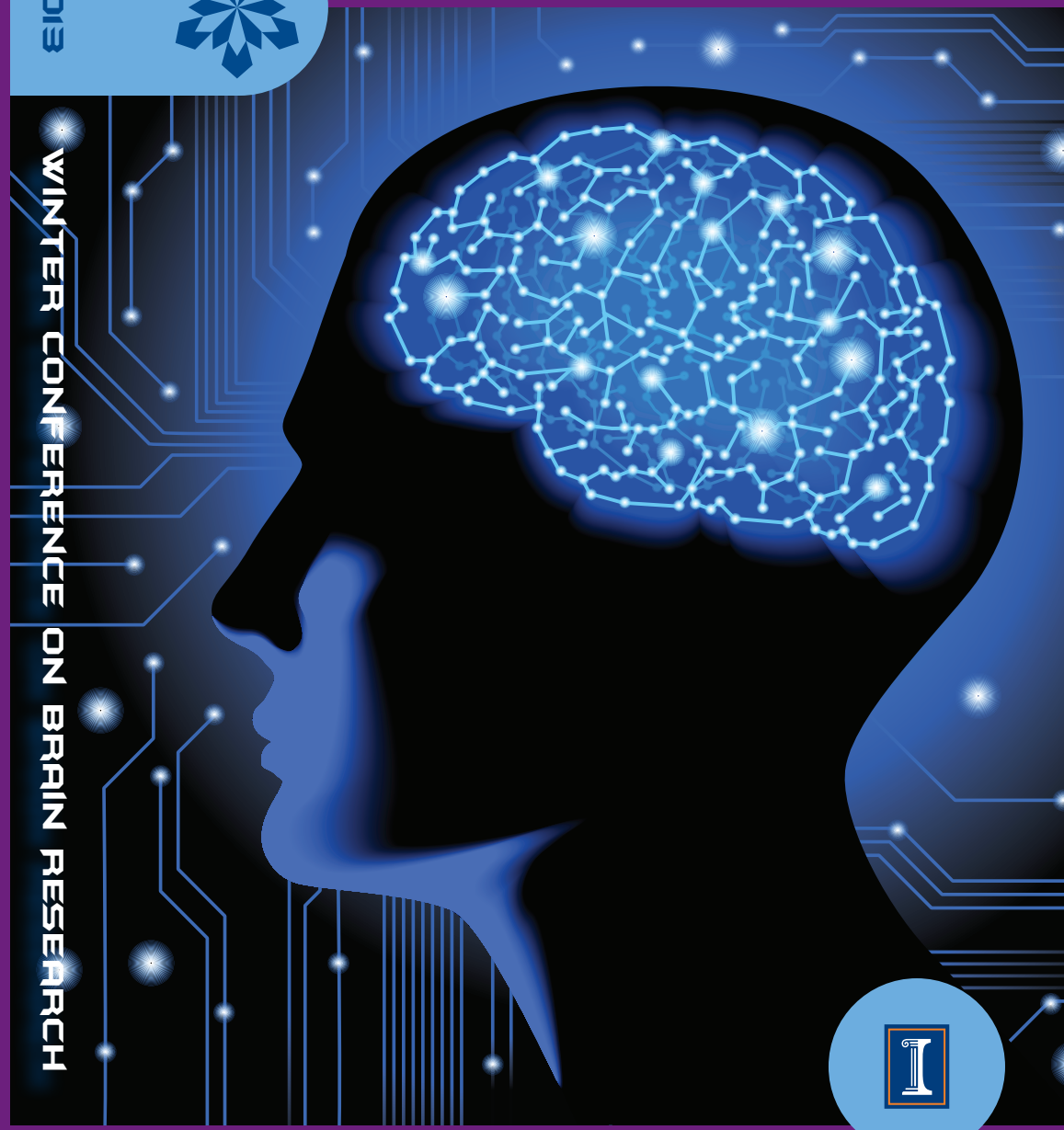
46TH ANNUAL WCBR

JANUARY 25–31, 2013

BRECKENRIDGE, COLORADO

WINTER CONFERENCE ON BRAIN RESEARCH

2013



WINTER CONFERENCE ON BRAIN RESEARCH

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

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

We begin the week with a **Welcome Reception** on Saturday, where you can meet with friends and colleagues and welcome new attendees (their badge is purple) and Travel Fellows (they have a purple dot on their badges). On Sunday, we kick off with an **Opening Breakfast** during which we feature our keynote speaker, Dr. **David Linden**, professor of neuroscience at Johns Hopkins University. David not only has provided very important contributions to the understanding of neural bases of memory but also is an outstanding communicator. Dr. Linden has written a couple of science books for the general public and delivers fantastic lectures to lay audiences. His presentation is entitled: "Writing about brain function for a general audience." In addition, Dr. Linden will be our **Town Meeting** speaker on Tuesday in the Imperial Ballroom, delivering a lecture on "Pleasure Circuits in the Brain." The Town Meeting is a traditional component of WCBR Outreach Program; its targeted audience is the local school population, and WCBR participants are welcome to join. I will encourage everyone to check out and volunteer in our **Outreach Program,** in which we present sessions at local schools throughout the week. It is a way to return something to the communities that host us at the meetings and to stimulate students' interest in science. We will also have vibrant poster sessions; and as in recent years, the best posters from young investigators are shown during a **Special Poster Session** on Tuesday evening. Awards will be given to the best posters identified by the program committee. Don't forget to visit the **Exhibits** during all poster sessions. Having them in such an informal meeting allows for more in-depth interactions. On Wednesday, we will have the **Smitty Stevens Memorial Race** for skiers and snowboarders, followed by a **Mountain Lunch**. Please be sure to attend the **Business Meeting** on

Wednesday following the afternoon sessions, as we will hold elections for conference chair-elect and board members. Additionally, we will discuss the program, budget, and future sites for the meeting. Because board members are critical for WCBR, we encourage you to nominate yourself or a colleague for open board positions in clinical, cellular/molecular, or systems/behavioral neuroscience. We will close the week on Thursday night with the **Annual Banquet**, at which we will give the awards to the best posters and the ski race competition; and we will wrap up the week dancing to live music.

We are an all-volunteer organization, and this meeting has been possible with the great effort of all those serving in the board of directors and committees, as well as by the generous donations of our sponsors, who allowed the Fellowship Program to select such an outstanding group of young scientists. We thank you all for your contributions.

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

Patricio O'Donnell
Conference Chair

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, third floor, Beaver Run Resort & Conference Center.

The desk hours are as follows:

	Morning	*Afternoon*
Saturday 1/26	8:00 a.m.–12:00 p.m.	3:30–9:00 p.m.
Sunday 1/27	6:30–10:00 a.m.	3:30–7:00 p.m.
Monday 1/28	7:00–10:00 a.m.	3:30–6:45 p.m.
Tuesday 1/29	7:00–10:00 a.m.	3:30–6:00 p.m.
Wednesday 1/30	7:00–10:00 a.m.	3:30–5:30 p.m.
Thursday 1/31	7:00–10:00 a.m.	

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

POSTER SESSION 1, SUNDAY

Posters will be available for viewing 3:30–10:00 p.m. on Sunday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Sunday. Posters can be set up after 12:00 p.m. on Sunday.

POSTER SESSION 2, MONDAY

Posters will be available for viewing 3:30–10:00 p.m. on Monday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Monday. Posters can be set up after 8:00 a.m. on Monday.

POSTER SESSION 3, TUESDAY

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

POSTER SESSION 4, WEDNESDAY
Posters will be available for viewing 3:30–10:00 p.m. on Wednesday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Wednesday. Posters can be set up after 8:00 a.m. on Wednesday.

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

EXHIBITS AND LOUNGE are in Peak 1–4. Refreshments are provided 3:30 to 4:30 p.m., Sunday through Wednesday. Exhibitor setup is Sunday, January 27, 12:00–3:00 p.m. All exhibitors should be packed up by 2:00 p.m. on Thursday, January 31.

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

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

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

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

Committees

Board of Directors

Sue Andersen
Kyle Frantz
Lloyd Fricker
Henry Holcomb
Gonzalo Laje
Steve Levison
Peter LeWitt
Carl Lupica
Thomas Newton
Carlos Paladini
Susanna Rosi
Elmer Yu
Jim Zadina

Conference Chairs

Patricio O'Donnell, Chair
Jill Becker, Past Chair

Exhibits

Denson Fujikawa, Chair
Gonzalo Laje
Peter LeWitt

Facilities Committee

Thomas Hyde, Chair
Elmer Yu, Chair-Elect
Eastman Lewis
Elyse Sullivan

Program Committee

Paul Phillips, Chair
Gretchen Snyder, Chair-Elect
Susan Andersen
Katherine Burdick
Susan Ferguson
Christopher Ford
Karen Gale
Amelia Gallitano
Edward Hall
Henry Holcomb
Tod Kippin
Joel Kleinman
Amanda Law
Carl Lupica
Thomas Newton
Carlos Paladini
Dale Pelligrino

School Outreach

Kyle Frantz, Chair
James Bamburg
Gong Chen
Joseph Cichon
Brad Cooke
Sonsoles de Lacalle
Paula Dore-Duffy
Onaivi Emmanuel
Nicole Fazo
Karen Greif
Laura Halpin
Tom Kuhn
Joaquin Lugo
Gretchen Neigh
John Sladek

Smitty Stevens Race Coordinator

Thomas Swanson

Town Meeting

Lloyd Fricker, Co-Chair
John Mendelson, Co-Chair

Treasurer

Jacqueline McGinty

Conference Arrangements

Michelle Chappell
Online & Continuing Education
University of Illinois
Phone 217-333-2880
Fax 217-333-9561
E-mail: winterbrain@mx.uillinois.edu

Travel Fellowship Program

Fellowship Committee

George Wilcox, Chair
Jill Becker
Karen Greif
Susanna Rosi
Kim Topp

2013 Fellowship Awardees

Alejandro Amador
Clemence Blouet
David Dietz
Shashank Dravid
Scott Edwards
Eun Ha Baeg
Laura Halpin
Michael Higley
Brian Iacoviello
Stephan Lammel
Rylan Larsen
Mary Kay Lobo
Marian Logrip
Magali Millecamps
Francesco Papaleo
Kelli Sharp
Matthew Wanat
Kate Wassum,
Ann Kelley Memorial Travel Fellow
Ilana Witten
Neil Woodward

Fellowship Mentors

Jill Becker
Kristi Bigos
Raphael Braga
Katherine Burdick
Catherine Cahill
Lakshmi Devi
Paula Dore-Duffy
Carolyn Fairbanks
Inna Gaisler-Salomon
Amelia Gallitano
Herbert Geller
Joshua Gordon
Faith Gunning
Lee Hong
Elizabeth Jonas
Leonard Kaczmarek
Jim Knowles
Tibor Koos
Gonzalo Laje
Ryan LaLumiere
Frances Leslie
Michael Levine
Peter LeWitt
Joaquin Lugo
Vicky Luine
Wendy Lynch
Jacqueline McGinty
John Mendelson
Paul Micevych
Jennifer Morgan
Thomas Newton
Saleem Nicola
Patricio O'Donnell
Mary Ann Ottinger
Paul Phillips
Lawrence Reagan
Steve Richardson
Gerard Sanacora
Celia Sladek
Neil Smalheiser
Leslie Sombers
Jeffrey Tasker
Ramon Trullas
Elizabeth Tunbridge
Kay Tye
Edward Wagner
Claude Wasterlain
George Wilcox
James Zadina
Grace Zhai

Sponsors

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

Gold Sponsors ($500–$100)

Jill Becker
Paula Dore-Duffy
Scott Edwards

Henry Holcomb
Joel Kleinman
Barry Levin
Michael Levine
Steve Levison
Bruce MacIver
Patricio O'Donnell
Paul Phillips
Thomas Swanson
Jeffery Tasker
George Wilcox

Silver Sponsors ($50–$99)

Tim Benke
Carol Colton
Karen Greif
Warren Hirst
Thomas Hyde
Vicky Luine
Hugh McIntyre
John Mendelson
A. Leslie Morrow
Charles O'Brien
James O'Callaghan
Steve Richardson

Sponsors (up to $49)

Susan Andersen
Akiva Cohen
John Curtin
Joshua Gordon
Paul Letourneau
Iris Lindberg
Lynn Raymond
Leslie Sombers

Exhibitors

ANDOR TECHNOLOGY

425 Sullivan Ave Suite 3
South Windsor, CT 06074
Contact: Michael Mohammadi
Tel 860-335-2808
m.mohammadi@andor.com

ASSOCIATION BOOK EXHIBIT

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

METABOLON, INC.

617 Davis Dr., Suite 400
Durham, NC 27713
Contact: Kathryn Lawrence
Tel 919-287-7401
klawrence@metabolon.com

SAGE LABS

3050 Spruce St
St. Louis, MO 63103
Contact: Kevin Gamber
Tel 314-771-5765
Kevin.gamber@sial.com

STOELTING CO.

620 Wheat Lane
Wood Dale, IL 60191
Contact: Richard Mills
Tel 800-860-9775
richard@stoeltingco.com

THERMO SCIENTIFIC

22 Alpha Rd
Chelmsford, MA 01824
Contact: Nick Santiago
Tel 978-250-7192
nicholas.santiago@thermofisher.com

Unstaffed Tables

ACS PUBLICATIONS

1155 Sixteenth Street NW
Washington, DC 20036
Contact: Tara Pritchett
Tel 202-872-4600
t_pritchett@acs.org

FINE SCIENCE TOOLS

Marketing/Technical Support
373-G Vintage Park Dr.
Foster City, CA 94404
Contact: Christina Callanta
Tel 1-800-521-2109
Fax 1-800-523-2109
ccallanta@finescience.com

MARY ANN LIEBERT, INC. PUBLISHERS

140 Huguenot Street
New Rochelle, NY 10801
Contact: Lisa Pierce
Tel 914-740-2100
lpierce@liebertpub.com

Special Events

SATURDAY, JANUARY 26

Welcome Wine and Cheese Reception • 6:00–7:30 p.m. • Peak 1–4

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

SUNDAY, JANUARY 27

Conference Breakfast and Plenary Address • Colorado Ballroom (Peak 1–5)

7:00–8:30 a.m. • Breakfast

8:00–9:30 a.m. • Plenary Address

The plenary keynote address is presented by:

David Linden, PhD, Professor of Neuroscience, The Johns Hopkins University School of Medicine, and Editor in Chief, *The Journal of Neurophysiology*

Writing about Brain Function for a General Audience

Have you ever thought about writing a book about neuroscience for a general audience? David Linden, author of two such books, The New York Times bestseller "*The Compass of Pleasure*" (2011) and "*The Accidental Mind*" (2007) will describe the process, from inception to publication with all of the gory real-world details (agents, publishers, contracts, translations, publicity) brought to light.

MONDAY, JANUARY 28

First Meeting of the Board of Directors • 6:30–8:30 a.m. • Peak 9/10

Town Meeting • 7:00–8:30 p.m. • Imperial Ballroom

Attendance is open to all.

Pleasure Circuits in the Brain

David Linden, PhD, Professor of Neuroscience, The Johns Hopkins University School of Medicine, and Editor in Chief, *The Journal of Neurophysiology*

Whether eating, taking drugs or drinking, engaging in sex, gambling, exercising, or doing good deeds, the pursuit of pleasure is a central

drive of the human animal. Johns Hopkins neuroscientist David Linden explains how recent research has enabled us to understand how pleasure affects us at the most fundamental level: in a section of the brain called the medial forebrain pleasure circuit, where pleasurable experiences are registered. Linden combines cutting-edge science with entertaining anecdotes to illuminate the source of the behaviors that can lead us to ecstasy but can easily become compulsive. Why are drugs like nicotine and heroin addictive, while LSD is not? Why has the search for safe appetite suppressants been such a disappointment? Why is new love really like a drug?

TUESDAY, JANUARY 29

Breakfast for Travel Fellows Meeting • 6:30–7:30 a.m. • Imperial Ballroom

Look for the reserved signs

Special Poster Session • 6:30–8:30 p.m. • Peak 1–4

The 18 top-ranked posters submitted by junior investigators will be on display, Tuesday from 6:30 to 8:30 p.m. in a special session with wine and cheese provided. Awards will be selected, including a "Best Poster" award. A grand prize will be given to the best poster and several prizes will also be given to runners-up. The awards will be announced at the Closing Banquet on Thursday, January 31.

WEDNESDAY, JANUARY 30

Smitty Stevens Memorial Ski Race • 10:00–11:30 a.m. • Peak 9, Sundown Run

Registration cards must be completed no later than Monday, January 28, 8:00 a.m. at the WCBR Information Desk.

Mountain Lunch • 11:30 a.m.–2:00 p.m. • Peak 8, Vista Haus

Non-skiers will need a **foot pass ticket** to ride the Colorado SuperChair from the base of Peak 8 up to the Vista Haus. Please purchase foot pass tickets at the WCBR Information Desk by Wednesday morning.

Skiers can take the Colorado SuperChair from the base of Peak 8 to access the Vista Haus or take the Peak 8 SuperConnect from Peak 9 to Peak 8. The Peak 8 SuperConnect will drop off directly above the Vista Haus.

Required lunch ticket is in your registration packet.

Business Meeting • 6:30 p.m. • Peak 5

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

THURSDAY, JANUARY 31

Second Meeting of the Board of Directors • 6:30–8:30 a.m. • Peak 9/10

Reception • 6:30 p.m. • Ballroom Lobby

Banquet and Dance • 7:30 p.m. • Colorado Ballroom (Peak 1–5)

Required ticket is in your registration packet.

ANY-maze
Behavioral Tracking Software

Automate ANY Stoelting Maze!

ANY-maze is the most flexible, easy-to-use video tracking system available and is designed to automate testing in animal behavior experiments, eliminate time-consuming methods of manual scoring, and provide video recording for achieving or re-testing.

ANY-maze can be used with all of Stoelting's behavioral testing apparatuses including pictured mazes: (from top) Y-Maze, Novel Object, Plus Maze, Radial-Arm Maze and Water Maze. Indeed, ANY-maze can easily adapt to new equipment or new testing protocols. The latest version of ANY-maze is faster and full of new features, many requested by users. Why not give it a try?

Download a FREE 30-day trial at www.ANY-maze.com!

For more information on ANY-maze or Stoelting Mazes, call 1-800-860-9775, fax (630) 860-9775, or visit **www.StoeltingCo.com**.

Stoelting
SINCE 1886

STOELTING CO • 620 WHEAT LANE • WOOD DALE, IL 60191
WWW.STOELTINGCO.COM • PHYSIO@STOELTINGCO.COM

ANY-maze is optimized for Windows 7 (XP and Vista)
© Copyright ANY-maze 1999-2012

SIGMA-ALDRICH®

SIGMA Life Science Where bio begins™

More translational and predictive animal models.

Plot your pathway for breakthroughs in neuroscience with knockout rat models from SAGE® Labs.

Biosynaptic.

Advancements in neuroscience are yours to discover with targeted knockout rats from SAGE Labs. Our comprehensive suite of rat models can help move your neuroscience research forward. Map your next breakthrough with smarter rat models for studying neurodegenerative, mood, and affective disorders, including seven new models of autism.

SAGE LABS
Sigma Advanced Genetic Engineering

Explore our collection of knockout rat models
sageresearchmodels.com

©2012 Sigma-Aldrich Co. LLC. All rights reserved. SIGMA and SIGMA-ALDRICH are trademarks of Sigma-Aldrich Co. LLC, registered in the US and other countries. SAGE is a registered trademark of Sigma-Aldrich Co. LLC. Where bio begins is a trademark of Sigma-Aldrich Co. LLC.

Program

PREAMBLE TO THE PROGRAM

The 2013 WCBR Program consists of panels and posters. Please consult the program book and posted announcements for details regarding the scientific presentations as well as inforamtion regarding the School Outreach program and the Town Meeting.

SUNDAY, JANUARY 27

7:00 A.M.

Breakfast • Colorado Ballroom (Peak 1–5)

8:00 A.M.

Plenary Address • Colorado Ballrom (Peak 1–5)

David Linden, PhD

Writing about brain function for a general audience

3:30–4:30 P.M.

Exhibits and Posters • Peak 1–4

4:30–6:30 P.M.

1. **Panel** • Peak 5

   AMPA receptors and addiction: The chicken or the egg?

   Jose Moron-Concepcion (Chair), R. Christopher Pierce, Mark Thomas, Jessica Loweth

2. **Panel** • Peak 17

   Affective processing in mood disorders: Pathophysiology and treatment targets

   Katherine Burdick (Chair), Gonzalo Laje, Faith Gunning, Brian Iacoviello

3. **Panel** • Peak 11/12

   The mesolimbic dopamine system in motivated behavior and action selection

   Kate Wassum (Chair), Matthew Wanat, Saleem Nicola, Linda Wilbrecht

4. **Panel** • Peak 14

   The ins and outs of synaptic glutamate-receptor trafficking

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

5. **Panel** • Peak 15/16

   Fast and furious electrochemistry: Recent advances in real-time neurochemical measurements

   Leslie Sombers (Chair), Parastoo Hashemi, Donita Robinson, Gregory McCarty

6. **Panel** • Peak 6/7/8

   Neural cilia—What do they do?

   Jerry Frankenheim (Chair), Shaoyu Ge, Alejandro Amador-Arjona, Daniel Storm, John Neumaier

8:30–10:00 P.M.

7. **Panel** • Peak 5

   NMDA receptors in human disease

   Stephen Traynelis (Chair), David Lynch, Lynn Raymond, Gerard Sanacora

8. **Panel** • Peak 17

   Susceptibility genes as targets for CNS drug development: New genes for new medicines

   Amanda Law(Chair), Thomas Hyde, Wendy Macklin, John McKew

9. **Panel** • Peak 11/12

   Investigations on excitatory/inhibitory synaptic balance

   Akiva Cohen (Chair), Colin Smith, Ivan Soltesz, Ofer Yizhar

10. **Panel** • Peak 14

    Noradrenergic mechanisms underlying effects of stimulants and potential treatments for stimulant dependence

    David Weinshenker, Colin Haile, **Thomas Newton (Chair)**

11. **Panel** • Peak 15/16

    Biomarkers on the trail of Parkinson's disease

    Peter LeWitt (Chair), Ken Marek, Jing Zhang

12. **Panel** • Peak 6/7/8

    Cerebral blood flow regulation during functional activation

    Olaf B. Paulson (Chair), Joseph C. LaManna, Dale Pelligrino, Leif Østergaard

MONDAY, JANUARY 28

7:30–9:30 A.M.

13. **Panel** • Peak 5

    New approaches for systems neuroscience: Dissecting circuits encoding emotional valence

    Geoffrey Schoenbaum, Stephan Lammel, Ilana Witten, **Kay Tye (Chair)**

14. **Panel** • Peak 17

    Do immediate early genes that regulate memory and synaptic plasticity play a role in psychiatric illnesses characterized by cognitive dysfunction?

    Jonathan Wisor, Diano Marrone, **Amelia Gallitano (Chair)**, Francesco Papaleo

15. **Panel** • Peak 11/12

    Fragile and broken potassium channels: And how to fix them

    Vitaly Klyachko, **Leonard K. Kaczmarek (Chair)**, Gary Bassell, Heike Wulff

16. **Panel** • Peak 14

    Imaging regulation of postsynaptic signaling, scaffolding, and trafficking underlying neuronal plasticity

    Paul De Koninck, Matthew Kennedy, Don Arnold, **Mark Dell'Acqua (Chair)**

17. **Panel** • Peak 15/16

    Maintenance matters: The roles of NMNATs in keeping neurons in shape

    Ming-Kuei Jang, Rui Chen, R. Grace Zhai, **Hui-Chen Lu (Chair)**

18. **Panel** • Peak 6/7/8

    Behavioral and neurobiological mechanisms of overeating: From cause to consequence

    Sarah Leibowitz, Alfonso Abizaid, Brian Baldo, **Mary Olmstead (Chair)**

3:30–4:30 P.M.

Exhibits and Posters • Peak 1–4

4:30–6:30 P.M.

19. **Panel** • Peak 5

    The yin and yang of dysphoria and euphoria

    Jacqueline McGinty (Chair), Bryan Yamamoto, Marian Logrip, Paul Phillips, Samuel Golden

20. **Panel** • Peak 17

    New tricks for old dogs: Discovering novel roles for neuronal genes in development

    Joel Kleinman, Karen Greif, **Thomas Hyde (Chair)**, Kristin Bigos, Tomasz Brudek

21. **Panel** • Peak 11/12

    Hit the black diamonds: Exercise counteracts stress, aging, and CNS trauma

    Monika Fleshner, Nicole Berchtold, Giselle Petzinger, **Kelli Sharp (Chair)**

22. **Panel** • Peak 14

    Physiology of identified inputs to dopaminergic neurons

    John Williams, Carl Lupica, Christopher Ford, **Carlos Paladini (Chair)**

23. **Panel** • Peak 15/16

    The role of novel small regulatory RNAs on gene regulation in schizophrenia

    Fabio Macciardi, Clark Jeffries, **Steven Potkin (Chair)**, Diana Perkins

24. **Panel** • Peak 6/7/8

    CSPGs in CNS injury and repair: A mammalian and nonmammalian perspective

    James Fawcett, Herbert Geller, Martin Oudega, **Jeffery Plunkett (Chair)**

7:00–8:30 P.M.

Town Meeting • Imperial Ballroom

8:30–10:00 P.M.

25. **Panel** • Peak 5

    Novel insights into monoamine networks

    Patricia Jensen, Mitsuko Watabe-Uchida, Marisela Morales, **Kathryn Commons (Chair)**

26. **Panel** • Peak 17

    Activity-dependent regulation of NMDAR phenotype and transport at developing synapses

    Hey-Kyoung Lee, **Suzanne Zukin (Chair)**, Robert Malenka

27. **Panel** • Peak 11/12

    Glutamate receptors and pain

    Juan Carlos Marvizon (Chair), Linda Sorkin, Susan M. Carlton

28. **Panel** • Peak 14

    Regulation of size and strength of postsynaptic sites

    Johannes Hell (Chair), Scott Soderling, Yasunori Hayashi, Eunjoon Kim, Jose Esteban

29. **Panel** • Peak 15/16

    Mitochondria, synapses, and neurodegeneration

    Elizabeth Jonas, **Zheng Li (Chair)**, Jennifer Morgan

30. **Panel** • Peak 6/7/8

    Chronic stress and plasticity in CNS pathways: Contrasting mechanisms underlying adaptive and maladaptive changes and implications for thinking about stress-related CNS disorders

    Serge Campeau, Jason Radley, **Victor Viau (Chair)**, David Morilak

TUESDAY, JANUARY 29

7:30–9:30 A.M.

31. **Panel** • Peak 5

    How nonmammalian model organisms shed new light on mechanisms of human neurologic diseases

    George R. Jackson, Christopher Gabel, **Michael Shifman (Chair)**, Ellen Chernoff

32. **Panel** • Peak 17

    Targeting the NMDA receptor hypofunction hypothesis of schizophrenia: Emerging clues from genetic models and drug discovery efforts

    Bita Moghaddam, Kazu Nakazawa, Kevin Ogden, **Shashank Dravid (Chair)**

33. **Panel** • Peak 11/12

    Different sex-difference patterns in rats vs. humans: Addiction-vulnerability mechanisms

    Wilson Compton, Marilyn Carroll, **Thomas Crowley (Chair)**, Wendy Lynch

34. **Panel** • Peak 14

    Posttranscriptional regulation of synaptic gene expression

    Murray Cairns (Chair), Oswald Steward, Neil Smalheiser, Belinda Goldie

35. **Panel** • Peak 15/16

    Cognition: From SNPs to nuts

    Anil Malhotra (Chair), Joey Trampush, Katherine Burdick, John Kane

36. **Panel** • Peak 6/7/8

    Treating the pains of aging: Can we do better?

    Megali Millecamps, Paula Bickford, Patrick Mantyh, **James Zadina (Chair)**

3:30–4:30 P.M.

Exhibits and Posters • Peak 1–4

4:30–6:30 P.M.

37. **Panel** • Peak 5

    Neuroadaptation along the path to addiction

    George Koob, **Paul Phillips (Chair)**, Jacqueline McGinty, Yann Pelloux

38. **Panel** • Peak 17

    Perishable potentials: Neural substrates of sex-specific risk for mental illnesses during adolescence

    Kyle Frantz, Jill Becker, **Bradley Cooke (Chair)**, Gretchen Neigh

39. **Panel** • Peak 11/12

    The path to oblivion: Do gamma rhythms lead the way?

    Misha Perouansky (Chair), Bruce MacIver, Anthony Hudetz, Robert Pearce

40. **Panel** • Peak 14

    Synaptic information processing and storage with CaMKII

    Karl Ulrich ("Ulli") Bayer (Chair), Johannes W. Hell, Roger J. Colbran, Haruhiko Bito

41. **Panel** • Peak 15/16

    Neuronal dysfunction: The blame goes beyond the brain

    Nicole Northrop (Chair), Aurelio Galli, Lawrence Reagan, Julio Ayala, Laura Halpin

42. **Panel** • Peak 6/7/8

    $GABA_A$ receptors, seizures, and the problem of pharmacoresistance

    Christopher Ransom, Ed Dudek, **Claude Wasterlain (Chair)**, David Naylor

6:30–8:30 P.M.

Special Poster Session & Reception • Peak 1–4

WEDNESDAY, JANUARY 30

7:30–9:30 A.M.

43. **Panel** • Peak 5

    The functional relevance of specific inputs to the prefrontal cortex in health and disease

    Joshua Gordon (Chair), Michael Higley, Andrew Rosen, Neil Woodward, Christoph Kellendonk

44. **Panel** • Peak 17

    BrainCloud: Global transcriptome and DNA methylome at your fingertips

    Joel Kleinman, Ryan Smith, **Barbara Lipska (Chair)**, Thomas Hyde

45. **Panel** • Peak 11/12

    Animal models of compulsive cocaine intake

    Adam Perry, **Tod Kippin (Chair)**, Sietse Jonkman, Friedbert Weiss

46. **Panel** • Peak 14

    New insights into the pharmacology and physiology of triheteromeric NMDA receptors

    Kasper B Hansen (Chair), Terunaga Nakagawa, Alasdair Gibb, Rylan Larsen

47. **Panel** • Peak 15/16

    Off-piste trails that link Parkinson disease genes

    Anurag Tandon (Chair), David Park, Warren Hirst, Haung Yu

48. **Panel** • Peak 6/7/8

    What is the function of striatal cholinergic interneurons?

    Jun Ding, **Tibor Koos (Chair)**, Joseph Cheer, Ilana Witten

10:00–11:30 A.M.

Smitty Stevens Memorial Ski Race • Peak 9—Sundown Run

11:30 A.M.–2:00 P.M.

Mountain Lunch • Peak 8—Vista Haus

3:30–4:30 P.M.

Exhibits and Posters • Peak 1–4

4:30–6:30 P.M.

49. **Panel** • Peak 5

    Heterogeneity of alcohol-use disorders: Possible underlying mechanisms

    John Crabbe, Charles O'Brien, **Sarah Leibowitz (Chair)**, George Koob

50. **Panel** • Peak 17

    Orchestrating the brain's immune response to disease

    Lisa Ridnour, Steve Levison, Kathy Maguire-Zeiss, **Carol Colton (Chair)**

51. **Panel** • Peak 11/12

    The role of catecholamines in anxiety and stress

    Michael Bruchas, Dennis Sparta, **Matthew Wanat (Chair)**, Joseph Cheer

52. **Panel** • Peak 14

    Neurons as metabolic sensors and regulators of energy homeostasis

    Barry Levin, **Celia Sladek (Chair)**, Clemence Blouet, Bret Smith

53. **Panel** • Peak 15/16

    New insights on mechanisms of sensory plasticity

    Marcos Frank, **Alfredo Kirkwood (Chair)**, Asaf Keller, Patrick Kanold

54. **Panel** • Peak 6/7/8

    Cell biology of the injured spinal cord

    Joel Levine (Chair), Yimin Zou, Jeffrey Twiss, James Fawcett

6:30 P.M.

Business Meeting • Peak 5

All are welcome and encouraged to attend.

THURSDAY, JANUARY 31

7:30–9:30 A.M.

55. **Panel** • Peak 5

    Drugs will change your brain

    Theodora Duka, Friebert Weiss, Nathalie Boutros, **Fulton Crews (Chair)**

56. **Panel** • Peak 17

    Merging structure and function in large-scale, high-resolution maps of brain circuitry

    Davi Bock, Kevin Briggman, **George Spirou (Chair)**, Mark Ellisman

57. **Panel** • Peak 11/12

    Codes in the snow: Neurophysiologic bases of prefrontal cortex function

    David Devilbiss (Chair), Jeremy Seamans, Eun Ha Baeg, Mark Laubach

58. **Panel** • Peak 14

    Predicting and avoiding trees on the slope: Efference copy mechanisms in the brain

    Charles Larson (Chair), Jeremy Greenlee, Amy Parkinson, Sabina Gonzales Flagmeier

59. **Panel** • Peak 15/16

    Cofilin-actin rods: An underappreciated mechanism for synaptic loss in aging and neurodegenerative disease

    James Bamburg (Chair), Thomas Kuhn, Gong Chen, Joseph Cichon

60. **Panel** • Peak 6/7/8

    Insights into common patterns of decline in brain and muscle with aging

    Lee Hong, Stacey Gorniak, Leslie Consitt, **Sonsoles de Lacalle (Chair)**

3:30–4:30 P.M.

Refreshment break • Ballroom Lobby

4:30–6:30 PM

61. **Panel** • Peak 5

    Evidence for perturbation of reward circuitry by pain and affective disorders

    Petra Schweinhardt, Scott Edwards, **Catherine Cahill (Chair)**, Alexandre DaSilva

62. **Panel** • Peak 17

    Alzheimer's disease: Complex pathology, challenging treatment

    Isabelle Aubert (Chair), JoAnne McLaurin, Emmanuel Planel, Steffany Bennett, Haung Yu

63. **Panel** • Peak 11/12

    Striatal circuits and genetics: Behavioral and molecular responses to drugs of abuse

    Mary Kay Lobo (Chair), David M. Dietz, Venetia Zachariou, X. William Yang

64. **Panel** • Peak 14

Sex, drugs, and … adolescence: The role of impulsivity

Susan Andersen (Chair), Louk Vanderschuren, Nadja Freund, Catharine Winstanley, Hugh Garavan

65. **Panel** • Peak 15/16

Highs and lows: Insights from the intracranial self-stimulation procedure about normal and abnormal brain reward function in neuropsychiatric disorders

Andre Der-Avakian (Chair), Sandra Boye, Clayton Bauer, C. J. Malanga

66. **Panel** • Peak 6/7/8

Signaling for sex, sugars, and senility: Estrogen's regulation of behavior and homeostasis

Kevin Sinchak, Paul Micevych, **Vicky Luine (Chair)**, Ed Wagner

6:30 P.M.

Reception • Ballroom Lobby

7:30 P.M.

Banquet and Dance • Colorado Ballroom (Peak 1–5)

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

POSTER SESSION I

SUNDAY, JANUARY 27 • PEAK 1–4

Posters will be available for viewing 3:30–10:00 p.m. on Sunday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Sunday. Posters can be set up after 12:00 p.m. on Sunday.

P1 An investigation of head accelerometry, cognitive function, and brain blood flow during intercollegiate boxing and its impact regarding head-injury assessment in combat

Michelle Butler

P2 Mate, a novel protein, suggests a role for nuclear speckles and DNA splicing in the pathology of the fragile X syndrome

Regina Dahlhaus

P3 The central role of the gut microbiota in the maternal-separation model of depression

Giada De Palma

P4 Gain insights on central nervous system diseases using global metabolomics

Kirk Pappan

P5 Neural response to visual nicotine cues in smokers: What predicts signal magnitude?

Henry Holcomb

P6 Characterization of a novel primary neuronal culture from adult zebrafish brainstem

Jeffery Plunkett

P7 Amyloid-dependent degeneration of subcortical monoaminergic and cholinergic neurons in mouse models of AD: Relevance of cognitive and neuropsychiatric symptoms

Michael Lee

P8 Nicotinic acetylcholine receptors (nAChRs) in neuroimmune and inflammatory responses: Modulation of effects in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS)

Ronald Lukas

P9 Expression of P450c17 in the human fetal nervous system

Synthia Mellon

P10 Antipsychotic-like actions of amylin in ventral striatal regions enriched in RAMP-1 and CT gene expression

Vaishali P. Bakshi

P11 Time for a change! An endocrine disruption index to predict neural impacts of xenoestrogens

Mary Ann Ottinger

P12 The role of axon regeneration from brainstem neurons in functional recovery after spinal cord injury in adult zebrafish

Martin Oudega

P13 Chronic cerebrospinal venous insufficiency and venous stenoses in multiple sclerosis

Olaf B. Paulson

P14 The antipsychotic-like effect of mGlu4-receptor-positive allosteric modulators in rodents

Andrzej Pilc

P15 Advances in neurochemical profiling of brain tissue samples using HPLC with a novel four-channel electrochemical array detector

Nick Santiago

P16 The role of perineuronal nets within the medial prefrontal cortex on cocaine-seeking behavior

Barbara Sorg

P17 Catechol-O-methyltransferase (COMT) influences the connectivity of the prefrontal cortex at rest

Elizabeth Tunbridge

P18 Hunger vs. hedonics: Investigating the role of the amygdala in opioid vs. energy deficit–driven feeding behavior

Matthew Will

POSTER SESSION 2

MONDAY, JANUARY 28 • PEAK 1–4

Posters will be available for viewing 3:30–10:00 p.m. on Monday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Monday. Posters can be set up after 8:00 a.m. on Monday.

P19 Status epilepticus–induced hippocampal microgliosis is blocked by rapamycin treatment

Anne Anderson

P20 A NET-mediated increase in DA reuptake: Implications for the treatment of L-DOPA–induced dyskinesia in Parkinson's disease

Tanya Chotibut

P21 The genetic and neural correlates of risky decision making in young adults with antisocial substance disorder

Helena Yardley

P22 Methamphetamine-induced neuronal necrosis occurs only in mice with electrographic seizure discharges

Denson Fujikawa

P23 The α1-antagonist doxazosin blocks cocaine-induced sensitization in rats and reduces cocaine use in cocaine-dependent individuals

Colin Haile

P24 Estimating the dynamic repertoire of brain states by fMRI under anesthesia

Anthony Hudetz

P25 Genome-wide expression profiling of brain areas involved in pain processing and depression in a mouse model of inflammatory bowel disease

William Lariviere

P26 Examination of gene expression over time using tissue microarrays provides insight into the progressive compensatory responses within the nigrostriatal tract following intrastriatal 6-hydroxydopamine in the rat

Jack Lipton

P27 Deletion of PTEN in brain leads to autism-like behavioral deficits and learning and memory deficits

Joaquin Lugo

P28 Intoxicating concentrations of alcohol enhance GABAA slow synaptic inhibition

Bruce MacIver

P29 Taste reward circuitry related brain structures characterize ill and recovered anorexia nervosa and bulimia nervosa

Guido K.W. Frank

P30 Prenatal nicotine exposure augments the trigeminocardiac reflex via 5-HT2A/C–receptor activation

David Mendelowitz

P31 The dopamine receptor–interacting protein S100B: D2-receptor site of interaction and functional consequences

Kim Neve

P32 Long-term behavioral and biochemical consequences of neonatal overexposure to NRG1 and NRG3 in mice

Clare Paterson

P33 Analysis of putative stem and neural progenitor cell populations following CNS injury in the adult zebrafish

Jeffery Plunkett

P34 Increased oxidative stress and loss of synaptic proteins in preclinical Alzheimer's disease

Stephen Scheff

P35 Escalation patterns of opioids used for pain treatment

Carrie Wade

P36 The role of glyoxalase 1 and methyglyoxal in diabetic neuropathy

Douglas Wright

POSTER SESSION 3

TUESDAY, JANUARY 29 • 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 with posters from 3:30–4:30 p.m. and returning for the special session 6:30–8:30 p.m. Posters must be removed by 10:00 p.m. Tuesday. Posters can be set up after 8:00 a.m. on Tuesday.

P37 Assessing the effects of cocaine use on different forms of value-based behavior and learning

Heather Wied

P38 Mesolimbic dopamine signaling during decisions between options of differing utility

Monica Arnold

P39 The medial prefrontal cortex inversely regulates toluene-induced alterations in excitatory synaptic transmission of mesolimbic dopamine neurons

Jacob Beckley

P40 Central orexin2-receptor signalling regulates alcohol taking but not alcohol seeking in rats

Robyn Brown

P41 Functional analysis of the schizophrenia-associated gene TCF4

Brady Maher

P42 DREADDed drug seeking: Isolating the contribution of corticostriatal projections in motivation for cocaine self-administration

Susan Ferguson

P43 The behavioral profile of the BDNF knockout rat

Melissa Glenn

P44 Posttraining optogenetic manipulations of basolateral amygdala activity modulate the consolidation of inhibitory avoidance memory in rats

Ryan LaLumiere

P45 NMDA modulates adult prefrontal cortical interneurons

Eastman Lewis

P46 The development of high-affinity inhibitors toward the allosteric binding site in the serotonin transporter

Claus Løland

P47 Cocaine, but not morphine, self-administration impairs overexpectation-induced extinction learning

Federica Lucantonio

P48 Cross-modal plasticity of excitatory synapses in auditory cortex following visual deprivation

Emily Petrus

P49 Ovarian steroids increase dendritic spine–dependent PSD-95 in the serotonergic dorsal raphe nucleus of macaques

Heidi Rivera

P50 Imaging the motility of inositol trisphosphate receptors in intact mammalian cells using single-particle-tracking photoactivated localization microscopy (sptPALM)

Ian Smith

P51 Cognition-enhancing actions of psychostimulants are dependent on noradrenergic α2- and dopamine D1-receptors within the prefrontal cortex

Robert Spencer

P52 Optogenetic manipulations of relapse neurocircuitry during cue-induced reinstatement of cocaine seeking

Michael Stefanik

P53 Noncompeting NMDA-receptor antagonists alter auditory event-related potentials (ERP) in the rat

Elyse Sullivan

P54 Basolateral amygdala-evoked heterosynaptic suppression of inputs from other temporal cortical structures in the prefrontal cortex

Hugo Tejeda

POSTER SESSION 4

WEDNESDAY, JANUARY 30 • PEAK 1–4

Posters will be available for viewing 3:30–10:00 p.m. on Wednesday. Presenters will be with posters 3:30–4:30 p.m. Posters must be removed by 10:00 p.m. on Wednesday. Posters can be set up after 8:00 a.m. on Wednesday.

P55 The effects of hESC-derived motor neuron transplantation on respiratory function in the SMNdelta7 mouse model of SMA

Tanya Wyatt

P56 The relationshi[WITHDRAWN]n circadian and c[WITHDRAWN]ysfunction in [WITHDRAWN] disorder

Raphael Braga

P57 Selective reduction of anxiety by alcohol: Psychophysiological evidence from laboratory manipulations of threat uncertainty

John Curtin

P58 A triple dissociation between delay, trace and contextual fear conditioning in glutaminase-deficient mice

Inna Gaisler-Salomon

P59 Thermal hyposensitivity in novel knockout rat models for pain research

Kevin Gamber

P60 Mild and moderate traumatic brain injury (mTBI) disrupts the diurnal glucocorticoid rise and fear-conditioning behaviors

Robert Handa

P61 Disruption of Arp2/3 models progressive synaptic and behavioral abnormalities of psychiatric disorders

Il Hwan Kim

P62 Neural control of intake by the medial prefrontal cortex

Mark Laubach

P63 Adrenergic and serotonergic effects on the duration of the laryngeal chemoreflex—Implications for SIDS

James Leiter

P64 A hierarchy of pathogenesis revealed by full-length and fragment models of Huntington's disease in Drosophila

J. Lawrence Marsh

P65 GAT1 expression during normal human brain development and in schizophrenia

Michelle Mighdoll

P66 Gene-expression profiling and pathway analyses reveal molecular signatures and relationships underlying enhanced methamphetamine neurotoxicity caused by protracted corticosterone exposure

James O'Callaghan

P67 Subarachnoid hemorrhage (SAH)–linked brain inflammation contributes to arteriolar dilating dysfunction and neuropathology in rats

Dale Pelligrino

P68 CHRNA5-promoter polymorphisms are associated with cognitive outcome after mild traumatic brain injury

C. Harker Rhodes

P69 Identification of a novel dopaminergic agonist that selectively activates the D2 dopamine receptor in a biased fashion

David Sibley

P70 Fasting-induced ghr[illegible]ation of vasopres[illegible]s via ret[illegible]ransneuronal-glial s[illegible]ulation of excitatory GABA circuits

WITHDRAWN

Jeffrey Tasker

P71 Mechanisms of regulation of mitochondrial length by neuronal activity

Ramon Trullas

P72 Abnormal mTOR and ERK signaling in cortical dysplasia associated with epilepsy

Angus Wilfong

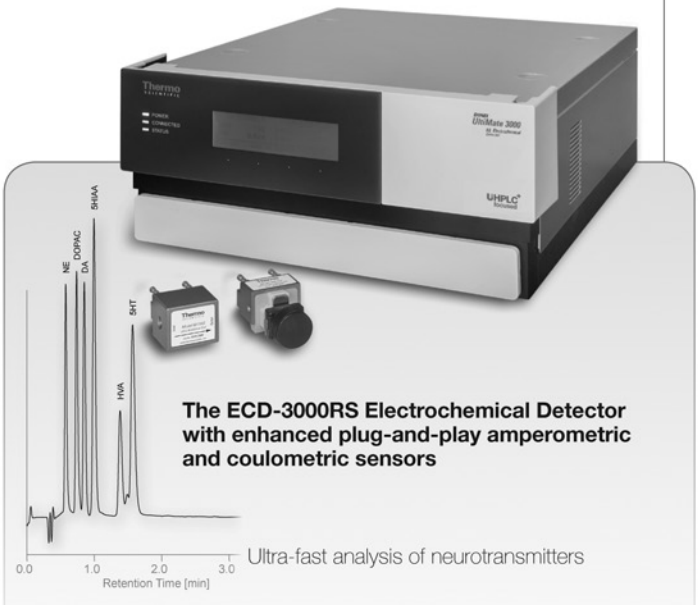
Thermo
SCIENTIFIC

sensitive, flexible

Analyzing precious, limited volume samples, such as microdialysis perfusates, requires sensitive and reliable detection. Introducing the Thermo Scientific Dionex UltiMate 3000 Electrochemical Detector—designed to routinely measure low femtogram levels in small volume samples using plug-and-play amperometric and coulometric sensors. This multichannel detector features gradient compatibility for method flexibility and enhanced auto-ranging capabilities so you will not have to reanalyze your sample.

electrochemical detection

www.thermoscientific.com/ECdetection



The ECD-3000RS Electrochemical Detector with enhanced plug-and-play amperometric and coulometric sensors

Ultra-fast analysis of neurotransmitters

© 2012 Thermo Fisher Scientific Inc. All rights reserved. All trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries.

Session Abstracts

PANEL • SUNDAY, 4:30–6:30 PM • PEAK 5

1. AMPA receptors and addiction: The chicken or the egg?

Chair: **Jose Moron-Concepcion**
Presenters: **Jose Moron-Concepcion, R. Christopher Pierce, Mark Thomas, Jessica Loweth**

Glutamatergic systems, including AMPA receptors (AMPAR), are involved in drug-induced neuronal and behavioral plasticity, although the mechanisms underlying these effects are not fully understood. This symposium will further discuss the changes in glutamatergic transmission that occur within the mesolimbic system and the hippocampal formation following drug administration. In addition, we will discuss how these neuroadaptations may drive the pathology of opiate and psychostimulant addiction. Jose Moron-Concepcion (Columbia University) will discuss data showing the role of hippocampal GluA2-lacking (Ca^{2+}-permeable) AMPAR in the mechanisms underlying context-dependent sensitization to morphine. In addition, he will also discuss results indicating that whether AMPAR are involved in the behavioral consequences following morphine exposure, NMDA receptors play a role in morphine-induced alterations in synaptic plasticity that may be responsible for relapse to drug use. Chris Pierce (University of Pennsylvania) will discuss results indicating that the reinstatement of cocaine seeking is promoted by the stimulation of mGluR5 receptors, which influence AMPAR trafficking by activating PKC. Mark Thomas (University of Minnesota) will discuss the characteristics and mechanisms underlying AMPAR plasticity in nucleus accumbens spiny neurons during drug-induced or stress reinstatement following abstinence from chronic psychostimulant treatment. Jessica Loweth (Rosalind Franklin University) will discuss recent results showing that mGluR1 negatively regulates Ca^{2+}-permeable AMPAR levels in the NAc and that a decrease in mGluR1 tone during withdrawal from extended-access cocaine self-administration enables Ca^{2+}-permeable AMPAR accumulation, whereas stimulating mGluR1 removes these receptors from NAc synapses and reduces cocaine craving.

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

2. Affective processing in mood disorders: Pathophysiology and treatment targets

Chair: **Katherine Burdick**
Presenters: **Katherine Burdick, Gonzalo Laje, Faith Gunning, Brian Iacoviello**

New, more effective treatments for unipolar and bipolar depression are greatly needed. The last decade has seen an increase in methods for investigating the mechanisms underlying depression, including genetics, brain imaging, and cognitive-behavioral tasks. These methods have begun to highlight potential new avenues for intervention based on knowledge of the underlying abnormalities in depression (neural circuitry, cognitive processing biases, etc). This panel will discuss novel data on the mechanisms underlying unipolar and bipolar depression, and will discuss potential intervention strategies based on this increased understanding. Katherine Burdick (Mount Sinai School of Medicine) will provide an overview of behavioral data related to affective attentional bias in bipolar disorder and provide data supporting its relationship with genetic risk. Gonzalo Laje (National Institute of Mental Health) will then discuss the effects of common genetic variation on the pharmacokinetic and pharmacodynamic aspects of rapid-acting antidepressants such as ketamine and scopolamine. He will also comment on the potential effect of rare genetic variants in pharmacogenetics of these antidepressants. Faith Gunning (Weill Cornell Medical College) will discuss brain-imaging parameters for investigating depression in late life, and brain changes associated with depression and treatment response. Brian Iacoviello (Mount Sinai School of Medicine) will then present the conceptualization and development of a cognitive-training paradigm that targets biased cognitive/affective processing as an intervention strategy for depression, and will present initial pilot data on its effectiveness.

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

3. The mesolimbic dopamine system in motivated behavior and action selection

Chair: **Kate Wassum**
Presenters: **Kate Wassum, Matthew Wanat, Saleem Nicola, Linda Wilbrecht**

The striatum serves as an interface between limbic and motor systems. Furthermore, striatal function can be modulated by the dense dopamine input emanating from the midbrain. While dopamine function within the striatum is implicated in facilitating motivation and influencing decision-making processes, the exact nature of this interaction is not fully understood. This panel will address this topic by presenting recent research examining phasic dopamine

release, striatal neural activity, and optogenetic perturbation of specific striatal pathways during motivated behavior and action selection. Kate Wassum will present data on how phasic mesolimbic dopamine changes are associated with reward seeking actions and the cue-induced motivation that invigorates those reward-seeking actions. Matt Wanat will present data on phasic changes in dopamine transmission preceding unreinforced transitions in behavior. Saleem Nicola will present his research on the encoding of predicted reward value and effort by nucleus accumbens neurons in rats performing an effort-based decision-making task. Linda Wilbrecht will present her data on the distinct biases produced by stimulating D1R and D2R expressing cells in the dorsal and ventral striatum during a decision making task.

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

4. The ins and outs of synaptic glutamate-receptor trafficking

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

Glutamatergic synapses are essential for the moment-to-moment communication among neurons in the brain as well as for the long-term storage of information. Glutamate-receptor composition and number are crucial for these roles. This panel will address aspects of receptor regulation for all three classes of ionotropic glutamate receptor: AMPA, NMDA, and kainate. Nicoll will present recent results indicating that, although LTP requires a reserve pool of glutamate receptors, there is no subunit requirement. Bredt will discuss the roles for auxiliary AMPAR subunits in gating of AMPARs. Roche will discuss the role of SAP102 and casein kinase 2 in the control of synaptic NMDARs. Maricq will present his findings on the interplay between AMPAR subunits and auxiliary subunits in *C. elgans*.

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

5. Fast and furious electrochemistry: Recent advances in real-time neurochemical measurements

Chair: **Leslie Sombers**
Presenters: **Leslie Sombers, Parastoo Hashemi, Donita Robinson, Gregory McCarty**

Fundamental progress toward understanding brain function in normal and pathological states is greatly enhanced by assessment of chemical communication between neurons. Microelectrodes coupled with electrochemical detection are ideally suited for the detection and quantification of rapid fluctuations of electroactive neurochemicals in live tissue. Traditional

voltammetric measurements have largely been limited to dopaminergic systems in the striatum. As our understanding of brain function develops, we are faced with increasingly complex questions that require new analytical tools, technological advancements, and innovative applications of existing electroanalytical detection schemes.

The speakers in this proposed panel are pioneers in the development, characterization and application of electroanalytical approaches to study neurochemical changes. They will describe work advancing fast-scan cyclic voltammetry to the detection of opioid neuropeptides (Sombers), the serotonergic mechanisms that underlie depression (Hashemi), and the monitoring of rapid catecholamine fluctuations in the prefrontal cortex (Robinson). Additionally, new analytical tools will be presented, including microelectrode arrays for unprecedented measurements of multiple neurotransmitters (McCarty). These cutting-edge advances promise to significantly expand the scope of electrochemical analyses of brain function.

PANEL • SUNDAY, 4:30–6:30 PM • PEAK 6/7/8

6. Neural cilia—What do they do?

Chair: **Jerry Frankenheim**
Presenters: **Shaoyu Ge, Alejandro Amador-Arjona, Daniel Storm, John Neumaier**

Many neuroscientists, until recently, did not know that practically all CNS neurons have a cilium (one per neuron—a "primary" (immotile), antenna-like appendage extending from the mother centriole, highly specialized by its receptor content, signal-transduction capabilities, and morphology). Neurons of adult and embryonic brain, and neural progenitors, all contain a cilium. Increasingly, brain disorders have been associated with disrupted cilia, including disorders of development, energy balance/obesity, neurodegeneration, cognitive deficits, and other higher brain functions. Shaoyu Ge (SUNY Stony Brook) will describe development of adult-born neurons, providing details of centrosome migration, cilia assembly, Golgi polarization, and physiological significance of cilia formation in maintenance of existing neural circuits, finally including the ciliary role in hippocampal behavior. Alejandro Amador-Arjona (Sanford-Burnham) will demonstrate that cognitive deficits associated with ciliopathies may be, in part, mediated by deficiency of cilia in adult hippocampal stem/progenitor cells. Daniel Storm (University of Washington) will discuss physiological roles of type 3 adenylyl cyclase (AC3) in cilia of hypothalamic

neurons as it relates to obesity, and AC3 in cilia of hippocampal neurons in learning and memory. John Neumaier (University of Washington) will discuss 5-HT6 receptors, the only serotonin receptor localized in cilia, and their impact on cilia morphology and function in striatal neurons. He will discuss their impact on cognitive function, habit learning, addiction-related behaviors, and the opportunity of modulating cilia function as a strategy for treating addiction and cognitive disorders. The chair (Jerry Frankenheim, NIDA) will briefly conclude that neural cilia are critically involved with complex mammalian behavior and brain plasticity, and that there remains much challenge/opportunity to investigate neural cilia functions.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 5

7. NMDA receptors in human disease

Chair: **Stephen Traynelis**
Presenters: **Stephen Traynelis, David Lynch, Lynn Raymond, Gerard Sanacora**

Advances in genetics, immunology, and clinical medicine have identified a number of human neuropathological conditions that directly involve NMDA receptors, abnormal autoantibodies against NMDA receptor subunits, or mutations in NMDA receptor subunits that perturb agonist binding, ion permeation, and gating. Dr. Stephen Traynelis (Emory University) will briefly introduce NMDA receptor structure and function, and describe de novo disease-causing mutations in the GluN2 subunit of the NMDA receptor. Understanding the contribution of the functional changes of these mutations to clinical symptoms may hold implications for broader treatment of epilepsy. Dr. David Lynch (University of Pennsylvania) will subsequently discuss a novel form of encephalitis that results from an autoimmune response against the GluN1 subunit, and how recent advances in understanding has implications for NMDA receptor structure and physiology. Next Dr. Lynn Raymond (University of British Columbia) will discuss the therapeutic implications of altered NMDA receptor synaptic signaling in neurodegenerative Huntington's disease. Lastly, Dr. Gerard Sanacora (Yale University) will present recent data showing that exploitation of NMDA receptor antagonists for the treatment of major depressive disorder may provide a new and highly beneficial approach to treatment-resistant patients. Together the presentations in this panel will provide a summary of compelling, new data showing both NMDA receptor dysfunction as the basis for human disease as well as the potential of NMDA receptors as a therapeutic targets.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 17

8. Susceptibility genes as targets for CNS drug development: New genes for new medicines

Chair: **Amanda Law**
Presenters: **Amanda Law, Thomas Hyde, Wendy Macklin, John McKew**

Identifying links between genes and neurobiological events, both normal and abnormal, provides a unique basis for the development of novel "target"-based therapeutics. This panel will present data describing systematic approaches to identifying genes associated with complex neurodevelopmental disorders and normal brain development, the characterization of the biological processes that they modulate and the prioritization of these genes on the basis of pharmacological targetability. Dr. Law will present work identifying a genetic pathway associated with schizophrenia, involving NRG1-ErbB4 and the PI3Kinase, PIK3CD. Targeted pharmacological modulation of PIK3CD shows promising results in reversing neurobiological abnormalities in several rodent models of schizophrenia, including a novel NRG1-targeted genetic model. Dr. Hyde will discuss novel GABA signaling targets for Schizophrenia drug development. Dr. Macklin will present data on genetic pathways that regulate CNS myelination, focusing on the role of NRG-AKT and mTOR in oligodendrocyte development and function and relationship to schizophrenia. Pharmacological targeting of genes in the pathway modulates myelination and may have broad translational applicability. Finally, Dr. McKew will highlight the unique public private partnership models developed within the National Center for Advancing Translational Sciences, NIH in relation to therapeutics for rare and neglected CNS diseases. Efforts to illuminate the functional role of genes in complex brain disorders are critical to understanding the mechanistic basis of disease and provide a new strategy for development of the next generation of therapeutics.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 11/12

9. Investigations on excitatory/inhibitory synaptic balance

Chair: **Akiva Cohen**
Presenters: **Colin Smith, Ivan Soltesz, Ofer Yizhar**

Disturbances to the balance between excitatory and inhibitory synaptic balance has been implicated in a variety of disorders of the nervous system. Alterations to the balance have been shown to affect physiological measures and cause changes in cognition and behavior in both patients with neurological and psychiatric disorders as well as various animals models. Various techniques have been employed to measure synaptic balance, ranging from molecular biology to

electrophysiology to behavior. The central goal of this panel is to compare and contrast the physiological and behavioral effects of alterations to excitatory/inhibitory synaptic balance across neurological disorders and to highlight the methods used to interrogate perturbations to this balance.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 14

10. Noradrenergic mechanisms underlying effects of stimulants and potential treatments for stimulant dependence

Chair: **Thomas Newton**
Presenters: **David Weinshenker, Colin Haile, Thomas Newton**

There is increasing evidence that noradrenergic mechanisms contribute to the effects of stimulants, including cocaine and methamphetamine. Dr. Weinshenker will discuss the impact of treatment with DBH inhibitors in multiple models of cocaine seeking in rats. He will also discuss how alpha-1 receptors in the prefrontal cortex are critical for cocaine-primed reinstatement. Next he will describe how DBH KO mice are hypersensitive to cocaine-induced locomotion and express a conditioned place aversion to cocaine at doses that support a place preference in normal mice and he will describe a likely mechanism for this. Dr. Haile will then present data showing how treatment with the DBH inhibitor disulfiram dose-dependently affects the reinforcing effects of cocaine in human volunteers. Dr. Newton will then present data showing how other noradrenergic medications alter the effects of cocaine and methamphetamine in drug-using volunteers.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 15/16

11. Biomarkers on the trail of Parkinson's disease

Chair: **Peter LeWitt**
Presenters: **Peter LeWitt, Kenneth Marek, Jing Zhang**

At the forefront of current Parkinson's disease (PD) research, biomarkers are critically needed for enhancing diagnostic capabilities, developing disease-progression surrogates for clinical trials, and gaining insights into its neurodegenerative processes. PD affects the brain long before its movement disorders emerge; recent evidence points to several systemic manifestations and to genetic factors sometimes involved in this disorder. Consequently, the search for PD biomarkers has travelled in many directions. This research has provided useful insights into investigating disease-specific clues for other neurodegenerative disorders as well. The loss of nigrostriatal dopaminergic neurons and the development of alpha-synuclein aggregations in neurons are key elements of PD pathophysiology. However, attempts to measure these

changes as biomarkers have not yielded useful ways for monitoring the disease. PD leaves its imprint in a numbers of ways and other biomarkers investigations have been more productive. This session will explore the range of these findings in state-of-the-art in presentations by three clinician–researchers who have contributed to this field of research. Peter LeWitt (Henry Ford Health System) will review CSF and blood neurotransmitter, other small-molecule biomarker studies (including his recent metabolomics findings), and systemic findings from methods as diverse as cardiac scintigraphy, cranial echosonography, and colonic biopsy. Next, Kenneth Marek (Institute of Neurodegenerative Disorders) will review his extensive experience of neuroimaging the brain with dopamine transporter ligands, as well as other studies using positron emission tomography, and functional and high-Tesla field MRI. Finally, Jing Zhang (University of Washington School of Medicine) will highlight his studies and those of others utilizing proteonomic analysis and other ways to analyze for protein biomarkers in specimens ranging from CSF to saliva.

PANEL • SUNDAY, 8:30–10:00 PM • PEAK 6/7/8

12. Cerebral blood flow regulation during functional activation

Chair: **Olaf B. Paulson**
Presenters: **Olaf B. Paulson, Joseph C. LaManna, Dale Pelligrino, Leif Østergaard**

Cerebral blood flow (CBF) and cerebral metabolic rate are normally coupled; that is, an increase in metabolic demand will lead to an increase in flow. However, during functional activation, CBF and glucose metabolism remain coupled as they increase in proportion, whereas oxygen metabolism only increases to a minor degree—the so-called uncoupling of CBF and oxidative metabolism. Multiple studies have addressed these issues, and hypotheses have been forwarded regarding the underlying mechanisms. Some reports have speculated about the existence of a potentially deficient oxygen supply to the tissue most distant from the capillaries, whereas other studies point to a shift toward a higher degree of non-oxidative glucose consumption during activation.

The symposium brings basic and clinical scientists together with the aim of discussing frontline research and new hypothesis to be tested in future studies. Olaf B. Paulson will give an introduction with a review of the state of the art. Joseph LaMana will discuss how the study of mechanisms of adaptation to

hypoxia may relate to oxygen utilisation during normal functional activation. Dale Pelligrino will discuss the key role of astrocytes in the process of neurovascular coupling, with some emphasis on purinergic mechanisms. Leif Østergaard will discuss new models of capillary recruitment and link it to new hypotheses.

PANEL • MONDAY, 7:30–9:30 AM • PEAK 5

13. New approaches for systems neuroscience: Dissecting circuits encoding emotional valence

Chair: **Kay Tye**
Presenters: **Geoffrey Schoenbaum, Stephan Lammel, Ilana Witten, Kay Tye**

The ability to differentiate and appropriately use stimuli associated with positive and negative emotional or motivational significance is critical for animal survival. Despite this well-conserved ability, we are only beginning to dissect the neural circuits that process reward or aversion. This session will focus on new insights into these neural circuits achieved through the application of cutting-edge techniques in behavior, optogenetics, pharmacology, in vivo electrophysiology and ex vivo electrophysiology. Integrating these approaches propels us forward in our investigation of how distal regions communicate, how different cell types interact locally, and how information is transmitted across synapses within neural circuits throughout the mesocorticolimbic system. Geoffrey Schoenbaum (NIDA) will compare and contrast neural coding dynamics across multiple brain regions that are critical in sensory preconditioning, blocking and unblocking, and other computations that occur in associative learning. Stephan Lammel (Stanford) will discuss his dissection of laterodorsal tegmentum and lateral habenula inputs to the ventral tegmental area and projections to the ventral striatum and prefrontal cortex mediating reward or aversion using optogenetic and ex vivo electrophysiological techniques. Ilana Witten (Princeton) will describe the role of cholinergic interneurons in the nucleus accumbens in modulating local circuit activity, as well as in mediating reward and fear behavior. Kay Tye (MIT) will discuss how amygdala projections to different targets provide unique contributions to anxiety-related and reward-related behaviors, using a combination of optogenetic, electrophysiolgoical and pharmacological approaches. Another purpose of this panel is to provide a look towards the future of systems neuroscience and the integration of multiple techniques.

14. Do immediate early genes that regulate memory and synaptic plasticity play a role in psychiatric illnesses characterized by cognitive dysfunction?

Chair: **Amelia Gallitano**
Presenters: **Jonathan Wisor, Diano Marrone, Amelia Gallitano, Francesco Papaleo**

Numerous genes that have been implicated in risk for major psychiatric illnesses also play critical roles in memory formation and synaptic plasticity. The proteins encoded by these genes form a signaling cascade that modulates synaptic strength. The final steps in this cascade involve immediate early genes (IEGs) such as the transcription factor early growth response 3 (EGR3) and its target, the effector IEG activity-regulated cytoskeleton-associated protein (ARC). The mental illnesses schizophrenia and bipolar disorder are characterized by deficits in cognitive function. Single nucleotide polymorphisms (SNPs) in EGR3 have been associated with both of these disorders, and expression of EGR3 is reduced in the brains of schizophrenia patients. In the rodent brain, Egr3 directly regulates Arc, suggesting that disruption of ARC function in humans may also influence risk for these mental illnesses. This panel will explore the roles of Arc in the molecular processes thought to underlie cognition, and in psychiatric illnesses in which cognition is disturbed. Dr. Wisor (Washington State University) will describe the robust relationship between sleep/wake cycles and the expression of Arc and other plasticity-related genes in cerebral structures associated with memory formation and recall. This relationship provides a mechanistic link for the parallel deficits in sleep and cognition in mental illness. Dr. Marrone (Wilfrid Laurier University) will discuss the behavioral regulation of plasticity-related genes such as Arc in the hippocampus, with emphasis on the formation of enduring memories and how this process changes over the lifespan. Dr. Gallitano (University of Arizona) will present results of studies to identify and test SNPs in the ARC gene for association with schizophrenia. Finally, Dr. Papaleo (Istituto Italiano di Tecnologia) will report on behavioral analyses of Arc-deficient mice, which display schizophrenia-like abnormalities.

15. Fragile and broken potassium channels: And how to fix them

Chair: **Leonard Kaczmarek**
Presenters: **Vitaly Klyachko, Leonard Kaczmarek, Gary Bassell, Heike Wulff**

A variety of diseases that result in intellectual disability and developmental delay are associated with neuronal hyperexcitability early in development. For example, in fragile X syndrome, the major cause of inherited intellectual disability, 15–25% of patients experience seizures early in life. Moreover, as many as 40% of severely autistic patients have seizures during early development. The occurrence of infantile seizures themselves, however, does not by itself herald subsequent intellectual impairment. This panel will present findings on how the regulation of potassium channels is impaired in fragile X syndrome and in other developmental disorders that produce intellectual impairment. Vitaly Klyachko will describe how loss of the Fragile X Mental Retardation Protein, FMRP, alters the firing properties of mammalian neurons. He will present evidence that FMRP also regulates excitability by directly interacting with the large-conductance calcium-activated potassium channel (BK channel), a mechanism that is independent of the well-known role of FMRP as an mRNA-binding protein that regulates local protein translation. Len Kaczmarek will describe a class of gain-of-function mutations in the sodium-activated potassium channel Slack, a channel that also directly binds FMRP through domains at its cytoplasmic C-terminus. In humans, these mutations produce complete developmental delay, rendering the patients with no communication skills. Gary Bassell will describe cellular and molecular mechanisms by which FMRP regulates the levels of expression of neuronal proteins, including the voltage-dependent Kv4.2 channel, which is required for the rapidly inactivating A-current in the dendrites of hippocampal neurons. Finally Heike Wulff will describe the design and testing of small molecules of that are being developed to activate or inhibit neuronal KCa2 or microglial KCa3.1 and Kv1.3 channels, with the goal of correcting abnormalities in channel expression or function.

16. Imaging regulation of postsynaptic signaling, scaffolding, and trafficking underlying neuronal plasticity

Chair: **Mark Dell'Acqua**
Presenters: **Paul De Koninck, Matthew Kennedy, Don Arnold, Mark Dell'Acqua**

Experience-dependent plasticity at excitatory and inhibitory synapses supports normal learning and memory, and alterations in synaptic plasticity are associated with nervous system disorders including Alzheimer's, epilepsy, schizophrenia, Down syndrome, fragile X, and autism. Recent advances in the development of fluorescence imaging methods, optical imaging probes, and optogenetic approaches have given neuroscientists new tools to study the cell biological mechanisms regulating synaptic plasticity in unprecedented detail. This panel will present recent findings using a variety of optical imaging approaches to elucidate the functions of postsynaptic signaling pathways, protein–protein scaffolding interactions, and membrane trafficking processes that control synaptic plasticity. Paul De Koninck (Laval University) will present studies using optical imaging approaches to characterize plasticity-associated regulation of CaMKII localization and protein–protein interactions in dendrites of living neurons. Matthew Kennedy (University of Colorado) will focus on the use of optical probes and optogenetic tools to image and control postsynaptic AMPA receptor and membrane trafficking processes underlying plasticity. Don Arnold (University of Southern California) will present recent findings using recombinant antibody-like proteins known as intrabodies to label endogenous PSD-95 and Gephyrin and allow real-time monitoring of excitatory and inhibitory synaptic strength in vivo without perturbing synaptic function. Finally, Mark Dell'Acqua (University of Colorado) will present new findings on AKAP-scaffolded calcineurin regulation of synapse to nucleus signaling that controls plasticity-associated gene expression. In particular, he will highlight use of calcium imaging in conjunction with local stimulation of L-type calcium channels to study NFAT transcription factor activation in dendrites that promotes its distal translocation to the nucleus.

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

17. Maintenance matters: The roles of NMNATs in keeping neurons in shape

Chair: **Hui-Chen Lu**
Presenters: **Ming-Kuei Jang, Rui Chen, R. Grace Zhai, Hui-Chen Lu**

Most neurons are born during embryogenesis and have to maintain proper function and integrity throughout an organism's life. Neurodegeneration can be triggered by a variety of genetic, epigenetic, or environmental factors and often leads to memory loss, cognitive deficits and substantial disability. Recent studies found that nicotinamide mononucleotide adenylyl transferases (NMNATs) play important roles in maintaining neuronal integrity in various species. Furthermore, NMNAT overexpression provides neuroprotection in a diverse array of neurotoxic models, including axonal injury, oxidative stress and neurodegenerative disease. At present, little is known how NMNATs maintain neuronal health and why exogenous NMNATs protect neurons from degeneration. Dr. Ming-Kuei Jang from MD Anderson at University of Texas will give an overview of NMNAT function in various species and briefly review the literature supporting neuroprotective roles of NMNATs. Dr. Rui Chen and his laboratory at Baylor College of Medicine have identified NMNAT1 mutations in human patients with Leber congenital amaurosis (LCA). Dr. Chen will describe their latest investigation in the molecular mechanisms of NMNAT1 in retina function using both model organism and cellular / biochemical approaches. Dr. R. Grace Zhai from University of Miami will discuss how NMNATs stabilize and maintain the integrity of the active zone structures in the presynaptic terminals in Drosophila. Dr. Hui-Chen Lu, Baylor College of Medicine, will present their latest finding on the cellular mechanisms of neuroprotection by NMNAT2 in mammalian brain. Dr. Lu's laboratory has found over-expressing NMNAT2 significantly reduced neurodegeneration in rTg4510 mice. These four talks will provide a thorough overview of our current understanding of the actions and the therapeutic potential of NMNATs.

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

18. Behavioral and neurobiological mechanisms of overeating: From cause to consequence

Chair: **Mary Olmstead**
Presenters: **Sarah Leibowitz, Alfonso Abizaid, Brian Baldo, Mary Olmstead**

Overeating may reflect an addiction-like cycle in which preexisting traits or conditions increase the propensity to consume sugar or fat. This excessive intake can, in turn, alter behaviors and neurobiological systems that promote

further intake, thereby perpetuating maladaptive eating and obesity. This panel will examine the trajectory of excessive food intake in animal models, outlining phenotypic and physiological traits that lead to overeating as well as behavioral and biological consequences of this overconsumption. Sarah Leibowitz (Rockefeller University NY) will present evidence that different subpopulations of rats are prone to consuming fat, and that these differences relate to behavioral and metabolic measures, and to early life experience. This vulnerability profile for overeating is manifested as neurochemical differences in peptide, dopamine (DA) and acetylcholine systems of the hypothalamus and mesocorticolimbic system. Alfonso Abizaid (Carleton University Ottawa CAN) will continue this theme, discussing the impact of chronic stress on both feeding and metabolism. He will present new data that these effects are mediated by grehlin, which acts at central sites to increase both eating and the accumulation of adipose tissue. Brian Baldo (University Wisconsin-Madison) will shift the discussion to the consequences overeating, focusing on the nucleus accumbens and prefrontal cortex. His work shows that sweetened-fat intake enacts opioid-mediated plasticity in GABA systems of the nucleus accumbens, a process that may help to explain maladaptive feeing. Mary Olmstead (Queen's University Kingston CAN) will then outline how excessive consumption of sucrose produces compulsive responding, and how this behavior is associated with a switch, from a reduction to enhancement, in DA modulation of GABA transmission in the bed nucleus of the stria terminalis. In sum, changes observed in animal models of overeating suggest that common mechanism may underlie excessive intake of food and drugs.

PANEL • MONDAY, 4:30–6:30 PM • PEAK 5

19. The yin and yang of dysphoria and euphoria

Chair: **Jacqueline McGinty**
Presenters: **Bryan Yamamoto, Marian Logrip, Paul Phillips, Samuel Golden**

The initial euphoria induced by addictive drugs can lead to dysphoria with repeated bouts of use and withdrawal. The dysphoria induced by chronic stress can lead to consumption of addictive substances in the search for euphoria. Both scenarios lead to complex changes in the brain. This panel will discuss interactions between chronic stress and drug taking/seeking along with concomitant changes in the brain that may be common to both conditions. Jakie McGinty will introduce the topic and speakers. Bryan Yamamoto (University of Toledo) will discuss results showing that chronic stress exacerbates the neurotoxic effects of methamphetamine on the dopamine and cerebral vascular systems. He will also present new findings that chronic stress alone can alter serotonerigic neurotransmission originating in a subregion

of the dorsal raphe that may have implications for the role of stress in mood disorders. Marian Logrip (Scripps Research Institute, La Jolla, CA) will report that a history of footshock stress, experienced prior to acquisition of alcohol self-administration, elevates relapse-like operant alcohol self administration. Further, stress history and alcohol self-administration correlates with regional changes in Pde10a mRNA expression, whereas PDE10A inhibition reduced alcohol self-administration even in high-relapsing rats. Paul Phillips (University of Washington) will discuss changes in the regulation of mesolimbic dopamine following swim stress and their implications for drug abuse. Sam Golden (Mount Sinai School of Medicine) will discuss the role of Rac1 in changes in spine morphology and neuroplasticity after chronic social defeat stress and psychostimulant administration. These presentations will undoubtedly foster robust discussion about the links between light and dark, stress and relief, euphoria and dysphoria.

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

20. New tricks for old dogs: Discovering novel roles for neuronal genes in development

Chair: **Thomas Hyde**
Presenters: **Joel Kleinman, Karen Greif, Thomas Hyde, Kristin Bigos, Tomasz Brudek**

The old view that a given gene product plays a singular role in nervous system development and/or function has been repeatedly challenged, with novel functions emerging even for "old dogs" in the nervous system. How are these novel functions discovered, and what can this tell us about approaches to study neural development? This panel will explore a few examples of recent discoveries of novel protein function that arose from anomalous expression patterns during development or linkage with other proteins. Discussion will focus on strategies to recognize potential multifunctional proteins.

Dr. Joel Kleinman (National Institute of Mental Health) will offer a brief overview of past and current strategies to discover multifunctional genes in the nervous system, and will moderate discussion. Dr. Karen Greif (Bryn Mawr College) will describe how synaptotagmin, the major Ca^{2+} sensor in regulated exocytosis at the synapse, also contributes to axonal morphology before synaptogenesis occurs. Dr. Thomas Hyde (Lieber Institute for Brain Development) will talk about alternate transcripts from GABA signaling pathway genes that are highly expressed in the fetal period and play a role in brain development and function. Dr. Kristin Bigos (Lieber Institute for Brain Development) will talk about cytochrome P450 genes, which are best known for metabolizing drugs, and their role in brain development and adult

brain function. Finally, Dr. Tomasz Brudek (Bispebjerg University Hospital) will discuss how alpha-synuclein, a presynaptic protein and one of the major components of intracellular fibrillary aggregates in the brains of a subset of Parkinsonian disorders, has an important role in the modulation of synapses in the developing brain.

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

21. Hit the black diamonds: Exercise counteracts stress, aging, and CNS trauma

Chair: **Kelli Sharp**
Presenters: **Monika Fleshner, Nicole Berchtold, Giselle Petzinger, Kelli Sharp**

Exercise is emerging as a powerful tool to improve CNS health and function in the face of a broad range of challenges including stress, normal aging, and neurodegenerative conditions. In this panel, we present new molecular, behavioral, and imaging data demonstrating the potential of exercise as a therapeutic intervention that has wide-reaching beneficial effects on the CNS. Monika Fleshner (University of Colorado) will discuss how exposure to acute traumatic stressors negatively impacts mental and physical health, and neurobiological mechanisms underlying exercise-dependent robustness to stress. Her recent work using Affymetrix microarrays identifies novel gene targets of exercise-induced stress resistance in the dorsal raphe nucleus, an important stress-responsive brain region. Nicole Berchtold (University of California, Irvine) will present Affymetrix microarray data from the human brain characterizing aging-related changes in gene expression profiles, and recent evidence that exercise counteracts many of these changes, notably the hippocampal declines in synaptic gene expression. Giselle Petzinger (University of Southern California) will discuss the role of exercise in enhancing neuroplasticity in Parkinson's disease. Finally, Kelli Sharp (University of California, Irvine) will present fMRI data on how physical activity and aging modify cortical activation patterns in individuals with incomplete spinal cord injury.

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

22. Physiology of identified inputs to dopaminergic neurons

Chair: **Carlos Paladini**
Presenters: **John Williams, Carl Lupica, Christopher Ford, Carlos Paladini**

To optimize future reward-related behavior, reward prediction error provides a teaching signal that is based on information extracted from complex

environmental stimuli. And, it is the firing pattern of dopaminergic neurons that encodes reward prediction error. However, dopaminergic neurons in the midbrain do not directly receive sensory inputs. In vivo, DA neurons fire in a continuum of patterns from single-spike to burst firing with pauses, whereas in vitro they fire only in the single-spike mode, indicating that afferents provide an important trigger for changes in firing pattern. Specific inputs to dopaminergic neurons may provide different components of the reward prediction error signal. However, until recently the contribution of identified afferents has remained elusive due to the inability to selectively activate inputs without affecting others, especially distinct afferents sharing the same neurotransmitter. First, John Williams (OHSU) will present recent data about the GABAergic inputs to dopaminergic neurons (interneurons, rostromedial tegmental nucleus (RMTg), nucleus accumbens, striatum), and the sensitivity of those inputs to opioids. Carl Lupica (NIDA) will present data on DA modulation of habenula inputs to RMTg and the ventral tegmental area (VTA), and discuss integration of DA signals for these pathways. Christopher Ford (Case Western) will talk about how local dopaminergic inputs within VTA activate D2-receptors to regulate the activity of dopaminergic neurons through feedback inhibition. Carlos Paladini (UTSA) will present data on how glutamatergic (subthalamic and pedunculopontine nuclei), and GABAergic (RMTg) inputs combine to affect the firing pattern of dopaminergic neurons.

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

23. The role of novel small regulatory RNAs on gene regulation in schizophrenia

Chair: **Steven Potkin**
Presenters: **Fabio Macciardi, Clark Jeffries, Steven Potkin, Diana Perkins**

Gene expression is controlled by a sophisticated combination of transcription factors (TFs), microRNAs (miRNAs), splicing factors, and other regulators. Discovery of small, noncoding, regulatory RNAs and transposable elements has ushered in a new era of genomics, with microRNAs (miRNAs) the first major class. MiRNAs have been identified for 20 years as one of the classes of small RNAs that post-transcriptionally regulate gene expression and are found exclusively in eukaryotic cells. In humans, approximately 940 miRNAs control the expression of about 60% of protein coding genes by inducing mRNA cleavage or translational inhibition in the miRNA target sites in their 3' untranslated (UTR) regions. A single miRNA can bind to and regulate many different mRNA targets and, conversely, several different miRNAs can bind to and cooperatively control a single mRNA target. miRNAs and their targets can form complex regulatory networks. miRNA silencing occurs at both protein and mRNA levels, especially when considering temporal regulation.

Fabio Macciardi will present data on the regulatory role that microRNAs play in gene regulation when functioning individually or more typically with one another, with data generated from RNAsequencing (transcriptome) of post-mortem DLPFC in schizophrenic and normal controls and from miRNA nanostring arrays from the same sample. Combining RNA-sequencing with miRNA expression levels allow building dynamic Gene Regulatory Networks that are involved in increasing the risk for schizophrenia. Clark Jeffries of UNC will present data on the evolving role of small noncoding RNAs and small nuclear RNAs on gene regulation. Steven Potkin will describe the identification of miR137 and miR137-controlled genes as susceptibility genes for schizophrenia using a brain imaging genetics approach. These findings were confirmed and expanded by the International Schizophrenia Consortium. The miR-137 rs1625579 risk allele (T) is associated with DLPFC hyperactivation which is shown to be a schizophrenia risk phenotype and considered a measure of brain inefficiency. Diana Perkins will present the results of small RNA sequencing with 10 schizophrenia and 10 unaffected subjects confirming the most interesting findings with TaqMan PCR in available RNA samples from 23 schizophrenia and 23 control subjects. Altered Differential expression of several miRNAs, as well as small regulatory RNAs derived from mitochondrial transfer RNAs, transfers RNAs, and small nucleolar RNAs show a pattern suggesting altered coordination of regulatory RNA expression in schizophrenia. In understanding neuropsychiatric illness, genetics and brain imaging are inextricably entwined as the genetic effects on neuropsychiatric illness can be revealed in brain imaging and because many aspects of brain imaging are genetically influenced. The strategies presented by the panel provide powerful ways to find and characterize genes associated with illnesses of the brain.

PANEL • MONDAY, 4:30–6:30 PM • PEAK 6/7/8

24. CSPGs in CNS injury and repair: A mammalian and nonmammalian perspective

Chair: **Jeffery Plunkett**
Presenters: **James Fawcett, Herbert Geller, Martin Oudega, Jeffery Plunkett**

After CNS injury, axonal regeneration is frustrated by scar tissue exerting inhibitory influences that limit the extension of damaged axons and thus limit functional recovery. The main cellular component of this scar is the reactive astrocyte which expresses chondroitin sulfate proteoglycans (CSPGs), a large family of growth-inhibitory molecules. This panel will discuss the involvement of CSPGs in axonal regeneration in the damaged mammalian and nonmammalian CNS and strategies to manipulate CSPGs presence after injury. First, Dr. James Fawcett (University of Cambridge, UK) will discuss proteoglycans and their role in the injured CNS. Then, Dr. Herbert Geller

(NHLBI, NIH, USA) will discuss molecular mechanisms of CSPG signaling and how they influence axonal regeneration. Next, Dr. Martin Oudega (University of Pittsburgh, USA) will discuss interventions to limit CSPG presence in the injured spinal cord and their effect on motor function recovery in mammals. Finally, Dr. Jeffery Plunkett (St. Thomas University, USA) will discuss CSPG expression in the injured CNS in zebrafish, where successful regeneration occurs. The presentations in this panel will provide an inclusive overview of the role of CSPGs in the failure or success of CNS repair, and in current and future therapies for CNS repair.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 5

25. Novel insights into monoamine networks

Chair: **Kathryn Commons**
Presenters: **Patricia Jensen, Mitsuko Uchida, Marisela Morales, Kathryn Commons**

Despite many years of study, novel features of the organization of monoamine networks are emerging, particularly as they are interrogated with new genetic and imaging techniques. Using dual recombinase-based genetic fate-mapping strategies to label subsets of noradrenergic progenitor cells, Patricia Jensen's studies demonstrate how position-dependent gene expression in the developing hindbrain contributes to the organization of the mature noradrenergic system. These studies modify our understanding of forebrain NE by identifying non-locus coeruleus sources of innervation to the prefrontal insular cortex. A popular theory of dopamine postulates that dopamine neurons signal reward or saliency prediction errors to motivate and guide learning, but the mechanisms underlying these computations remain unknown. Nao Uchida's lab employs a combination of novel viral tracing and electrophysiology in behaving mice to explore this question. Mitsuko Uchida (Uchida Lab) will discuss how modified rabies virus has revealed cell-type specific connectivity, and can be used to elucidate detailed neural circuits mechanisms underlying error calculations. The sources of afferent innevation of dopamine neurons include the serotonergic dorsal raphe nucleus. Marisela Morales will present studies that show optogenetic activation of this pathway promotes dopamine release in the nucleus accumbens and promotes place preference. Several lines of evidence now suggest that glutamate is a key neurotransmitter in this pathway by virtue of the presence of the vesicular glutamate transporter VGLUT3. Kathryn Commons' lab is using a high-resolution light microscopy technique, array tomography, to visualize up to seven antigens in the same tissue sections. She will discuss how this approach has given new insight into the organization of afferent innervation of the dorsal raphe nucleus, and specifically has implicated GABA as a master regulator.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 17

26. Activity-dependent regulation of NMDAR phenotype and transport at developing synapses

Chair: **Suzanne Zukin**
Presenters: **Hey-Kyoung Lee, Suzanne Zukin, Robert Malenka**

Dynamic regulation of synaptic efficacy is thought to play a critical role in synaptogenesis, experience-dependent synaptic remodeling and long-lasting changes in synaptic efficacy such as NMDA receptor (NMDAR)-dependent LTP and LTD. The molecular and cellular mechanisms by which synapses are formed and undergo experience-dependent structural remodeling are the focus of intense interest. This session will present recent findings that NMDARs undergo dynamically regulated transport to nascent synapses and that the switch in NMDAR subunit composition and function at immature synapses are regulated by REST-dependent epigenetic remodeling. The session will also highlight the impact of adverse experience in the form of maternal deprivation on the developmental switch. Suzanne Zukin (Albert Einstein College of Medicine) will present introductory comments. Hey-Kyoung Lee (Johns Hopkins University) will speak on a novel role for NMDARs in homeostatic synaptic plasticity in the visual cortex. Suzanne Zukin will speak on the role of REST-dependent epigenetic remodeling in the developmental switch in synaptic NMDARs during postnatal development. She will also discuss how maternal deprivation blocks the rise in REST and switch in synaptic NMDARs. Rob Malenka (Stanford University) will speak on recent findings that dopamine neurons in the ventral tegmental area (VTA) have important roles in adaptive and pathological brain functions related to reward and motivation and will review recent evidence that distinct VTA circuits generate reward and aversion, thereby providing a new framework for understanding the circuit basis of adaptive and pathological motivated behaviors. These findings are of clinical relevance in that NR2B-containing NMDARs are implicated in cocaine abuse and the neuronal death associated with stroke, Parkinson's disease and Huntington's disease.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 11/12

27. Glutamate receptors and pain

Chair: **Juan Carlos Marvizon**
Presenters: **Juan Carlos Marvizon, Linda Sorkin, Susan M. Carlton**

Treating chronic pain, a major challenge in health care, can be achieved by targeting molecular mechanisms in pain pathways. We will present exciting new data showing how three major classes of glutamate receptors—NMDA (NMDAR), AMPA (AMPAR), and metabotropic glutamate receptors

(mGluRs)—are involved in pain modulation in sensory afferents and spinal cord.

Dr. Juan Carlos Marvizon (UCLA) will chair the panel and talk about presynaptic NMDARs on afferent nociceptor terminals in the spinal cord. He will show that these receptors are normally in a nonfunctional state due to lack of an essential Tyr-phosphorylation by Src family kinases. During the induction of neuropathic pain, they become Tyr-phosphorylated through a signaling pathway involving BDNF release from microglia. Intriguingly, activation of opioid receptors brings these NMDARs back to their nonfunctional state.

Dr. Linda Sorkin (UCSD) will present work on spinal cord AMPAR trafficking. Inflammation increased the number of AMPAR, in particular Ca^{2+}-permeable AMPARs in dorsal horn neurons. This is dependent on tumor necrosis factor release and activation of PI3-kinase-β and PKA, and is roughly analogous to processes seen in hippocampal LTP. The same processes occur in motor neurons with variations in receptor subtypes and kinase isoforms. This points to the universality of the mechanism while raising more questions regarding relevance of the differences.

Dr. Susan M. Carlton (UTMB) will present work demonstrating that group II and III mGluRs are expressed by primary sensory neurons and modulate nociceptor hyperexcitability. In particular, they alter transmission of heat and cold sensations to the CNS by preventing overactivation of TRPV1 and TRPA1, respectively. If mGluRs are blocked by antagonists or knocked-out, there is an enhanced response to TRP activation at the cellular and behavioral level. These findings will be discussed in relation to the processing of acute and chronic pain.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 14

28. Regulation of size and strength of postsynaptic sites

Chair: **Johannes Hell**
Presenters: **Scott Soderling, Yasunori Hayashi, Eunjoon Kim, Jose Esteban**

Synaptic strength is remarkably stable under physiological conditions. A change in it is thought to mediate information storage. At the same token, dysregulation of synapse transmission underlies many mental and neurological disorders. Spine and PSD size is strongly correlated with postsynaptic AMPAR abundance. This panel will explore mechanisms that regulate spine size and with it AMPAR content at the PSD. After a brief introduction by the chair (Johannes Hell, UC Davis), Scott Soderling (Duke University) will talk about the role the Arp2/3 complex plays in remodeling synaptic F-actin. He will discuss how dysfunctional signaling by Arp2/3 might lead to multiple forms of neuropsychiatric disorders. Yasunori Hayashi (Brain Science Institute, RIKEN)

will provide evidence that CaMKII serves as an activity-dependent neuronal scaffold in the dendritic spine that controls the stability of F-actin. Ca^{2+}/calmodulin displaces CaMKII from F-actin to allow unbundling of F-actin, which opens a time window during which F-actin can be remodeled by proteins such as cofilin, Arp2/3, and gelsolin to enable structural plasticity of spine. Eunjoon Kim (KAIST, South Korea) will focus on the association between postsynaptic signaling scaffolds that determine spine structure and size, including Shank2 and autism spectrum disorders (ASD). Based on synaptic defects underlying ASD-like phenotypes in transgenic mice, he will illuminate the importance of normal levels of NMDAR function in preventing autism. Jose Esteban (CSIC, Spain) will wrap up the panel by discussing intracellular signaling and membrane trafficking mechanisms that control the transport of AMPA receptors to synapses during synaptic plasticity.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 15/16

29. Mitochondria, synapses, and neurodegeneration

Chair: **Zheng Li**
Presenters: **Elizabeth Jonas, Zheng Li, Jennifer Morgan**

The synapse is the functional unit of the brain, and hence molecules and signaling pathways regulating its structure and activity are crucial for brain performance. Abnormalities of synapses contribute to brain dysfunctions in neurodegeneration. The need for ATP and Ca^{2+} handling are especially great at synapses, therefore it is perhaps not wholly surprising that mitochondria have been found recently to play an important role in the development and experience-dependent modification of synapses. Intriguingly, not only metabolic, but also nonmetabolic functions of mitochondria, such as the regulation of apoptosis, have been implicated in synaptic plasticity. Mitochondrial dysfunction often manifests as neurological disease. For example, PINK 1, a gene linked to familial Parkinson's disease, when mutated alters the morphology and function of mitochondria; dysfunction of α-synuclein, the main component of the Lewy bodies, the pathological markers of Parkinson's disease, also impacts mitochondrial function. This panel will discuss the cellular processes regulated by mitochondria in synapses, and their relevance to neurodegeneration. There are three speakers in the panel. Elizabeth A. Jonas (Yale University) will present findings that Bcl-xL and a familial Parkinson's disease-related gene DJ-1 are involved in regulation of mitochondrial metabolic efficiency within synapses. Zheng Li (National

Institute of Health) will discuss the modulation of mitochondrial localization by synaptic activities and the regulation of synaptic properties by mitochondria. Jennifer R. Morgan (Marine Biological Lab) will show evidence that excess α-synuclein severely disrupts synaptic vesicle trafficking, and discuss the cellular and molecular mechanisms by which this occurs.

PANEL • MONDAY, 8:30–10:00 PM • PEAK 6/7/8

30. Chronic stress and plasticity in CNS pathways: Contrasting mechanisms underlying adaptive and maladaptive changes and implications for thinking about stress-related CNS disorders

Chair: **Victor Viau**
Presenters: **Serge Campeau, Jason Radley, Victor Viau, David Morilak**

Stress responses entail neuroendocrine, autonomic, and behavioral changes to promote effective coping with real or perceived threats to one's safety. While these responses are critical for the survival of the individual, adverse effects of repeated exposure to stress are widely known to have deleterious effects on health, not through the failure of the capacity to mount these responses, but through over-activity of these vital systems. Thus, a considerable effort in the search for treatments to stress-related CNS disorders necessitates unraveling the brain mechanisms responsible for neuroendocrine, autonomic, and behavioral adaptation under acute conditions and their perturbations under chronic stress. This panel will be geared toward providing insight on whether vulnerability to stress-related disorders reflects a failure of these stress-adaptive circuits, or activation of distinct neural pathways. First, Serge Campeau will present evidence for a novel brain pathway involving the posterior hypothalamus that may be critical for habituation of stress responses in the face of repeated exposure to stress. Jason Radley will discuss whether over-activity of the HPA axis following chronic stress results from an attrition of restraining influences imparted from a limbic cortical network. Victor Viau will focus on the extent to which stress related pathways register changes in sex steroid hormone levels, and will provide novel insights into why male and females show different vulnerabilities to stress-related disorders. Finally, David Morilak will discuss the role of noradrenergic modulation of the prefrontal cortex in facilitating cognitive flexibility, and how sustained activity in this system during chronic stress may lead to impaired prefrontal function and cognitive impairment.

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

31. How nonmammalian model organisms shed new light on mechanisms of human neurologic diseases

Chair: **Michael Shifman**
Presenters: **George R. Jackson, Christopher Gabel, Michael Shifman, Ellen Chernoff**

The study of simple creatures like nematode *(Caenorhabditis elegans),* fly *(Drosophila melanogaster),* and lamprey *(Petromyzon marinus)* has provided a basic understanding of the role that developmental pathways play throughout evolution. Despite their simplicity—or perhaps because of it—these organisms can also yield profound insight into processes perturbed in human disease. As such, modeling disease in simple organisms can peel away the complexity of human disease to help reveal the core defective processes. These nonmammalian models will reveal the cellular and molecular profiles that need to be achieved in mammals in order to promote restoring function to damaged or diseased nervous tissues in mammals and could accelerate search for pharmacological treatments of traumatic and neurodegeneration diseases in humans. This panel will discuss how nonmammalian experimental models provide powerful tools to study the cellular and molecular foundations of neurologic diseases. First, George R. Jackson (The University of Texas) will discuss how using genetics of the simple model organism Drosophila in order to provide new understanding of human neurodegenerative diseases. Then Christopher Gabel (Boston University School of Medicine) will discuss the use of advance biophotonic techniques, including high resolution in vivo laser surgery, time-lapse microscopy and optical neurophysiology in combination with genetic analysis to study nerve damage and regeneration in the nematode worm *Caenorhabditis elegans.* The third speaker is Michael Shifman (Temple University School of Medicine) will present data on the role of axonal guidance molecules, such as netrins and semaphorins in the spinal cord regeneration in the lamprey CNS. Finally, Ellen Chernoff (Indiana University-Purdue University) will discuss amphibian spinal cord and limb regeneration and involvement of the stem cell and dorsoventral patterning genes in this process.

32. Targeting the NMDA receptor hypofunction hypothesis of schizophrenia: Emerging clues from genetic models and drug discovery efforts

Chair: **Shashank Dravid**
Presenters: **Bita Moghaddam, Kazutoshi Nakazawa, Kevin Ogden, Shashank Dravid**

The NMDA receptor (NMDAR) hypofunction hypothesis of schizophrenia, first proposed in the 1980s, is rooted in observations that NMDAR channel blockers like phencyclidine produce schizophrenic-like symptoms in healthy individuals. Effective therapeutic interventions based on this hypothesis now seem to be on the horizon. Bita Moghaddam (University of Pittsburgh) will review recent work which supports a reevaluation of current theories related to NMDAR hypofunction hypothesis. Kazutoshi Nakazawa (NIMH) will review his work with cell type-specific GluN1 knockout mice; highlighting the differential contributions that NMDAR hypofunction at cortical excitatory neurons and at GABAergic neurons play in the emergence of schizophrenia-like phenotypes. He will also stress the importance of NMDARs at fast-spiking interneurons in maintaining the high-fidelity spike transmission at GABAergic presynaptic terminals—the basis of cortical synchronization. Kevin Ogden (Emory University) will present the results from drug discovery efforts that led to the identification of selective potentiators for the GluN2C/GluN2D subtypes of NMDARs. He will also present data on how these potentiators modulate the inhibitory tone in the hippocampus, where reduced NMDAR function could lead to excessive drive of dopaminergic neurons. Shashank Dravid (Creighton University) will provide a review of the unique biophysical properties and expression pattern of GluN2C receptors that position these subtypes for modulating the cortico-limbic-thalamic circuitry implicated in schizophrenia. He will present novel findings from GluN2C genetic model and novel potentiator of GluN2C/GluN2D subtypes that support GluN2C receptors as a potential therapeutic target to reverse schizophrenia-like phenotype. Thus the panel will provide compelling evidence that cell type-specific or NMDAR subunit-specific targeting may provide novel means to overcome NMDAR hypofunction to improve treatment in schizophrenia.

33. Different sex-difference patterns in rats vs. humans: Addiction-vulnerability mechanisms

Chair: **Thomas Crowley**
Presenters: **Wilson Compton, Marilyn Carroll, Thomas Crowley, Wendy Lynch**

More human males than females develop substance use disorders. However, female rats self-administer drugs more avidly than males. Female rats and humans both progress faster than males to high-dose self-administration and respond better to treatment. Biological or environmental mechanisms behind these Species X Gender interactions might include differences in brain function, age, hormones, or cultural conditions. Understanding such mechanisms could lead to more effective detection, prevention, and treatment of human addictions. Dr. Compton (NIDA Epidemiology Division) will review human epidemiologic studies showing that males are more likely than females to progress from nonuse to problematic drug use, and less likely to become abstinent, even after considering psychiatric comorbidity, family history, marital status, age, and race/ethnicity, but he cautions that males may have greater opportunities to use. Dr. Carroll (University of Minnesota) will address rat studies showing that gender (female > male) is additive with impulsivity, novelty reactivity, adolescence, and sweet preference in predicting initiation of drug self-administration, bingeing, withdrawal severity, relapse, and treatment response. Dr. Crowley (University of Colorado Denver) will show that during risky vs. cautious decision making, despite much greater decision-related fMRI activity, normal adolescent boys persist (more than girls) in risky behaviors with low reward probability; moreover, brain-activity patterns of youths with substance and conduct disorders differ from normals, and differ by gender. Dr. Lynch (University of Virginia) will speak on DA versus glutamate signaling in motivation for cocaine in male rats, and also in intact and OVX females with and without estradiol replacement at different stages of cocaine self-administration. She suggests that estradiol interacts with D1 dopamine signaling to influence sex differences in vulnerability to cocaine early, but not later, in addiction processes.

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

34. Posttranscriptional regulation of synaptic gene expression

Chair: **Murray Cairns**
Presenters: **Murray Cairns, Oswald Steward, Neil Smalheiser, Belinda Goldie**

Neural circuitry, which forms the basis of learning and cognition, is established and regulated through changes in protein concentration and structure in the postsynaptic membrane. As the activity-dependent response to each of the many thousands of presynaptic inputs in each neuron is relatively independent, the localized change in gene expression is largely posttranscriptionally regulated. This means that active synapses are specifically earmarked for translational modulation. It also means that trafficking and translation of mRNA encoding synaptic proteins produced in the nucleus must be silenced and transported to dendritic spines in response to, or in anticipation of localized excitation from presynaptic termini. Some details of the complex life cycle and patterning of synaptic RNA are emerging and feature an array of ribonucleoproteins and small RNA specificity factors known as microRNA (miRNA). These molecules appear to work together in concert with discrete translational apparati to facilitate complex patterns of input-restricted, activity-dependent translation. This panel discussion will be opened by Murray Cairns (Schizophrenia Research Institute, Sydney) with an overview of this fascinating research topic and the potential for dysfunction in neuropsychiatric conditions. Oswald Steward (University of California, Irvine) will discuss his seminal work in this area and highlight more recent discovery of activity-dependent regulation of mRNA degradation at the synapse exemplified by activity-regulated cytoskeleton-associated protein (Arc). Neil Smalheiser (University of Illinois, Chicago) will discuss his work on calcium/activity-dependent miRNA biogenesis in the postsynaptic density. Belinda Goldie (University of Newcastle, Callaghan) will conclude the session with discussion of her work investigating the activity-associated changes in miRNA-mRNA interaction and distribution in the synaptodentritic fraction and the potential role of exosomal release.

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

35. Cognition: From SNPs to nuts

Chair: **Anil Malhotra**
Presenters: **Anil Malhotra, Joey Trampush, Katherine Burdick, John Kane**

The identification of genes that influence cognitive ability may have broad implications for the understanding of brain function, and provide insight into the neuropsychiatric disorders associated with cognitive impairment. Moreover, treatment strategies that target cognitive dysfunction may have widespread

impact on the outcome of patients with these disabling disorders. Presenter 1 will discuss candidate gene and genome-wide association studies (GWAS) leading to the identification of variants that influence cognitive ability in the general population, as well as empirical support for overlap between genes that influence cognition and those that increase schizophrenia risk. Presenter 2 will discuss findings from a study of Schizophrenia Genetics. Data will be presented in a hierarchical fashion starting from the use of genome-wide SNP information to determine the heritability of cognitive traits; at the gene level, pathway analysis of the link between genes involved in synaptic function and cognition; and finally, individual SNP associations with cognition from a schizophrenia GWAS. Presenter 3 will present on a study of siblings discordant for bipolar disorder. Results suggest that specific deficits in verbal memory and affective processing are directly related to genetic risk for illness. Finally, Presenter 4 will report on pharmacologic and nonpharmacologic approaches to treatment of cognitive dysfunction and related aspects of these illnesses. He will discuss new technologies to enhance outcome, as well as clinical trial design strategies to enhance the power of these approaches. Taken together, this panel aims to provide a comprehensive synthesis of recent data on the genetic underpinnings of cognitive impairment, as well as provide the bases for new treatment strategies for this critical manifestation of illness.

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

36. Treating the pains of aging: Can we do better?

Chair: **James Zadina**
Presenters: **Megali Millecamps, Paula Bickford, Patrick Mantyh, James Zadina**

Older adults are among the most likely to suffer from pain, but are often the least likely to receive adequate treatment. Co-morbidities complicate treatments, and augmented inflammatory processes are a common thread in pathologies faced by older adults. This panel will characterize behavioral changes with age, mechanisms of pain and neurodegenerative diseases in older age, and potential new therapeutic approaches to these problems. Magali Millecamps (McGill University) will describe sensory, motor, cognitive and affective differences in young vs. old mice. Paula Bickford (VA/University of South Florida) will discuss the effects of inflammatory and oxidative processes in the mechanisms of altered neurogenesis and neurodegenerative diseases as well as novel, synergistic natural therapies for these pathologies. Patrick Mantyh (University of Arizona) will discuss recent advances in our understanding of, and novel therapies for skeletal pain which is extremely common in older adults. James Zadina (VA/Tulane University) will discuss novel opioids that have a favorable profile for side effects of particular importance in aging, including reduced respiratory depression, motor and cognitive impairment, tolerance and inflammation.

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

37. Neuroadaptation along the path to addiction

Chair: **Paul Phillips**
Presenters: **George Koob, Paul Phillips, Jacqueline McGinty, Yann Pelloux**

Abused substances have many acute effects on neural systems, some of which can have persistent consequences through initiating transcriptional effects and synaptic modifications. However, it is the additional neuroadaptations that come about only after chronic drug use that ultimately underlie escalated drug use and compulsive drug seeking characteristic of addiction. This panel focuses in neurobiological changes that take place with extended drug use and their regulation of drug-related behavior that confers the progression through stages of the addictive process. First, George Koob (Scripps Research Institute) will discuss brain arousal/stress neurocircuits that alter the emotional landscape during chronic drug use and transform the motivational qualities of abused substances. Next, Paul Phillips (University of Washington) will describe changes in dopamine transmission that take place with extended drug access and show how they promote escalation of drug consumption. Jacqueline McGinty (Medical University of South Carolina) will discuss changes in phosphoproteins in the prefrontal cortex that take place during drug withdrawal and regulate drug seeking. Finally, Yann Pelloux (Aix-Marseille University) will describe changes in serotonergic function that produce compulsive drug seeking.

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

38. Perishable potentials: Neural substrates of sex-specific risk for mental illnesses during adolescence

Chair: **Bradley Cooke**
Presenters: **Kyle Frantz, Jill Becker, Bradley Cooke, Gretchen Neigh**

Adolescence is when youth transform into adults. Marked by rapid changes in emotion, motivation, and cognition, as well as reoriented social priorities, adolescence is also a period of vulnerability for several complex psychiatric conditions, including anxiety, depression, addiction, and schizophrenia. The risk and the severity of these disorders is exacerbated by stress and influenced by gender. Puberty normally occurs during early adolescence, and the rising levels of sex steroid hormones of puberty may play a major role in the sex-specific patterns of psychopathology that emerge at this age. This symposium will endeavor to provide an engaging, multifaceted perspective on the unique vulnerabilities of male and female adolescents to maladaptive behavior and mental illness. Dr. Frantz will review research on reward and reinforcement

in adolescence, with highlights on age differences in drug-related behavior and the medial prefrontal cortex as a key locus for age-dependent effects. Dr. Becker will focus on sex steroid hormone effects on ascending monoamine systems and the contribution of those changes to male- and female-typical patterns of drug self-administration. Dr. Cooke will describe an animal model of child abuse and its sex-specific effects on behavior, as well as sex differences in the circuits that process juvenile abuse. Finally, Dr. Neigh will describe an adolescent social stress model that precipitates sex-specific changes in behavior, metabolism, and immune function. She will contend that the sex-specific effects of adolescent stress are mediated by glucocorticoid receptor co-regulators, which are modulated by stress and sex steroids. Together, these presentations will bring together four researchers that share a common interest in mental illness, adolescence, and sex differences. We expect their presentations will spark a lively discussion about future directions and opportunities to translate these findings into sex- and age-specific interventions.

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

39. The path to oblivion: Do gamma rhythms lead the way?

Chair: **Misha Perouansky**
Presenters: **Misha Perouansky, Bruce MacIver, Anthony Hudetz, Robert Pearce**

Out of the three essential desirable general anesthetic endpoints (that also include amnesia and immobility), loss of consciousness has attracted most public interest. Despite that, the question of what neurobiological alteration underlies the loss of this essential quality of the central nervous system is indeed of scientific interest. Interregional and cross-frequency synchronization of neuronal oscillations, especially in the gamma frequency band have been linked to the emergence of consciousness since the 1990s. Considering the essential role attributed to fast GABAA–ergic synaptic activity in supporting gamma-band rhythms and its sensitivity to modulation by numerous general anesthetics, it is not surprising that gamma-modulation has been a prime suspect for the hypnotic effects of anesthetics. This panel will discuss data supporting and contradicting this contention.

Misha Perouansky (University of Wisconsin, Madison) will provide a brief introduction to the world of gamma oscillations and then lead the discussion of the presentations. Bruce MacIver (Stanford University) will present data obtained with whole-cell and micro-EEG recordings from hippocampal slices demonstrating that despite marked slowing of IPSCs, kainate-induced gamma rhythms persist under supra-hypnotic concentrations of isoflurane. Tony

Hudetz (Medical College of Wisconsin, Milwaukee) will take the audience to in vivo recordings analyzing anesthetic effects on neuronal avalanches in the gamma frequency range recorded with chronically implanted multielectrode arrays from rat visual cortex. Finally, Bob Pearce (University of Wisconsin, Madison) will discuss the effects of anesthesia on gamma oscillations in human subjects, with a particular focus on stimulus-induced responses under wakefulness versus loss of consciousness.

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

40. Synaptic information processing and storage with CaMKII

Chair: **Karl Ulrich ("Ulli") Bayer**
Presenters: **Karl Ulrich ("Ulli") Bayer, Johannes Hell, Roger J. Colbran, Haruhiko Bito**

How does synaptic information processing occur during the decision whether or not the information should also be stored? The Ca^{2+}/Calmodulin(CaM)-dependent protein kinase II (CaMKII) has several regulatory features ideal for molecular information processing and storage. CaMKII is activated by Ca^{2+}/CaM, but becomes partially "autonomous" (Ca^{2+}-independent) upon autophosphorylation at T286. This hallmark feature of CaMKII regulation provides a form of molecular memory and is indeed important in long-term potentiation (LTP) of excitatory synapse strength and memory formation. However, emerging evidence supports a direct role in information processing, while storage of synaptic information may instead be mediated by regulated interaction of CaMKII with the NMDA-receptor (NMDAR) complex. Here, we will discuss these and other novel CaMKII regulation mechanisms in context of their impact on postsynaptic functions.

Ulli Bayer (University of Colorado Denver) will provide an updated background on CaMKII regulation and how "autonomy" relates to information procession versus storage. Johannes Hell (University of California Davis) will describe knock-in mice with CaMKII binding-incompetent GluNB and their phenotype regarding CaMKII targeting, LTP, and memory. Roger Colbran (Vanderbilt University) will discuss novel roles of CaMKII protein–protein interactions for synaptic functions in the striatum and motor function. Haruhiko Bito (University of Tokyo) will provide evidence for inverse synaptic tagging by CaMKII, a previously unrecognized form of synaptic information storage.

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

41. Neuronal dysfunction: The blame goes beyond the brain

Chair: **Nicole Northrop**
Presenters: **Aurelio Galli, Lawrence Reagan, Julio Ayala, Laura Halpin**

It is typically thought that neuronal dysfunction or diseases of the central nervous system are caused by an initial event that occurs within the brain. However, recent findings suggest the role of peripheral organs in neuronal dysfunction. This panel focuses on the ability of small molecules released from peripheral organs to modulate brain function. The data presented in this panel will provide evidence that molecules released from the pancreas, adipocytes, gut and liver during metabolic dysfunction play a role in neuronal dysfunction and damage. Nicole Northrop will provide introductory comments and lead discussions throughout the session. Aurelio Galli will discuss how insulin dysregulates Akt phosphorylation and how dysregulated Akt signaling disrupts cortical noradrenergic function, which may explain the high comorbidity of metabolic diseases and mood disorders such as depression. Larry Reagan will present evidence that the adipokine, leptin, impacts hippocampal structure and function leading to depression-like behaviors. Julio Ayala will present data illustrating the effects of the gut hormone, glucagon-like peptide-1 (GLP-1), on feeding behavior and obesity. He will discuss the effects of GLP-1 on homeostatic centers in the brain, particularly the hypothalamus, as well as the novel action of GLP-1 on reward centers and how this may be affected by bariatric surgery. Laura Halpin will discuss her findings that liver damage and increases in ammonia, a neurotoxic byproduct of protein metabolism, contribute to the neurotoxicity of methamphetamine. Her results suggest that METH causes liver damage and increased peripheral and brain ammonia, which contribute to the long-term monoaminergic depletions caused by the drug through elevations in extracellular glutamate and subsequent excitotoxic terminal damage. This panel will bring to light how the periphery can impact brain function and the necessity to look beyond the brain for mediators of neuronal dysfunction.

PANEL • TUESDAY, 4:30–6:30 PM • PEAK 6/7/8

42. $GABA_A$ receptors, seizures, and the problem of pharmacoresistance

Chair: **Claude Wasterlain**
Presenters: **Christopher Ransom, Ed Dudek, Claude Wasterlain, David Naylor**

Seizures induce major changes in synaptic and extrasynaptic physiology, which in turn modulate network excitability, seizure expression and therapeutic responses. One of the major problems in treating seizures is the rapid

development of seizure-induced pharmacoresistance in $GABA_A$ networks, with synaptic and extrasynaptic responses sometimes going in opposite directions. This can rapidly lead to reduced efficacy of GABAergic agonists such as benzodiazepines. Recent efforts to understand GABAergic signaling in hippocampal networks are shedding new light on pharmacoresistance and seizure pathophysiology. This session's speakers will try to translate their observations of synaptic physiology into new approaches for the treatment of pharmacoresistant epileptic seizures. Chris Ransom will discuss regulation of tonic $GABA_A$ currents and how this may affect network excitability and seizures. Ed Dudek will describe the remarkable success of a valproic acid derivative in overcoming benzodiazepine pharmacoresistance, and will speculate on the mechanisms involved. Claude Wasterlain will use the receptor trafficking hypothesis of benzodiazepine pharmacoresistance to identify synergistic drug combinations which can mitigate the problem, or block seizures with hypothermia. David Naylor will show dramatic temperature-dependent changes in frequency, amplitude and kinetics of $GABA_A$ IPSCs on hippocampal granule cells somas, suggesting that hypothermia has potent pre- and post-synaptic effects which enhance $GABA_A$ synaptic function. It is hoped that the discussion of those results will highlight aspects of GABAergic signaling and function that hold promise for treatment of medically-refractory epilepsy and refractory status epilepticus. The audience is encouraged to bring its own set of comments and ideas to the general discussion which will conclude the session.

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

43. The functional relevance of specific inputs to the prefrontal cortex in health and disease

Chair: **Joshua Gordon**
Presenters: **Michael Higley, Andrew Rosen, Neil Woodward, Christoph Kellendonk**

The prefrontal cortex (PFC) plays a crucial role in working memory, a cognitive deficit central to schizophrenia. In rodents as in humans, the PFC receives major inputs from the mediodorsal thalamus and the hippocampus. Communication between these three brain regions has been proposed to be crucial for working memory, and dysfunction within each region has been implicated in schizophrenia. Here we will present data from a variety of approaches aimed at clarifying the mechanisms by which thalamic and hippocampal afferents influence PFC activity, and how disruptions in these inputs may relate to cognitive dysfunction and schizophrenia.

After a brief introduction to the topic by Joshua Gordon, Michael Higley will describe his efforts to understand the organization and convergence of distinct

afferents into the PFC. He will present data combining viral fluorescent tracers and optogenetic tools to elaborate the laminar and subcellular distribution of excitatory inputs to neurons in the mouse PFC. Next, Andrew Rosen will show data from multisite neural recordings in a genetic mouse model of schizophrenia. These data implicate the ventral hippocampal-PFC pathway in working memory deficits, as observed in the disorder. Neil Woodward will then present resting state fMRI data documenting a thalamocortical network dysfunction in schizophrenia characterized by decreased prefrontal-thalamic connectivity. Finally, Christoph Kellendonk will explore the causal relationship between thalamic dysfunction and the cognitive dysfunction typical of patients with schizophrenia. Using pharmacogenetic tools in combination with in vivo recordings from awake behaving mice, he will demonstrate how even a subtle decrease in medidorsal thalamus activity can lead to altered thalamocortical functional connectivity and deficits in working memory. The session will conclude with a discussion of the implications of these findings involving all the panelists.

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

44. BrainCloud: Global transcriptome and DNA methylome at your fingertips

Chair: **Barbara Lipska**
Presenters: **Joel Kleinman, Ryan Smith, Barbara Lipska, Thomas Hyde**

This panel will introduce BrainCloud, a publicly available application created by NIMH and Lieber Institute for Brain Development. We will explain its multiple uses enabling transcription and DNA methylation data mining. Genome-wide data have been obtained from a large number postmortem human brain samples, across the entire lifespan, including the fetal period. We will show how to easily access and use BrainCloud, a web-based tool, and how the neuroscientists can use this resource to investigate molecular features of human brain development, expression of alternative transcripts in human brain, and associations with genetic variance. We will also show how these data pertain to psychiatric disorders, such as autism, Williams Syndrome, and schizophrenia. Joel Kleinman will introduce BrainCloud projects, discuss the methods of collecting postmortem brains, highlight the importance of toxicological analyses, and the significance of using fetal brain samples for elucidating splicing, genetic associations, and mechanisms underlying neurodevelopmental brain disorders. Ryan Smith will discuss computational methods used to generate and analyze genome-wide data, including the surrogate variable analysis, and associations of genotypes with molecular phenotypes. He will also present the strategies used to examine nonlinear

age-related patterns of gene expression. Barbara Lipska will focus on DNA methylation data, show dramatic epigenetic changes during development of the human brain, and discuss the mechanisms by which genetic variance regulates DNA methylation. Thomas Hyde will present examples of utilizing BrainCloud transcriptome and methylome data for elucidating pathophysiological mechanisms of brain disorders, such as schizophrenia and Williams Syndrome. This panel will present a unique set of publicly available genome wide data that enable understanding molecular mechanisms that fine-tune and regulate developmental changes in gene expression and neuronal function.

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

45. Animal models of compulsive cocaine intake

Chair: **Tod Kippin**
Presenters: **Adam Perry, Tod Kippin, Sietse Jonkman, Friedbert Weiss**

Compulsive drug seeking and taking are cardinal characteristics of addiction. Such behavior is exhibited in addiction by either foregoing of normally pleasurable or rewarding activities, as well as, the inability to abstain from drug seeking despite suffering associated negative consequences. Recent studies have developed animal models of both of these aspects of addiction. Studies examining the propensity to forego normally rewarding activities have employed a competing or alternative reinforcer approach to drug reinforcement and can be referred to as models of appetitive compulsive intake. Conversely, studies examining continued drug seeking in the presence of negative consequences have employed punishment of cocaine taking or seeking behaviors and can be referred to as models of aversive compulsive intake. The goal of this panel is to present recent developments in animal models of appetitive and aversive compulsive drug taking to allow comparison of the current models. Adam Perry will present findings that females are more vulnerable to developing appetitive compulsive cocaine intake reflecting changes in motivation and reinstatement behavior. Tod Kippin will describe the hormonal basis of sex differences in vulnerability to appetitive compulsive cocaine intake. Sietse Jonkman will describe findings that cocaine history strongly influences aversive compulsive cocaine intake in a punishment model under a seeking-taking reinforcement procedure, as well as the differential roles for subregions of the lateral striatum in mediating this behavior. Friedbert Weiss will present findings on the significance of stimuli conditioned to drug availability during withdrawal states for subsequent reinstatement of drug seeking and maintaining this behavior despite punishment. Overall, this panel will foster a comprehensive view of individual differences in and neurobiology of the compulsive aspects of addictive disorders.

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

46. New insights into the pharmacology and physiology of triheteromeric NMDA receptors

Chair: **Kasper B Hansen**

Presenters: **Kasper B Hansen, Terunaga Nakagawa, Alasdair Gibb, Rylan Larsen**

NMDA receptors (NMDARs) play essential roles in many normal processes in the CNS. They are also implicated in neuropathological conditions and have received considerable interest as therapeutic targets. NMDARs are tetrameric assemblies of GluN1 subunits, GluN2 subunits, of which four have been cloned (GluN2A-D), and GluN3 subunits (GluN3A-B). Studies on recombinant NMDARs almost exclusively describe diheteromeric NMDARs that are assembled from GluN1 and only one type of GluN2 (e.g., GluN1/GluN2A). However, at least two different GluN2 subunits have been identified in most, if not all, NMDAR-expressing cells, and a large proportion of native NMDARs may be triheteromeric in that they contain GluN1 and two different GluN2 subunits (i.e., GluN1/GluN2A/GluN2B). Little is known about triheteromeric NMDARs, and a dichotomy therefore exists in our understanding of recombinant diheteromeric and native triheteromeric NMDARs. The first presenter, Kasper B. Hansen (Emory), will compare properties of recombinant GluN1/GluN2A/GluN2B triheteromers with respective GluN1/GluN2 diheteromeric receptors. The unique modulation of these triheteromeric receptors by subunit-selective ligands such as ifenprodil, TCN-201, and Zn2+ will be discussed. Terunaga Nakagawa (Vanderbilt) will discuss the role of the NMDAR amino-terminal domain in assembly. Information about assembly could provide insights into the subunit combinations that can form triheteromeric NMDARs. Alasdair J. Gibb (University College London) will provide evidence for native GluN1/GluN2B/GluN2D receptors in substantia nigra dopaminergic neurons. Finally, Rylan Larsen (University of North Carolina) will demonstrate a role for native triheteromeric, GluN3A-containing NMDARs in regulation of neurotransmitter release and spike timing–dependent plasticity in the visual cortex. These presentations will provide a comprehensive discussion of triheteromeric NMDARs.

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

47. Off-piste trails that link Parkinson disease genes

Chair: **Anurag Tandon**

Presenters: **Anurag Tandon, David Park, Warren Hirst, Haung Yu**

Familial forms of Parkinson's disease (PD) are associated with mutations in a small number of genes that regulate very disparate cellular pathways including

synaptic vesicle trafficking and neuronal connectivity, autophagic and lysosomal protein degradation, and mitochondrial fission and fusion. Despite their diverse functions, the overlapping neuropathology and clinical phenotypes of genetic and sporadic PD suggest the presence of reciprocal molecular links that converge upon a common molecular pathway, which could serve as a potential source of biomarkers and for directly targeting with therapeutics. To identify potential commonalities, this panel will discuss recent findings that examine novel binding partners and regulators of PD genes. Anurag Tandon (University of Toronto) will discuss the control of alpha-synuclein vesicle binding by Rab3a recycling machinery, which includes chaperones GDI and Hsp90, and its role in exocytosis. David Park (University of Ottawa) will discuss roles of the PD linked genes in mitochondrial dynamics and degeneration. Warren Hirst (Pfizer) will discuss substrates and interaction partners of Leucine Rich Repeat Kinase 2 (LRRK2) which plays a major role in the etiology of PD. Haung Yu (Columbia University) will discuss the role of autophagic-lysosomal function and quality control of proteins, lipids and organelles, and how this relates to neurodegeneration in PD. The ensuing panel discussion will attempt to find converging links between these multiple paths.

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

48. What is the function of striatal cholinergic interneurons?

Chair: **Tibor Koos**
Presenters: **Jun Ding, Tibor Koos, Joseph Cheer, Ilana Witten**

Although acetylcholine has long been recognized to be important for the functioning of the basal ganglia based on its effects in idiopathic and experimental Parkinsonism, until recently almost nothing was known about the normal function of neostriatal cholinergic interneurons (CIN). In particular, while recordings in behaving primates provide compelling evidence that CINs control behavioral responses by signaling the reinforcement value of external stimuli neither the network mechanisms that transmit these signals nor their behavioral function has been identified. The panel will present results that recently revolutionized the understanding of this problem. Jun Ding (Stanford University) will discuss how phasic activation of cholinergic interneurons elicits biphasic and cell-type specific muscarinic modulation of cortical inputs to striatal projection neurons that may contribute to the reorientation of behavior in response to salient stimuli. Tibor Koos (Rutgers University) will describe the organization and function of a network of GABAergic interneurons that are activated by nicotinic synaptic inputs and may play a synergistic role in responding to unanticipated events. Perhaps the most interesting and unexpected recent finding about cholinergic signaling will be described by

Joseph Cheer (University of Maryland), showing that synchronous CIN activity elicits phasic dopamine release that is comparable in magnitude to dopaminergic transients generated by the synchronous firing of nigrostriatal dopaminergic neurons. Finally, Ilana Witten (Princeton University) will discuss optogenetic, in vivo electrophysiological and behavioral results that elucidated the main behavioral function of cholinergic interneurons in the nucleus accumbens and may provide an integrated interpretation of the cellular mechanisms of action of acetylcholine in this structure.

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

49. Heterogeneity of alcohol-use disorders: Possible underlying mechanisms

Chair: **Sarah Leibowitz**
Presenters: **John Crabbe, Charles O'Brien, Sarah Leibowitz, George Koob**

There is considerable heterogeneity among people with alcoholism, underscoring the need for personalized treatment methods. This panel will describe some different approaches being used to characterize the various aspects of alcoholism and identify the diverse genetic and neurochemical mechanisms that contribute to excessive alcohol use and related behaviors. John Crabbe will describe his recent studies of HDID mice (High Drinking in the Dark mice bred for attaining high blood ethanol levels) and present results showing that some ethanol responses, including sensitivity and tolerance, share common genetic control with this binge-like drinking. Chuck O'Brien will speak about the pharmacogenetics of alcoholism treatment and describe his new studies revealing a SNP in the gene for the μ opioid receptor, which in humans is associated with greater behavioral stimulation at given blood alcohol levels, dopamine release in response to alcohol, and treatment response to naltrexone in clinical trials, and which when "knocked in" in C57/Balb mice is associated with greater voluntary alcohol ingestion and dopamine release in ventral striatum. Sarah Leibowitz will describe her recent studies in outbred rats, which have linked particular neurochemicals to specific patterns of ethanol drinking and pre-binge anticipatory behavior and have revealed heterogeneity in the high-drinking population in terms of their specific neurochemical phenotype and responsiveness to pharmacological agents. George Koob will focus on dependence-induced excessive drinking, presenting his new findings related to the "dark side" of dependence, with a focus on the neurocircuitry of the extended amygdala. This panel underscores the need to understand the different forms of alcohol abuse and to characterize the variety of neurochemical and genetic substrates that mediate the positive or negative reinforcement from alcohol and the differential responsiveness of subpopulations to specific therapeutic agents.

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

50. Orchestrating the brain's immune response to disease

Chair: **Carol Colton**

Presenters: Lisa Ridnour, Steve Levison, Kathy Maguire-Zeiss, Carol Colton

Production of cytokines that target killing of pathogens is a well-described and central feature of inflammation in the brain. However, the brain's immune response can be viewed through a wider lens, with microglia seen as the maestro that orchestrates multiple events within the tissue. In this panel, some of these nontraditionally viewed functions of microglia will be discussed. Dr. Lisa Ridnour will show how NOS2 and NO help to set up and take down the stage (the extracellular matrix), through its action on matrix metalloprotease 9 (MMP9) and its inhibitor, TIMP1. She will discuss how pathological outcomes can arise when TIMP1 is kept high. Rebuilding also requires new players in the form of new neurons. Steve Levison and his colleagues will evaluate the hypothesis that microglia and the cytokines that they produce regulate expansion of neural precursors in the SVZ. He will talk about the types of cytokines that participate in CNS regeneration, the specific precursors that are affected, and how these cytokines exert their positive and negative actions on precursor expansion. Dr. Kathy Maguire-Zeiss will discuss how neurons talk back to the microglia and how a specific structure of a-synuclein induces microglia to express and release proinflammatory molecules while also producing a chorus of antioxidants. She will discuss how toll-like receptors and matrix metalloproteinases act in this neuroinflammatory response. Finally Dr. Carol Colton will show how once the food is gone the audience may leave, too. She will discuss how immune-mediated nutrient deprivation can arise during chronic neuroinflammation and which cells may participate in this nontraditional mechanism of initiating neuronal death.

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

51. The role of catecholamines in anxiety and stress

Chair: **Matthew Wanat**

Presenters: **Michael Bruchas, Dennis Sparta, Matthew Wanat, Joseph Cheer**

Activation of neural circuits within the limbic system play an integral role in the response to stressful stimuli and the expression of anxiety-related behaviors. Furthermore, both the noradrenergic and dopaminergic systems are engaged by exposure to aversive events, which in turn can influence an organism's behavioral response. This panel will present recent findings examining how modulating catecholamine function within specific neural circuits of the limbic system influences stress- and anxiety-related behaviors. Michael Bruchas (Washington University) will discuss how selective activation of

noradrenergic locus coeruleus neurons promote anxiety-like behavior and how presynaptic and postsynaptic noradrenergic mechanisms in the basolateral amygdala modify this anxiogenic response. Dennis Sparta (University of North Carolina) will discuss the opposing behavioral phenotypes elicited by selective activation of glutamatergic or GABAergic neurons of the bed nucleus of the stria terminals that project to the ventral tegmental area (VTA). Matt Wanat (University of Washington) will present data on how stress reduces motivation through the actions of corticotropin-releasing factor (CRF) in the VTA and how CRF modulates phasic dopamine release. Finally, Joe Cheer (University of Maryland) will discuss endocannabinoid control of dopaminergic signaling in conditioned punishment and its successful avoidance. Collectively, these studies highlight specific pathways and neuromodulators that can be targeted for therapeutic interventions to reduce the maladaptive responses inherent to stress- and anxiety-related disorders.

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

52. Neurons as metabolic sensors and regulators of energy homeostasis

Chair: **Celia Sladek**
Presenters: **Barry Levin, Celia Sladek, Clemence Blouet, Bret Smith**

Obesity continues to be a growing health concern worldwide. Currently over two-thirds of the adult population of the US is obese or overweight. The brain utilizes distributed systems of specialized "metabolic sensing" neurons localized in brain areas such as the hypothalamus and brainstem to monitor and regulate energy homeostasis. As opposed to other neurons, metabolic sensing neurons utilize ambient levels of metabolic substrates such as glucose, amino and fatty acids and hormones such as insulin and leptin to directly regulate their activity. This panel will explore the mechanisms by which these specialized neurons utilize various metabolic and hormonal signals to alter their activity and regulate food intake and body weight. Levin will discuss the mechanisms whereby such neurons and their partnering astrocytes act together to "sense" ambient glucose and fatty acid levels and their role in the regulation of energy and glucose homeostasis in the body. Sladek will present evidence for glucose and insulin responsiveness of the magnocellular oxytocin and vasopressin neurons. This relatively overlooked system has important anorexic potential. Blouet will discuss nutrient sensors in the nucleus of the solitary tract (NTS) in the caudomedial brainstem, and the consequences of direct NTS nutrient detection on energy balance. She will focus on L-leucine detection and the intracellular signaling and neurochemical pathways it engages. Smith will discuss the roles of insulin and glucose in modulating gastric-related neural circuitry in the dorsal vagal complex, and the participation of these metabolic

substrates in mediating neuroplasticity of vagal circuits associated with changes in metabolic status. These data demonstrate the distributed nature of central nutrient detection. Presenters will discuss the potential of a distributed system to enhance body weight homeostasis and to undermine targeted weight loss therapies.

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

53. New insights on mechanisms of sensory plasticity

Chair: **Alfredo Kirkwood**
Presenters: **Marcos Frank, Alfredo Kirkwood, Asaf Keller, Patrick Kanold**

Proper sensory experience is essential for establishing the proper wiring of neural circuits during development, and for maintaining them in the mature brain. Indeed, altering sensory experience can have deleterious consequences for neural function. For example, sensory deprivation during a brief postnatal critical period can permanently impair perception, while sensory deafferentation in adults can result in debilitating conditions like central and phantom limb pain. According to the current consensus, most of the experience-dependent remodeling occurs in the cortex before adulthood and is driven by changes in the patterns of local neural activity (through the action of mechanisms like LTP and LTD, for example). The four presentations in this panel will review interesting and insightful departures from this view. Marcos Frank (University of Pennsylvania) will discuss the finding that visual cortical changes in ocular dominance induced by the closure of one eye are consolidated and enhanced during the various sleep stages. Alfredo Kirkwood (Johns Hopkins) will discuss how in visual cortex the rules for synaptic strengthening and weakening are controlled by neuromodulatory inputs, and how this mechanism can be exploited to induce ocular dominance plasticity in adults. Asaf Keller (University of Maryland) will discuss the hypothesis that chronic pain can have a subcortical substrate and results from maladaptive plasticity in inhibitory inputs to thalamic nuclei. Patrick Kanold (University of Maryland) will discuss the idea that building up of circuitry in sensory cortices depends on the activity of subplate neurons; in adults, this organizational "seed" would be subserved by direct top-down inputs from prefrontal cortex.

PANEL • WEDNESDAY, 4:30–6:30 PM • PEAK 6/7/8

54. Cell biology of the injured spinal cord

Chair: **Joel Levine**
Presenters: **Joel Levine, Yimin Zou, Jeffrey Twiss, James Fawcett**

Injury to the brain or spinal cord results in the loss of function of the damaged neurons with catastrophic consequences for the affected individuals. Injury

causes rapid changes in the environment of the spinal cord and alters the physiology and behavior of the damaged neurons and glial cells. These changes include rapid increases in the expression of multiple growth and trophic factors, deposition of altered extracellular matrix molecules, loss of myelin, and disruption of normal homeostatic mechanisms. This panel presents recent cell biological studies of how the behavior of neurons and glia is altered after injury with an emphasis on the intracellular mechanisms responsible for these changes. Injury leads to increases in the expression of multiple members of the Wnt family of morphogens. Joel Levine will discuss how canonical Wnt signaling is necessary and sufficient to initiate reactive changes among different classes of glia and how reducing this signaling promotes axon regeneration. One well-known experimental paradigm for stimulating axon regeneration is a prior conditioning lesion of peripheral nerve. Yimin Zou will discuss studies showing that conditioning lesions induce noncanonical Wnt signaling components and that inhibition of this signaling improves axon growth and functional recovery after injury. Successful axon regeneration requires multiple changes in gene expression as neurons shift to a "growth state." Many growth-associated mRNAs are actively transported into axons and Jeff Twiss will discuss recent findings showing that mRNAs compete for limiting constituents of the transport machinery so that changes in transcription can shift the population of axonally localized mRNAs. Lastly, James Fawcett will discuss how increasing integrin function in neurons can promote axon regeneration. Together, this panel will discuss new intracellular and extracellular targets for novel therapies to improve function after spinal cord injury.

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

55. Drugs will change your brain

Chair: **Fulton Crews**
Presenters: **Theodora Duka, Friebert Weiss, Nathalie Boutros, Fulton Crews**

Numerous studies support the hypothesis that increased stress and drug taking combine to alter neurocircuitry function that increases risk of addiction and risk of relapse. Addiction is a chronic relapsing disorder that progresses through cycles of withdrawal and abstinence characterized by compulsive drug taking, difficulty changing behavior and delaying rewards. Presentations will stress altered neurocircuitry and signaling related to drug addiction. Dr. Duka will discuss frontal cortex, limbic and striatal brain circuits, through human brain imaging, that show progressive alterations associated with dependence in humans. These data support progressive changes in connectivity associated with cycles of drug withdrawal that contribute to cognitive, affective and reward aspects of dependence. Dr. Weiss will discuss how circuits involved in relapse and craving, including new data on metabotropic glutamate and nociception/

orphanin FQ receptor, contribute to compulsive drug use and relapse in rats. Dr. Boutros will discuss how adolescence exposure to alcohol increases adult acute alcohol reward and alcohol-induced increases in discounting the value of delayed rewards, as well as decreasing reward deficits associated with alcohol withdrawal in adulthood; these observed effects are likely to lead to increased alcohol consumption. Dr. Crews will introduce a recently discovered brain signaling system involving HMGB1 and Toll-like receptors collectively referred to as "Danger Signaling." His data will show drug activation of Danger Signaling persists for long periods in brain and alters brain frontal cortical circuits consistent with the loss of executive functions. His studies in postmortem human brain are consistent with dependent-induced changes in neuroimmune activation being primarily neuronal and mediated through increased Danger Signals. These presentations will identify novel behavioral and pharmacological targets for new addiction therapies.

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

56. Merging structure and function in large-scale, high-resolution maps of brain circuitry

Chair: **George Spirou**
Presenters: **Davi Bock, Kevin Briggman, George Spirou, Mark Ellisman**

Interest in mapping the brain connectome has acquired new purpose in recent years through the realization of several technologies to reconstruct neural tissue at ultrastructural resolution over large volumes. These approaches offer complementary advantages and challenges in tissue processing, image acquisition and image alignment that are amenable to solution through improvements in instrument design and automated image processing. These solutions permit new kinds of experiments that map large-scale neural circuitry, utilize these neural networks to understand information representation and processing, assess changes in neural circuitry associated with changing functional states and explore novel techniques that amplify information gleaned from these image volumes. This panel will provide up-to-date information on techniques to merge information about cellular properties of individual neurons to organization and function of neural circuits. First, George Spirou (West Virginia University) will briefly introduce the session format. Davi Bock (HHMI Janelia Farm) will describe advances in methods to combine in vivo 2-photon calcium imaging of cerebral cortex with neural network anatomy using transmission electron microscopy camera array (TEMCA) techniques. Kevin Briggman (NIH/NINDS) will discuss application of serial block-face scanning electron microscopy (SBEM), in conjunction with 2-photon calcium imaging, to reconstruct functionally identified retinal circuits responsible for motion processing. George Spirou (WVU) will discuss application of SBEM

across days to monitor synaptic growth and pruning and synaptic interactions with glia during development of brain circuits. Finally, Mark Ellisman (UCSD) will describe new genetic probes for use with multiscale microscopy applied to the nervous system, methods to extend field of view for high resolution structural maps and data archiving for public access.

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

57. Codes in the snow: Neurophysiologic bases of prefrontal cortex function

Chair: **David Devilbiss**
Presenters: **David Devilbiss, Jeremy Seamans, Eun Ha Baeg, Mark Laubach**

The prefrontal cortex (PFC) is critical for a number of executive functions and cognitive processes, including attention, working memory, and decision making. A large body of evidence indicates that firing rates of individual PFC neurons reflect important aspects of PFC function. In this regard, persistent activity of individual neurons during delay periods of working memory tasks has provided a foundation for understanding the neurophysiological bases of PFC function. However, a number of lines of evidence indicate that the PFC utilizes sparse and distributed coding schemes to represent cognitive processes and function. Such distributed neural codes may play an important role in cognition and affect beyond the contributions of single neurons. The manner in which ensembles of PFC neurons encode information in a behaviorally relevant manner remains poorly understood. This panel will codify recent advancements to study PFC coding schemes beyond simple firing rate measures and describe observations that indicate the importance of these codes for optimal cognitive function. David Devilbiss will describe recent studies examining the behavioral relevance of recursive activity within populations of PFC neurons related to performance in a goal-directed task. Jeremy Seamans will describe recent studies examining the behavioral relevance of distributed coding schemes related to goal directed behaviors. Eun Baeg will present data from simultaneous recordings of orbital frontal cortex (OFC), anterior cingulate cortex (ACC), and dorsal and ventral striatum in monkeys during a task in which drug-conditioned cues produce cognitive conflict despite irrelevance to task performance. Mark Laubach will report common correlates of the adaptive control of action based on event-related theta oscillations in the ACC of rodents and human beings and will describe how these signals are impacted by aging during an action-timing task.

58. Predicting and avoiding trees on the slope: Efference copy mechanisms in the brain

Chair: **Charles Larson**
Presenters: **Charles Larson, Jeremy Greenlee, Amy Parkinson, Sabina Gonzales Flagmeier**

The ability to predict outcomes based on sensory experience and correct prediction errors based on feedback mechanisms lies at the heart of understanding sensory motor control and human performance in health and across multiple processing domains (e.g., voice production, reaching movements, pain perception). The brain mechanisms that underlie error prediction and correction include efference copy (EC). EC mechanisms generate predicted sensory consequences of self-actions in the brain (known as corollary discharge), and sensory feedback from our own actions is compared to EC. When there is a match, no error signal is generated and actions continue as planned. When there is a mismatch in predicted and actual sensory consequences of an action, an error signal is generated and a correction is made. This session, driven by our multi-institutional collaborative work, is organized and introduced by Chuck Larson and will focus on converging evidence from 3 different methodological approaches to understand the neural systems involved in error prediction and correction of self actions. The tasks will address (1) electrophysiological (EEG) approaches to EC mechanisms involved in voice and speech control (Chuck Larson, PhD, Northwestern University, USA) (2) ECoG data from subjects during brain surgery (Jeremy Greenlee, MD, University of Iowa, USA), (3) functional and effective connectivity modeling of fMRI and EEG data to examine EC (Amy Parkinson, PhD, University of Texas Health Science Center San Antonio, USA) and (4) error detection and correction in neurological diseases with a focus on Parkinson's disease and apraxia (Sabina Gonzales Flagmeier, Imaging Institute at the University of Texas Health Science Center in San Antonio).

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

59. Cofilin-actin rods: An underappreciated mechanism for synaptic loss in aging and neurodegenerative disease

Chair: **James Bamburg**

Presenters: James Bamburg, Thomas Kuhn, Gong Chen, Joseph Cichon

A progressive loss of neuronal connectivity is responsible for the decline of cognitive function typical for Alzheimer's as well as most chronic CNS pathologies and during aging. In many CNS neuronal cell types, neurodegenerative stimuli, including amyloid beta, inflammatory cytokines, or a loss of energy balance, induce oxidative-dependent cofilin-saturated actin filament bundling into rods. Cofilin-actin rods disrupt transport and neuronal morphology and cause synaptic dysfunction impairing neuronal connectivity. This panel will focus on molecular mechanisms leading to the formation of cofilin-actin rods and their consequences for neuronal survival and function in chronic CNS pathologies. James Bamburg (Colorado State University) will provide new insight on rods in early development of Alzheimer disease, the role of reactive oxygen species in rod generation, and the prion-dependence of rod induction by amyloid beta and TNFalpha. Tom Kuhn (University of Alaska) will present research addressing neuronal NADPH oxidases as a principal source of oxidative stress mediated by TNFalpha, the key role for lipid rafts, and the inhibition of cofilin-actin rod formation by blueberry-derived natural products. Gong Chen (Pennsylvania State University) will elaborate on synaptic deficits of neurons containing cofilin-actin rods and rod formation in aging animals. Joe Cichon (NYU School of Medicine) will show dramatic images of rod formation in brains of living mice in the context of neuroinflammation and mouse models for stroke, and will address the suitability of this live animal model for studies aimed at prevention or reversal of cofilin-actin rod formation. Together, the speakers at this session will demonstrate the potential of cofilin-actin rods as a common denominator to neurodegeneration.

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

60. Insights into common patterns of decline in brain and muscle with aging

Chair: **Sonsoles de Lacalle**

Presenters: **Lee Hong, Stacey Gorniak, Leslie Consitt, Sonsoles de Lacalle**

In general, discussions of the neuromuscular system with respect to aging and neurodegeneration address changes at the level of the brain in isolation from that of the musculature and related behavioral manifestations. There are, however, many common patterns of age-related declines across brain, muscle,

and behavior. Specifically, aging and neurodegeneration result in a restriction in the functional range of musculature and brain activity. Such functional restrictions take the form of dedifferentiation, which will be the emphasis of this interdisciplinary panel. Lee Hong (Ohio Musculoskeletal and Neurological Institute) will present a broad theoretical perspective on the effects of aging and neurodegeneration on restricting the brain's capacity to effectively redistribute variability, integrating both animal and human research. Stacey Gorniak (University of Houston) will consider behavioral evidence of the effects of aging on limiting coordination patterns between different muscle groups during motor performance. Leslie Consitt (Ohio University) will discuss the changes in musculature that are associated with aging, particularly evidence of reduced range of metabolic response to bioenergetic challenges. Finally, Sonsoles de Lacalle (Ohio University) will present new data for the role of myostatin in brain function. The panel will finish with a discussion of new research directions and therapeutic modalities that could arise from improved insight into common patterns of decline in brain and muscle.

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

61. Evidence for perturbation of reward circuitry by pain and affective disorders

Chair: **Catherine Cahill**
Presenters: **Petra Schweinhardt, Scott Edwards, Catherine Cahill, Alexandre DaSilva**

Understanding how chronic illness perturbs reward circuitry is fundamental to address societal concerns of increasing drug abuse (including prescription analgesics) in patient populations. It is clear that avoiding pain and seeking reward are two fundamental motivations, so it is not surprising that there is overlap between involved brain circuitry. Importantly, diseases such as affective disorders and chronic pain lead to a dysregulation of the brain reward system that may be responsible for drug dependence as well as tolerance to analgesic efficacy in chronic pain patients. Dr. Schweinhart will present the interaction of experimental pain and reward in human volunteers. She will discuss how pain influences different aspects of reward processing and how the possibility of pain avoidance interacts with the possibility of reward omission. Dr. Edwards will present evidence that neuroanatomical sites involved in the negative emotional states of dependence also play an important role in pain transmission. His data suggest that traumatic stressors and injury are each capable of dysregulating a common set of neural substrates to engender sensory and affective pain states that are integral to comorbid conditions such as anxiety, depression, and chronic pain. Dr. Cahill will present data on mechanisms underlying altered reward processing in an animal model of neuropathic pain. Her data suggests

that neuropathic pain engages reward circuitry similar to opioid-dependent conditions and is influenced by gliosis. Wrapping up the session, Dr. DaSilva will present recent data, stemming primarily from neuroimaging studies, showing that chronic pain appears to induce neuroplastic changes at multiple levels in the human central nervous system, especially in the reward circuitry. He will discuss the correlation of clinical pain and availability of mu-opioid receptors in the reward circuitry of chronic pain patients.

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

62. Alzheimer's disease: Complex pathology, challenging treatment

Chair: **Isabelle Aubert**
Presenters: **JoAnne McLaurin, Emmanuel Planel, Steffany Bennett, Haung Yu**

Alzheimer's disease (AD) is characterized by cognitive deficits, amyloid-beta peptides accumulation, tau pathology, aberrant synaptic membrane remodeling, and neuronal loss in several brain regions. Panelists will provide insight on pathological features of AD, which may require consideration in order to lead to new therapeutic strategies. Isabelle Aubert (Sunnybrook Research Institute) will provide introductory comments on AD. JoAnne McLaurin (University of Toronto) will give an overview of clinical trial data released in the last year with an emphasis on what it tells us about the disease process and therapeutic development. She will discuss the advances that have lead to changes in clinical trial design and FDA requirements for new drug approval for AD. She will highlight these changes describing preclinical developmental work that she has contributed to. Emmanuel Planel (Centre Hospitalier Universitaire de Québec, Université Laval) will address the multifactorial aspects of AD pathogenesis. Drawing from his research focusing on diabetes, obesity and anesthesia, he will illustrate how biological and environmental factors interact with genetic background to affect tau and β-amyloid pathologies in laboratory animals. Steffany Bennett (University of Ottawa) will discuss how aberrant membrane phospholipid remodeling is likely required for transition from presymptomatic to symptomatic AD. She will address the importance of mechanistically dissecting critical lipid pathways required for this transition, which represents a new strategy for adjuvant AD therapy. Finally, Haung Yu (Columbia University) will discuss protein quality control mechanisms and relationship to AD. Further, he will discuss how modulation of these pathways can influence pathogenesis and cognition. The panel will conclude with an open discussion.

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

63. Striatal circuits and genetics: Behavioral and molecular responses to drugs of abuse

Chair: **Mary Kay Lobo**
Presenters: **Mary Kay Lobo, David M. Dietz, Venetia Zachariou, X. William Yang**

The striatum is a critical mediator of behavioral responses to drugs of abuse. However, a comprehensive understanding of the selective roles of striatal cell subtypes and their circuits, in these behavioral processes, was previously understudied due to the inability to selectively manipulate and study distinct subregions and cell subtypes within the complex striatal cytoarchitecture. This panel will discuss current insights into genetic and functional roles of striatal neurons and their circuits in mediating behavioral responses to drugs of abuse. Mary Kay Lobo will provide a brief introduction and then discuss opposing behavioral roles of the two ventral striatal (nucleus accumbens-NAc) medium spiny neurons (MSNs) during drug reward using optogenetic tools and present data on chromatin regulated adaptations occurring in striatal circuits after cocaine reinforcing and sensitization behaviors. David Dietz will discuss the use of novel light activated proteins to identify the temporal role of Rac-1 a small Rho-GTPase, in mediating cocaine induced structural plasticity in NAc MSNs and in mediating cocaine reward. Venetia Zachariou will present work on the role of Regulator of G Protein Signaling-9-2 (RGS9-2) activity in the NAc in modulating morphine analgesia and accelerating morphine tolerance and the use of optogenetics to determine which NAc subtype mediates this RGS9-2 behavioral response. Finally, X. William Yang will discuss a novel conditional BAC rescue strategy to show that targeted mu opioid receptor (MOR) expression in a subpopulation of striatal MSNs enriched in the striosome compartments and NAc, in an otherwise MOR-null background, can fully restore opiate reward and striatal dopamine release, and partially restore motivation to self-administer opiates. These presentations will highlight the functional and genetic roles of distinct striatal subtypes and compartments in mediating behavioral responses and/or molecular adaptations to drugs of abuse.

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

64. Sex, drugs, and … adolescence: The role of impulsivity

Chair: **Susan Andersen**
Presenters: **Louk Vanderschuren, Nadja Freund, Catharine Winstanley, Hugh Garavan**

One of the main goals of adolescence is to prepare teens to ultimately leave the house (or nest) and live independently from their parents. While some degree of impulsivity may facilitate the leaving, the right amount of impulsivity is

needed for a successful launch into a brave new world. Too much impulsivity and the effects can have deleterious consequences, including risk taking that leads to drug use and sexual promiscuity. Whether such scenarios can be encapsulated by impulsive measures and their underlying mechanisms will be the topic of this panel. Susan Andersen will provide brief introductory comments and will lead the discussion at the end. We will set the stage and discuss the evolutionary significance that impulsivity plays in the development of social behavior. Data will then be presented showing how a single mechanism found in adolescent rats increases delayed discounting (impulsive choice) and increases risk for elevated drug use and sexual behavior that is related to the adolescent brain. Effective intervention may also be possible, and recent data that suggests pharmacological intervention during the teen years may reduce impulsive behavior in adulthood. Finally, neuroimaging findings identify underlying neural networks involved in human impulsivity and high-risk behaviors.

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

65. Highs and lows: Insights from the intracranial self-stimulation procedure about normal and abnormal brain reward function in neuropsychiatric disorders

Chair: **Andre Der-Avakian**
Presenters: **Andre Der-Avakian, Sandra Boye, Clayton Bauer, C. J. Malanga**

Deficits in reward and motivation characterize several neuropsychiatric disorders, including dependence to drugs of abuse, depression, schizophrenia and genetic disorders, such as autism and fragile X syndrome. The purpose of this panel is to explore how the use of the intracranial self-stimulation (ICSS) procedure has provided information about the neurobiology of normal brain reward function, and how abnormalities in these brain processes lead to the expression of reward deficits. Such reward abnormalities are significant because they may also contribute to cognitive and social deficits that further impair the functioning of these patient populations. Andre Der-Avakian (University of California San Diego) will provide a brief historical perspective on the use of this procedure, and how chronic stress and drug dependence lead to reward deficits in rats with relevance to depression and the negative symptoms of schizophrenia. Sandra Boye (University of Montreal) will describe drug and lesion studies in rats that explore the anatomy of brain reward circuits in the healthy brain with emphasis on the habenula and its connections. Clayton

Bauer (Virginia Commonwealth University) will discuss how monoamine releasers alter the reward value of ICSS, reflecting properties of these substances hypothesized to contribute to, or limit, their abuse liability. He will expand upon how the ICSS procedure provides an efficient assessment of abuse liability. Finally, C.J. Malanga (University of North Carolina) will discuss the use of ICSS in mouse models of neurodevelopmental disorders, such as prenatal exposure to drugs of abuse and mutations relevant to autism, including fragile-X (Fmr1) and Angelman syndromes (Ube3a m-/p+), to explore changes in reward function. This panel will cover a wide array of research in exploring normal and abnormal reward function in rodent models of neuropsychiatric and neurodevelopmental disorders.

PANEL • THURSDAY, 4:30–6:30 PM • PEAK 6/7/8

66. Signaling for sex, sugars, and senility: Estrogen's regulation of behavior and homeostasis

Chair: **Vicky Luine**
Presenters: **Kevin Sinchak, Paul Micevych, Vicky Luine, Ed Wagner**

Over the years, our ideas about estrogen signaling have greatly expanded. In addition to estradiol's direct nuclear actions that mediate transcription and translation, more recent experiments from several behavioral domains and physiological processes have demonstrated membrane-initiated signaling by estrogens. Both direct nuclear and estradiol membrane signaling can be mediated by the classical estrogen receptors, ERα and ERβ, which are two of the numerous putative membrane estrogen receptors. Participants will provide novel behavioral, anatomical, and neurochemical results demonstrating estrogenic activation of various signaling pathways to regulate sexual behavior, cognition and energy balance. Previously, these neural effects of estrogen were believed to be mediated solely by transcription through classical actions of estrogen receptor complexes with nuclear DNA. Sinchak will highlight that multiple estrogen signaling pathways facilitate sexual receptivity in a time-dependent manner, and Micevych will describe how activity regulated cytoskeletal-associated protein (Arc) regulates estradiol-induced receptivity. Luine will present evidence for rapid increases in dendritic spines and enhanced memory through membrane-mediated mechanisms. Wagner will provide information on multiple receptor subtypes and signal transduction mechanisms which contribute to estrogenic regulation of energy balance.

SIGMA-ALDRICH®

SIGMA® Life Science Where bio begins™

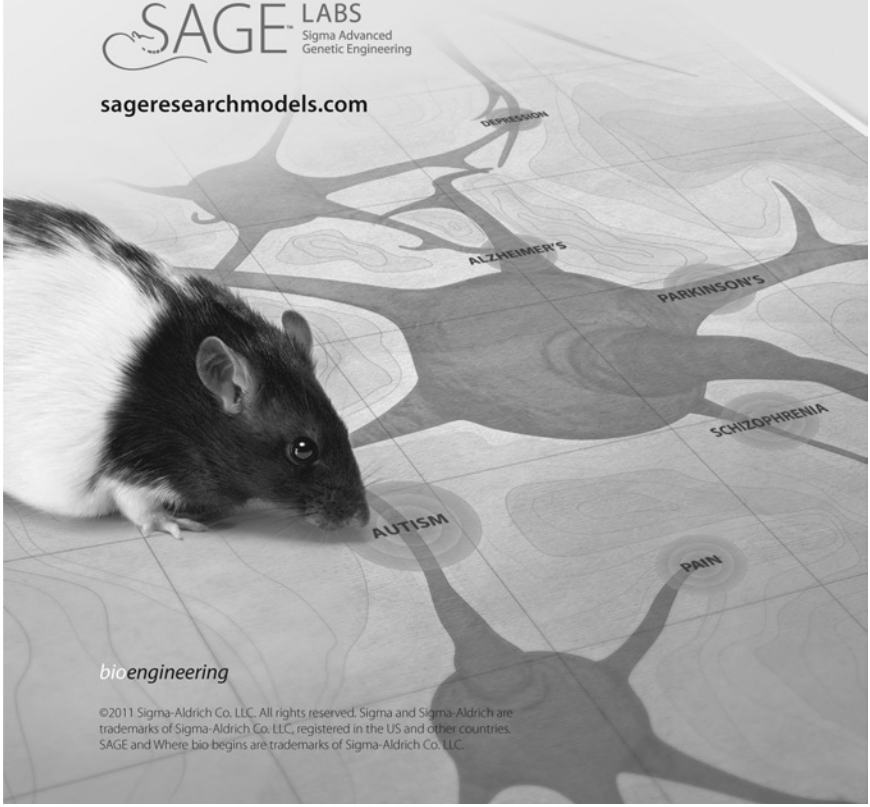
Biosynaptic.

Plot your pathway for breakthroughs in neuroscience with **next-generation research models** from SAGE™ Labs.

Advancements in neuroscience are yours to discover with targeted knockout rats from SAGE™ Labs. Our comprehensive suite of rat models can help move your neuroscience research forward. Map your next breakthrough with smarter rat models for studying neurodegenerative, mood, and affective disorders, including seven new models of autism.

SAGE™ LABS
Sigma Advanced Genetic Engineering

sageresearchmodels.com



*bio*engineering

©2011 Sigma-Aldrich Co. LLC. All rights reserved. Sigma and Sigma-Aldrich are trademarks of Sigma-Aldrich Co. LLC, registered in the US and other countries. SAGE and Where bio begins are trademarks of Sigma-Aldrich Co. LLC.

Poster Abstracts

SUNDAY, JANUARY 27, 2013

P1 • An investigation of head accelerometry, cognitive function, and brain blood flow during intercollegiate boxing and its impact regarding head-injury assessment in combat

Michelle Butler*, Brandon Doan, Michael Hanna, Gina Adam, Al Wile, Brian Self, Kristin Heaton, Teresa Brininger, Elizabeth Kryskow

The goal of this study was to investigate head impacts, neuropsychological performance, and cerebral blood flow in intercollegiate boxers to increase understanding about consequences of head impacts in this population. If significant correlations were found between measures, recommendations for increasing efficiency of head impact assessment in combat environments might be made. Participants—31 intercollegiate male boxers mean age 20.74 yrs., height 70.14 in., weight 164.32 lbs., and experience 1.5 yrs. Assessments occurred before and after two full-effort 2-minute sparring rounds. The Impact Headgear system tracked location/number of head impacts, translational acceleration, and rotational forces. The ImPACT test and Automated Neuropsychological Assessment Metrics (ANAM) measured neuropsychological performance and the Brain Acoustic Monitor (BAM) measured cerebral blood flow. Sparring bouts were videotaped to validate head impacts. Impact Headgear recorded an average of 26.81 impacts per boxer, most of which were below the 25% probability for brain injury. The ImPACT test showed a decrease in verbal memory ($p < .05$), delayed memory ($p < .01$) and improved reaction time ($p < .01$). The ANAM showed a decrease in delayed memory ($p < .01$) and improved reaction time ($p < .01$). BAM detected no significant changes and no significant correlations were found between the BAM and the neuropsychological measures. In the current sample, head impacts were below threshold to cause brain disturbance detectable through BAM; however, consistent with research in amateur boxing, mild decline in memory function was detected. Research with a larger sample across greater impacts is recommended to further investigate the efficacy of the BAM.

P2 • Mate, a novel protein, suggests a role for nuclear speckles and DNA splicing in the pathology of thefragile X syndrome

Regina Dahlhaus*, Kristin Derlig, Andreas Gießl, Helmut Brandstätter, Ralf Enz

The fragile X syndrome (FXS) is the most common form of inherited mental retardation in all human populations and ethnic groups. Affected individuals display a variety of intellectual deficits, including learning impairments and autism.

Caused by a transcriptional silencing of the fragile x mental retardation protein FMRP, a mRNA binding protein itself, misregulation of activity dependent translation is thought to be a leading cause of FXS. Interestingly, recent studies identified an increasing number of mRNAs associated with FMRP, and it has been estimated that 4% of all proteins of the mammalian brain are regulated by FMRP.

Thus far, four motifs have been found responsible for mediating interactions between FMRP and mRNAs, but in particular G-quartets and G-rich sequences have been demonstrated to bind to FMRP with high affinity.

Here, we present a novel protein, which's mRNA contains several G-quartets and binds to FMRP upon co-precipitation. Sequence analysis revealed that the protein evolved app. 1.7 billion years ago to 2.3 billion years after the origin of life, when eukaryotes developed. The rise of eukaryotes from prokaryotes represents an important step in evolution since these cells introduced a more complex organisation including the invention of mitochondria and a well-organized genome in the nucleus. We therefore developed antibodies against Mate and performed immunhistochemistry analyses as well as 3D reconstructions of Mate in FMR1 –/– and wildtype mice. Our results show that the protein is present in many tissues and localises to heterochromatin and nuclear speckles in neuronal and non-neuronal cells. Moreover, we show that Mate and nuclear speckles experience specific alterations in FMR1 –/– mice. These findings suggest not only an important role for Mate in FXS, but also provide the first evidence for a function of nuclear speckles in the disease. Indeed, splicing and gene transcription are two fundamental mechanisms of long-term memory formation.

P3 • The central role of the gut microbiota in the maternal-separation model of depression

Giada De Palma*, Patricia Blennerhasset, Amber J. Park, Stephen Collins

Early life stress has been associated with psychiatric and gastrointestinal disorders in adulthood. Maternal separation (MS) is a potent stressor, with adult MS mice displaying altered hypothalamic-pituitary-adrenal axis, anxiety and depression-like behavior, gut dysfunction and intestinal dysbiosis. Recent studies have demonstrated that intestinal microbiota can determine the mouse behavioral phenotype. Thus, here, we have investigated the role of gut commensal bacteria in behavioral and physiological changes induced by MS.

Pups of germ-free and conventional C57BL/6 mice were randomly assigned to MS. Adult mouse behavior was assessed by step-down and dark/light preference tests. Brain BDNF, catecholamines and serum corticosterone levels were measured using ELISA. Acetylcholine (ACh) release from the myenteric plexus was assessed by superfusion technique. Inflammatory markers were evaluated in the serum and intestine.

Conventional MS mice displayed anxiety-like behavior and higher corticosterone levels compared to controls. ACh release was increased in the colon, but reduced in the small intestine of MS mice. Colonic microbiota composition was altered in MS mice, with increases in Bacteroides fragilis group, Bifidobacterium and Enterobacteriaceae, and lower Clostridium coccoides counts. Germ-free MS mice displayed similar behavior as controls despite exhibiting higher corticosterone levels. ACh release in jejunum and colon was altered in MS mice compared to controls ($P < 0.05$). No overt inflammation was found in conventional or germ-free mice.

This study demonstrates the importance of gut microbiota for the expression of altered behavior in mice subjected to MS and further supports the key role played by commensal bacteria in gut–brain axis and psychiatric comorbidities seen in chronic gastrointestinal disorders.

P4 • Gain insights on central nervous system diseases using global metabolomics

Kirk Pappan*, Lining Guo, Thomas Jonsson

Global metabolomics is a new and powerful technology that can provide a relatively complete picture of metabolism in biological systems. We have developed an unbiased global metabolomics platform based on a combination of three independent systems: ultrahigh performance liquid chromatography/

tandem mass spectrometry (UHLC/MS/MS2) optimized for basic species, UHLC/MS/MS2 optimized for acidic species, and gas chromatography/mass spectrometry (GC/MS). Following sample extraction, full scan mass spectral analyses are carried out to record retention time, molecular weight (m/z) and MS/MS2 of all detectable ions presented in the samples. Rapid identification of metabolites in the experimental samples with high-confidence is achieved by automated comparison of the ion features in the experimental samples to a comprehensive chemical reference library. After data generation, integrated tools including statistical analysis, pathway mapping, and data visualization can rapidly provide powerful insights for understanding biological systems. We have applied this metabolomics platform to gain insights in various CNS diseases. Results will be presented on the characterization of an Alzheimer mice disease mice model, characterization of spinal cord injury and recovery process in a rat model, and biomarker discovery for amyotrophic lateral sclerosis (ALS).

P5 • Neural response to visual nicotine cues in smokers: What predicts signal magnitude?

Henry Holcomb*, Jef West, Laura Rowland, David Gorelick

In those addicted to nicotine, cigarette cues are known to increase neural reactivity of brain regions associated with reward and addiction. The determinants of that excitability are not well understood. In this study we ask to what extent a measure of acute nicotine exposure, expired carbon monoxide (CO), or a measure of chronic nicotine exposure, Pack Year (PY) history (adjusted for age), account for the BOLD response associated with nicotine cues. Using functional magnetic resonance imaging (fMRI) we demonstrate a heterogeneous pattern of effects. Neither the caudate nor the thalamus differs significantly in its BOLD response associations between acute versus chronic nicotine exposure. Those two structures are equally affected by acute and chronic exposure. The insula and the substantia nigra (S.nigra), in contrast, are highly sensitive to the amount of acute but not chronic nicotine exposure. When assessed for an association with Pack Year history, these two structures shift from being significant to nonsignificant after the contribution of the acute exposure has been partialed out using multiple linear regression methods. These findings suggest that acute nicotine exposure has a potent effect on neural responsivity in the context of nicotine visual cues. Historical exposure to nicotine is less reliable than acute exposure as a predictor of neural activity bias in these regions. Activity in the caudate and thalamus appears to be highly sensitive to the magnitude of acute and chronic exposure.

P6 • Characterization of a novel primary neuronal culture from adult zebrafish brainstem

Jeffery Plunkett*, Alexis Tapanes-Castillo, Francelethia Shabazz, Isaac Chacon, Jossias Genao, Arjena Valls, Katarina Vajn, Martin Oudega

The ability of the adult zebrafish *(Danio rerio)* to regenerate specific tracts within its central nervous system (CNS) after injury has been well-documented. Our lab developed a novel primary adult brainstem neuronal culture technique to better understand the molecular and cellular biology underlying this phenomenon. Characterization of the cultures, which can be maintained over 14 days under serum-containing or serum-starved conditions, revealed a heterotypic population of cells, consisting primarily of neuronal cells, with subpopulations of glial and putative stem/progenitor cells at various stages of differentiation. We are currently utilizing our culture to investigate axonal responses to growth inhibitory chondroitin sulfate proteoglycans (CSPGs), which are expressed within the zebrafish CNS pre- and post-injury. We have particularly focused on the CNS-expressed CSPG neurocan. Our lab has performed cultures utilizing CSPGs, as well as purified Myc-tagged full-length zebrafish neurocan b (Myc-NcanB) protein, as substrates. Based on in vivo data, which demonstrates that brainstem neurons have different regenerative capacities, we hypothesized that our culture would contain different neuronal populations that would respond distinctively to CSPGs or Myc-NcanB presented under controlled culture conditions. Our results supported this hypothesis revealing different populations of brainstem neurons with regard to their response to CSPGs or Myc-NcanB in vitro. Taken together, our results suggest that the ability or disability to grow across and beyond a CSPG-rich area is intrinsic to the neuron and likely involves unique sets of axon growth-related genes.

P7 • Amyloid-dependent degeneration of subcortical monoaminergic and cholinergic neurons in mouse models of AD: Relevance of cognitive and neuropsychiatric symptoms

Michael Lee*, Ying Liu, Gang Chen

Alzheimer's disease (AD) is characterized with loss neurons the in cortex and subcortical regions. Currently, lack of progressive neurodegeneration in animal models have hampered understanding of how neurons degenerate in AD. However, analysis of subcortical monoaminergic (MAergic) neurons reveals that the progressive degeneration of MAergic neurons occurring in human AD is recapitulated in the APPswe/PS1ΔE9 (APP/PS1) transgenic mouse

model. Degeneration of MAergic neurons follow the events consistent with dying back process where the afferents are initially lost at 8–12 mos of age followed by the loss the cell bodies between 12–18mos of age. Significantly, the loss of MAergic afferents are followed by the progressive loss of cortical and hippocampal cholinergic (Ach) afferents. Consistent with later onset neurodegeneration, there is no loss of Ach neuron at 18 mos of age. The loss of afferents from subcortical MAergic and Ach neurons are associated with onset and progression of cognitive deficits. Moreover, sever loss of MAergic afferents at 18 mo of age is associated with increased aggressive behavior, suggesting that loss of MAergic signaling in human AD could be responsible for some of the neurobehavioral abnormalities, including aggression. These results indicate that the APP/PS1 model recapitulates the progressive loss of multiple subcortical neurotransmitter systems. Consistent with the proposed early vulnerability of MAergic neurons in AD, degeneration of Ach afferents occurs later than the MAergic neurodegeneration. Moreover, loss of subcortical neurotransmitters may be relevant for understanding neurobehavioral deficits associated with AD and other dementias.

P8 • Nicotinic acetylcholine receptors (nAChRs) in neuroimmune and inflammatory responses: Modulation of effects in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS)

Ronald Lukas*, Alain Simard, Yan Gan, Qiang Liu, Ning Su, Greg Turner, Paul Whiteaker, Barbara Morely, Fu-Dong Shi

Nicotine can have immunosuppressive and anti-inflammatory effects that potentially could be leveraged to advantage. We and others have shown that nicotine has protective effects in mice in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS).

Because many immune cell types express various nicotinic acetylcholine receptor (nAChR) subunits, we have begun to assess roles for nAChR subtypes containing different subunits on the EAE response and its sensitivity to nicotine exposure. Nicotine's protective effects are not observed in nicotinic acetylcholine receptor α7 subunit knock-out mice, although nicotine exposure does have effects on other indices of inflammation and autoimmunity. The EAE response in the absence of nicotine is the same in wild-type (WT) or α7–/– mice. Deletion of nAChR α9 subunits whether in the presence or absence of nicotine, has the same protective effect as does nicotine exposure in WT mice. Nicotine's protective effects during the onset of and at the peak EAE response are evident in nAChR β2 subunit knock-out mice, but the typical recovery from EAE is not seen in β2–/– animals. Other studies suggest exacerbation of EAE indouble knock-out, α7–/– α9–/– mice. Considering

nicotine's antagonism of α9-nAChRs and assuming that it activates function of α7- or β2-containing nAChRs, these findings minimize roles for α7-nAChR in endogenous neuromodulation but point to such roles for α9-nAChRs (being pro-inflammatory), and for β2-containing nAChRs (in recovery mechanisms). Moreover, and although deletion of both nAChR subtypes seems to be deleterious, nicotine's antagonism of α9-nAChRs and presumed activation of α7-nAChRs could account for nicotine's protective effects. Ligands selectively targeting specific nAChR subtypes could offer alternative therapies for treatment of MS and perhaps other neuroimmune and/or inflammatory diseases.

P9 • Expression of P450c17 in the human fetal nervous system

Synthia Mellon*, Marcus Schonemann, Marcus Muench, Meng-Kian Tee, Walter Miller

P450c17, encoded by the CYP17A1 gene, is the sole enzyme that converts pregnenolone to DHEA. DHEA acts as a potent neurotrophin, increasing axonal growth in neocortical neurons. P450c17 is abundant in human fetal and postnatal adrenals and gonads, and is also expressed in the developing mouse nervous system, but there has been limited information about expression in the human nervous system. We sought to delineate the pattern of expression of P450c17 in the early human fetal nervous system. Morphologically identifiable portions of 9-, 10-, and 11-week gestation human fetuses were studied by immunohistochemistry using multiple antisera. P450c17 was readily detected in the developing dorsal root ganglia (DRG) and spinal cord. The identity of the detected antigen as P450c17 was confirmed using multiple antisera directed toward different regions of the P450c17 protein and by using antisera immunodepleted with authentic human P450c17. Identification of P450c17 in Neu+ and Neu- neurons suggests that P450c17 is expressed in both immature and mature neurons. P450c17 is expressed in both cell bodies and in efferent fibers of the DRG. As we showed in mouse DRG, human P450c17 co-localizes with some TRK-expressing neurons. We also found expression of the cholesterol side-chain cleavage enzyme, P450scc (encoded by CYP11A1), in the human dorsal root ganglia; however, unlike P450c17, P450scc was found only in cell bodies and not in DRG fibers. P450 Oxidoreductase (POR), the requisite electron donor for P450c17 and necessary for functional P450c17 enzymatic activity, co-localized with P450c17 in DRG cell bodies, but was absent from P450c17-expressing DRG fibers. These data suggest that neurosteroids synthesized via these two enzymes may act in the developing human nervous system. The expression of P450c17 in structures lacking POR means that P450c17 may not be steroidogenic in those locations, suggesting that P450c17 may have additional functions that do not require POR.

P10 • Antipsychotic-like actions of amylin in ventral striatal regions enriched in RAMP-1 and CT gene expression

Vaishali P. Bakshi*, Sarah K. Baisley, Quentin Bremer, Brian Baldo

The AMY1 receptor, a high-affinity receptor for CGRP-related peptides such as amylin (AMY) and salmon calcitonin, is highly concentrated in the nucleus accumbens shell (AcbSh). Because AcbSh is a crucial neural substrate for antipsychotic actions, and because AMY infusion into the AcbSh produces behavioral effects reminiscent of functional dopamine antagonism, we explored possible antipsychotic-like effects of the AcbSh AMY1 receptor with prepulse inhibition (PPI). PPI is the normal diminution of the startle response when a barely detectable prepulse is presented immediately prior to an intense startling stimulus, and is perhaps the most widely validated operational measure of the sensorimotor gating abnormalities seen in schizophrenia. We also mapped striatal expression of AMY1-related genes: the Receptor Activity Modifying Proteins (RAMPs), which regulate the ligand binding affinity of the CGRP receptor genes CL and CT; RAMP-1 association with CT produces the high-affinity AMY1 receptor. Separate groups of male Sprague-Dawley rats received amylin (0, 30, or 100 ng) into either AcbSh or caudate with systemic amphetamine (AMPH: 0 or 1.75 mg/kg) prior to PPI testing. Separately, the effect of AcbSh infusion of a selective AMY1 receptor antagonist, AC187 (0, 10, or 20 ug), was studied. AMPH disrupted PPI, and AcbSh infusion of AMY reversed this deficit; AC187 in AcbSh disrupted PPI; no effects were seen in caudate. RAMP-1 (but not RAMP-2 or RAMP-3) and CT (but not CL) were highly and selectively expressed in AcbSh, where the behavioral effects of AMY1 ligands were mediated. Thus, stimulation of Acb shell AMY1 receptors improves deficient PPI, and blocking endogenous ligand "tone" at these AMY1 receptors disrupts PPI, suggesting that AMY1 signaling may represent an important new modulatory influence on sensorimotor gating in the ventral striatum. Hence, the AMY1 receptor shows promise as a novel target for the development of antipsychotic drugs.

P11 • Time for a change! An endocrine disruption index to predict neural impacts of xenoestrogens

Mary Ann Ottinger*, Meredith Bohannon, Leah Baltos, Anna Schlappal, Karen Dean

Environmental pollutants encompass a vast array of compounds. A large number of these compounds are endocrine-disrupting chemicals (EDCs); many exert estrogen-like actions. A challenge to assessing the potential impacts of these EDCs is to distinguish toxicological impacts from nonlethal endocrine

effects. Most studies in wildlife, especially birds, have focused on toxicological effects, with little attention to nonlethal effects. Consequently, it has proven difficult to assess potential risk associated with exposure to neural systems and to behavioral outcomes. Risk assessment is further complicated by variations in reproductive strategies, life span, sexual differentiation, and migration. As such, steroids and the steroid-like EDCs may have different effects in precocial versus altricial species. We have investigated the effects of EDCs in captive Japanese quail and wild songbirds. Our studies have shown that embryonic exposure to a range of EDCs affected neural systems, immune response, thyroid axis and impaired male reproductive behavior in quail. Our studies considered single compounds as well as complex mixtures at levels that bracket environmentally relevant exposures to higher doses aimed at understanding mechanisms of action. Results have shown that the predictive value of the Toxic Equivalency (TEQ), based on comparative activation of the aryl hydrocarbon receptor (AhR) relative to dioxin were not as accurate as expected. Other approaches have been developed to address inconsistencies in effects and to incorporate diverse data into the potency estimates. We are developing a more inclusive estimation method for endocrine and neuroendocrine effects, termed an Endocrine Disruption Index (EDI), which would complement other indices and focus on endocrine disruption and includes effects beyond those mediated by the AhR for a comparative assessment of nonlethal EDC effects.

P12 • The role of axon regeneration from brainstem neurons in functional recovery after spinal cord injury in adult zebrafish

Martin Oudega*, Denis Suler, Alexander Betz, Alexis Tapanes-Castillo, Francis Shabazz, Jeffrey Plunkett, Katarina Vajn

In contrast to mammals, zebrafish *(Danio rerio)* exhibit remarkable locomotor recovery within six weeks after complete spinal cord injury (SCI). In the first weeks after SCI, neurons located in the reticular nucleus (RT), nucleus of medial longitudinal fasciculus (NMLF), and magnocellular octaval nucleus (MaON) regenerate their axons as far as 4000 μm into the caudal spinal cord. Here we investigated if these regenerating axons contribute to the swimming recovery. In adult zebrafish with a complete SCI, we investigated the temporal profiles of axonal regeneration from neurons in the RT, NMLF ,and MaON and of the recovery of swimming. Neurons that regenerated their axon 4000 μm caudal to the transection site were identified using retrograde tracing. We quantified the total number of labeled neurons in the brainstem as well as in individual brainstem nuclei. The total swimming distance was assessed using open field video tracking. Our results demonstrate that the number of neurons in the RT, NMLF, and MaON that regenerate their axon increases during the

first 8 weeks post-injury. Axons from RT neurons regenerate into the caudal spinal cord before those of NMLF and MaON neurons. The neurotransmitter profile of the regenerating neurons is being investigated. The swimming performance gradually improved as well, with full swimming recovery around 8 weeks post-injury. Our results suggest that the regeneration of different descending tracts contributes to spontaneous swimming recovery after SCI in zebrafish. Current work focuses on revealing the critical molecular determinants underlying the axonal regeneration in the injured spinal cord. *Support:* United States Department of Defense grant W81XWH-09-1-0403.

P13 • Chronic cerebrospinal venous insufficiency and venous stenoses in multiple sclerosis

Olaf B. Paulson*, Morten Blinkenberg, Per Åkeson, Henrik Sillesen, Susanne Lövgaard, Finn Sellebjerg, Hartwig R. Siebner, Per Soelberg Sørensen

Objectives. The traditional view that multiple sclerosis (MS) is an autoimmune disease has recently been challenged by the claim that MS is caused by chronic cerebrospinal venous insufficiency (CCSVI). Although several studies have questioned this vascular theory, the CCSVI controversy is still ongoing. Our aim was to assess the prevalence of CCSVI in Danish MS patients using sonography and compare these findings with MRI measures of venous flow and morphology.

Methods. We investigated cervical and cerebral veins in 24 patients with relapsing–remitting MS (RRMS) and 15 healthy controls, using extracranial high-resolution ultrasound colour Doppler (US-CD) and transcranial colour Doppler sonography (TCDS), as well as magnetic resonance imaging (MRI) and phase-contrast MR blood flow measurements (PC-MR) of the cervical veins.

Results. US-CD could not identify the left internal jugular vein (IJV) in one MS patient, other ultrasound examinations were normal in patients with MS. There was no difference in mean cross-sectional area of the IJV in MS patients compared with controls. Only one patient with MS and two healthy controls fulfilled one CCSVI criterion, and none fulfilled more than one CCSVI criterion. MR venography showed insignificant IJV stenosis (1–49%) in two patients with MS, whereas 50–69% IJV stenosis was detected in two healthy controls. There was no difference in PC-MR measurements of mean IJV blood flow between patients with MS and controls.

Conclusion. Our results do not corroborate the presence of vascular pathology in RRMS and we found no evidence supporting the CCSVI hypothesis.

P14 • The antipsychotic-like effect of mGlu4-receptor-positive allosteric modulators in rodents

Andrzej Pilc*, Anna Sławińska, Joanna Wieronska, Magdalena Łasoń-Tyburkiewicz, Piotr Gruca, Mariusz Papp, Magdalena Kusek, Krzysztof Tokarski, Darío Doller

Several studies have suggested that modulation of the glutamatergic system via metabotropic glutamate receptors (mGlu) could be a new, efficient way to achieve antipsychotic-like effects. Herein, we report the pharmacological actions of LuAF21934 and LuAF32615, both previously characterized as selective and brain-penetrant positive allosteric modulators (PAMs) of the mGlu4 receptor, in several tests reflecting positive, negative, and cognitive symptoms of schizophrenia in rodents. MK-801- and amphetamine-induced hyperactivity, as well as DOI-induced head twitches in mice were used as models for positive symptoms. Furthermore, the effect of LuAF21934 on DOI-induced frequency of spontaneous excitatory postsynaptic currents (EPSCs) in slices from mouse brain frontal cortices was investigated. The MK-801-induced disruption of social interaction and of spatial delayed alternation in rats were used as models for negative and cognitive symptoms, respectively. LuAF21934 (0.1, 0.5, 1, 2, and 5 mg/kg) and LuAF32615 (2, 5, and 10 mg/kg) dose-dependently inhibited both MK-801- and amphetamine-induced hyperactivities. Moreover, the drugs antagonized DOI-induced head twitches in mice and DOI-induced increased frequency of spontaneous EPSCs.

The MK-801-induced disruption in the social interaction test was abolished by LuAF21934 at a dose of 0.5 mg/kg and LuAF32615 at a dose of 10 mg/kg. In the delayed spatial alternation test, the effective doses of LuAF21934 were 1 and 2 mg/kg, while LuAF32615 was active at a dose of 10 mg/kg. Altogether, we propose that mGlu4 receptor can be considered as a promising target for the development of novel antipsychotic drugs, acting as positive allosteric modulators of the receptor.

P15 • Advances in neurochemical profiling of brain tissue samples using HPLC with a novel four-channel electrochemical array detector

Nick Santiago*, Bruce Bailey, Marc Plante, David Thomas, Qi Zhang, Ian Acworth

The ability to measure many different biogenic amine neurochemicals and their metabolites simultaneously is challenging due to their similarities in chemical structures and detector sensitivity requirements. Most of the biogenic amines and metabolites can be oxidized electrochemically so the use of electrochemical detection is routine for the analysis of these compounds. Chromatographic

techniques have advanced over the years; however, even with the use of UHPLC columns baseline, resolution of many different analytes still remains difficult due to the constraints of isocratic HPLC mode for their separation. The isocratic mode is typically required to allow for optimal performance and sensitivity of the electrochemical detector. A new modular electrochemical detector has been developed that uses multiple coulometric electrodes in series with each electrode having a unique potential setting. This provides additional resolution of analytes beyond chromatographic separation using voltammetric techniques. The detector is compatible with gradient HPLC techniques and provides an autoranging feature that enables the simultaneous measurement of low and high level analytes Qualitative information is thereby enhanced while still maintaining quantitative sensitivity requirements for specific analytes at low concentrations. Examples illustrating the content of biogenic amines and acid metabolites in brain tissue samples will be presented using a four-channel electrochemical array combined with UHPLC chromatographic separation.

P16 • The role of perineuronal nets within the medial prefrontal cortex on cocaine-seeking behavior

Barbara Sorg*, Ryan Todd, Gemaine Stark, Megan Slaker, Lynn Churchill

Perineuronal nets (PNNs) are a specialized extracellular matrix that wraps around certain neuronal cell bodies and proximal dendrites. PNNs are most often found surrounding fast-spiking, parvalbumin-containing GABAergic neurons and may function to prevent plasticity during adulthood. Removal of PNNs with chondroitinase ABC (Ch-ABC) has been shown to reinstate plasticity in the CNS. The goal of this study was to determine the extent to which Ch-ABC treatment within the prelimbic region of the medial prefrontal cortex (mPFC) would alter cocaine-seeking behavior in a cocaine-induced, conditioned place preference (CPP) task in male Sprague-Dawley rats. In the prelimbic region of the mPFC, PNNs double-labeled with Wisteria floribunda agglutinin (WFA) and GAD-67 represent 70% of WFA-labeled neurons. Ch-ABC treatment prior to training for cocaine CPP blunted both the acquisition of CPP and, as expected, later cocaine-primed reinstatement after extinction. Ch-ABC treatment just prior to extinction training did not alter the rate of extinction or subsequent cocaine-primed reinstatement. Ch-ABC treatment just prior to reinstatement also did not alter cocaine-primed reinstatement. However, extinction training in the same rats after testing for cocaine-primed reinstatement blocked subsequent cocaine-primed reinstatement. A separate group revealed that this blockade did not occur in rats given withdrawal during the same interval. These findings suggest that there may be time- and/or experience-dependent changes in the effects of Ch-ABC such that PNN-containing neurons alter output of mPFC to suppress cocaine-seeking behavior.

P17 • Catechol-O-methyltransferase (COMT) influences the connectivity of the prefrontal cortex at rest

Elizabeth Tunbridge*, Sarah Farrell, Paul Harrison, Clare Mackay

Catechol-O-methyltransferase (COMT) modulates dopamine in the prefrontal cortex (PFC) and influences PFC dopamine-dependent cognitive task performance. A human COMT polymorphism (Val158Met) alters enzyme activity and is associated with both the activation and functional connectivity of the PFC during task performance, particularly working memory. Here, we used functional magnetic resonance imaging and a data-driven, independent components analysis (ICA) approach to compare resting state functional connectivity within the executive control network (ECN) between young, male COMT Val158 and Met158 homozygotes. COMT genotype effects on grey matter were assessed using voxel-based morphometry. COMT genotype significantly modulated functional connectivity within the ECN, which included the head of the caudate, and anterior cingulate and frontal cortical regions. Val158 homozygotes showed greater functional connectivity between a cluster within the left ventrolateral PFC and the rest of the ECN. This difference occurred in the absence of any alterations in grey matter. Our data show that COMT Val158Met affects the functional connectivity of the PFC at rest, complementing its prominent role in the activation and functional connectivity of this region during cognitive task performance. The results suggest that genotype-related differences in prefrontal dopaminergic tone result in neuroadaptive changes in basal functional connectivity, potentially including subtle COMT genotype-dependent differences in the relative coupling of task-positive and task-negative regions, which could in turn contribute to its effects on brain activation, connectivity, and behavior.

P18 • Hunger vs. hedonics: Investigating the role of the amygdala in opioid vs. energy deficit–driven feeding behavior

Matthew Will*, Kyle Parker, Howard Johns

We have previously demonstrated that the DAMGO-induced feeding is dependent upon activation of the basolateral amygdala (BLA); as intra-BLA infusion of the GABAA agonist muscimol blocks the DAMGO-induced bingeing of high-fat diet, yet has no effect on feeding induced by 24-hr food deprivation. In contrast to the BLA findings, muscimol inactivation of the central nucleus of the amygdala (CeA) blocks high-fat feeding driven by either DAMGO or food deprivation. In order to further our understanding of this dissociated role of the BLA (but not CeA) in mediating these models of hedonic and homeostatic feeding models, we have conducted two sets of

experiments. The first experiment examined the role of endogenous opioids within the amygdala by administering naltrexone into the BLA or CeA amygdala subregions prior to intra-Acb DAMGO or 24-hr food deprivation. The results demonstrated that intra-BLA naltrexone blocked DAMGO, but not food deprivation–induced feeding. In contrast, intra-CeA naltrexone produced the opposite pattern, blocking food-deprived but not DAMGO-induced feeding of high-fat diet. In the second experiment, rather than a free-feeding task, we used an operant task to examine the role of the BLA (via muscimol inactivation) in mediating the effects of intra-Acb DAMGO and home cage chow food deprivation on progressive ratio breakpoint task to earn sugar pellets. The results demonstrated that both DAMGO and food deprivation produced a dose-dependent effect on increasing breakpoint. However, while BLA inactivation reduced breakpoint driven by both treatments, the breakpoint was significantly more effective in reducing operant behavior driven by DAMGO treatment. These studies suggest key distinctions in both the regional and neurochemical nature underlying two widely used models to understand feeding behavior.

P19 • Status epilepticus–induced hippocampal microgliosis is blocked by rapamycin treatment

Anne Anderson*, Amy Brewster, Wai Ling Lee, Yi-Chen Lai

Status epilepticus (SE) is associated with molecular and structural hippocampal changes, epilepsy, and cognitive deficits. The molecular mechanisms underlying the long-term consequences of SE are not fully understood. One candidate mechanism is activation and proliferation of microglia (microgliosis) and hyperactivation of the mammalian target of rapamycin (mTOR) pathway in the hippocampus. Microglial activation is mTOR dependent and is suppressed by rapamycin, an mTOR inhibitor and immunosuppressant. Whether rapamycin reduces SE-induced microgliosis has not been evaluated. Pilocarpine was used to induce SE (1 hr) and two weeks later rats were treated with rapamycin (Rap) or vehicle (Veh). Immunohistochemistry was performed before and after the treatments. Antibodies against the phosphorylated ribosomal S6 protein (P-S6), IBA1 and NeuN were used. Analyses focused on the hippocampal formation. Increased P-S6 and IBA1 staining was evident 2 and 3 weeks after SE. The SE-induced increase in P-S6 signal was apparent throughout the hippocampus in the principal cell layers and in cells scattered throughout CA1 strata radiatum and lacunosum moleculare. In hippocampi from Sham+Veh and SE+Veh rats, P-S6 signal co-localized with NeuN, indicating neuronal activation of mTOR. However, relatively more P-S6 staining was co-localized with IBA1

in the SE+Veh group, where microglial cells were hypertrophied (an indication of microglial activation). Rapamycin decreased the P-S6 signal below basal levels in both sham and SE groups, and dramatically reduced IBA1 staining and reversed the microglial hypertrophy in the SE+Rap group. Our findings reveal that mTOR dysregulation occurs in neurons and reactive microglia, and that rapamycin suppresses microgliosis induced by SE. These data suggest that SE-induced mTOR dysregulation alters neuronal and glial properties, which together may contribute to the molecular and behavioral phenotypes associated with epileptogenesis.

P20 • A NET-mediated increase in DA reuptake: Implications for the treatment of L-DOPA–induced dyskinesia in Parkinson's disease

Tanya Chotibut*, Deana Apple, Michael Salvatore

Parkinson's disease (PD) is characterized by the loss of nigrostriatal dopamine (DA) neurons. For half a century, the main treatment for PD is L-DOPA, a precursor to DA. Unfortunately, chronic L-DOPA therapy induces abnormal involuntary movements termed L-DOPA–induced dyskinesia (LID) in over 90% of PD patients over time. The motoric deficits of LID may be mediated by an imbalance of monoamine neurotransmission. Our work suggests that DA uptake is not parallel to the loss of dopamine transporter (DAT) following 6-OHDA lesion, given that DA uptake does not decline as severely as DAT. Examining the effect of L-DOPA on this accelerated DA reuptake, we observed that L-DOPA blocked DA uptake to a nearly twofold greater extent in the lesioned striatum. Thus, L-DOPA could produce its therapeutic effect by increasing synaptic DA levels necessary for locomotion. However, this observed effect could accelerate the onset of LID based on the theory that increased dopaminergic signaling drives LID. We investigated if the norepinephrine transporter (NET) might be involved in this paradoxical enhancement of DA reuptake and found that DA uptake was norepinephrine-sensitive and that DA was less effective at inhibiting DA reuptake in lesioned striatum. In addition, we found NET to be upregulated within the lesioned striatum compared to its contralateral control. These results indicate that NET upregulation may be initially neuroprotective in PD, posing the prospect that L-DOPA may have efficacy in treating PD motor symptoms primarily through NET-mediated reuptake of L-DOPA. However, this effect could also be involved in LID manifestation, given that excessive DA may drive LID. Indeed, chronic NET blockade using Desipramine with L-DOPA administration seemed to worsen dyskinesia in rats compared to L-DOPA alone. Taken together, these data implicate NET as a novel therapeutic entity that when targeted, could not only slow PD progression but also prevent dyskinesia onset.

P21 • The genetic and neural correlates of risky decision making in young adults with antisocial substance disorder

Helena Yardley*, Manish Dalwani, Joseph Sakai, Susan Mikulich-Gilbertson, Thomas Crowley, Matthew McQueen

Background: Behavioral disinhibition (BD), an underlying vulnerability and a highly heritable trait, encapsulates separate behavioral manifestations, including impulsivity, conduct disorder, substance dependence, and other externalizing behaviors. We aim to uncover the common pathways associated with this behavior by combining functional magnetic resonance imaging (fMRI) and analysis of genomic pathways to shed light upon the genetic and neural determinants of these behaviors. *Methods:* We recruited 43 young adults scoring high for BD and antisocial substance disorder, aged 24–32 years from the Colorado Longitudinal Twin Study, as well as 41 age-matched controls. Functional scans were acquired using a risk-taking fMRI paradigm called the Colorado Balloon Game (CBG). A genome-wide association study (GWAS) pathway analysis of BD was conducted on a larger sample from which these subjects were recruited. We will then test for associations between brain activation during risky and cautious decisions in the BD subjects with the genetic summary score after adjusting for age and IQ. *Results:* Hi-BD subjects ($n = 43$, 21 males, mean age = 28.18 ± 1.53) in comparison with average BD subjects ($n = 41$, 19 males, mean age = 27.96 ± 1.71) made significantly higher risky button presses on the CBG (Hi-BD: mean 53.05 ± 15.78, Avg-BD: mean 46.39 ± 13.39, $p < 0.05$). We are awaiting results on BD vs. genetic score association and brain activation association with genetic score after adjusting for covariates. *Conclusion:* This study provides a unique opportunity to study individuals with high BD and understand if severity of BD is associated with genetic underpinnings, and to understand to what extent brain activation during risky and cautious decision making is associated with their genetic profile. Such an analysis would be the first step to understand the contribution of genetics to biological brain vulnerability during decision making in BD individuals.

P22 • Methamphetamine-induced neuronal necrosis occurs only in mice with electrographic seizure discharges

Denson Fujikawa*, Emil Pais, Ernesto Aviles, Jr.

We determined whether electrographic seizure discharges are necessary for methamphetamine (METH)-induced neuronal death. We implanted skull screws for EEG recording and 7 d later 12 25 g male C57BL/6 mice were given 40 mg/kg METH s.c. or i.p.; 6 controls received normal saline. EEGs, behavior, and rectal temperatures were monitored for 4 h, and 24 h after METH or saline injection they were euthanized and underwent transcardiac brain perfusion-fixation; brains were removed and processed for H & E staining of coronal

sections. Fifty-eight percent (7 of 12) had repetitive electrographic seizure discharges (RESDs). The time from METH injection to the appearance of RESDs was 47.8 ± 15.2 min, the duration of RESDs was 8.53 ± 4.21 min, and the total time that RESDs were present was 321 ± 124 min (mean ± SEM, n = 7). Only 43% of mice with RESDs (3 of 7) had the clonic forelimb movements characteristic of seizures induced in rodents (stage 3, Racine, 1972). Five of 7 mice with RESDs had acidophilic neurons (the light-microscopic appearance of necrotic neurons by electron microscopy) in the hippocampal CA1-CA3 regions and hilus, amygdala, piriform cortex and entorhinal cortex, and the overall mean damage scores were significantly greater than those for both the METH group without RESDs (0.69 ± 0.06 vs. 0.01 ± 0.01, $p < 0.001$) and controls (0.69 ± 0.06 vs 0.00 ± 0.00, $p < 0.001$). The damage scores for each brain region were also significantly greater than those for both the METH group without RESDs (except piriform cortex) and controls ($p < 0.001$ for each comparison). Maximum rectal temperatures did not differ significantly in mice with and without RESDs. Thus, in mice EEG recording to document RESDs is mandatory to document seizure activity. Moreover, METH-treated mice with RESDs had acidophilic neurons in many of the same brain regions as in generalized seizures, and RESDs are necessary for METH-induced neuronal necrosis.

P23 • The α1-antagonist doxazosin blocks cocaine-induced sensitization in rats and reduces cocaine use in cocaine-dependent individuals

Colin Haile*, Daryl Shorter, Patrick O'Malley, Jan Lindsay, James Mahoney, Richard DeLaGarza, Therese Kosten, Thomas Kosten, Thomas Newton

Medications that target norepinephrine neurotransmission alter the behavioral effects of cocaine (COC) and may be beneficial for stimulant-use disorders. In rats, we showed previously that the short-acting, α1-adrenergic antagonist prazosin blocked COC-induced reinstatement of COC-seeking. We also demonstrated that the longer-acting α1 antagonist doxazosin (DOX) significantly attenuated COC's subjective effects in cocaine-using volunteers. To further characterize DOX as a possible pharmacotherapy we assessed its impact on the development and expression of COC-induced sensitization in rats and conducted an out-patient pilot study to determine whether DOX would reduce COC consumption in treatment-seeking individuals with COC-use disorder. Rats (n = 6–8) were administered saline, COC (10mg/kg, IP), or DOX (0.3 or 1.0 mg/kg, IP), alone or in combination for 5 consecutive days (development). Following 10 days of no drug treatment, all rats were administered COC and sensitization was again assessed (expression). In a 13-week outpatient clinical trial participants received either placebo (N = 13), DOX (8mg/day) titrated over 4 weeks (DOX-fast, N = 9) or 8 weeks (DOX-slow, N = 8). All participants

received cognitive behavioral therapy and urine toxicology was assessed 3 times per week. In rats, the high dose (1.0mg/kg), but not the low dose (0.3mg/kg) of DOX significantly blocked the development ($p < 0.01$) and expression ($p < 0.001$) of COC sensitization. In the clinical trial, DOX fast-titration significantly increased COC-negative urines (45%) compared to the other groups (14%, DOX slow-titration; 16%, placebo; $p < 0.0001$) and was associated with a greater percentage of participants who achieved two or more consecutive weeks of abstinence (55%, DOX-fast; 12% DOX-slow; 7% for placebo; $p = 0.023$). These results lend additional support for DOX as a possible pharmacotherapy for COC-use disorder.

P24 • Estimating the dynamic repertoire of brain states by fMRI under anesthesia

Anthony Hudetz*, Xiping Liu, Siveshigan Pillay, Christopher Pawela

Tononi and Koch *(Annals NY Acad Sci* 2008) postulated that the level of consciousness is related to the repertoire of causal states available to brain. Functional magnetic resonance imaging (fMRI) can reveal various intrinsic functional networks of the brain that change dynamically over time. We developed a method to estimate the repertoire of brain states represented by the number of distinct networks accessed by the brain over time. We hypothesized that anesthetics remove consciousness by reducing the repertoire of brain states as reflected by a reduction in the temporal diversity of resting state networks. fMRI images were obtained in rats from 1 hour-long scans of whole brain resting-state BOLD activity (9.4T, 1s TR, 0.36x0.36x1 mm voxels) before and after loss of consciousness verified by simultaneous EEG, produced by propofol infusion at 20 and 40 mg/kg/h. RSNs were extracted with Independent Components Analysis (ICA) or Regional Homogeneity (ReHo) with thresholding using the sliding window method (200s window, 90% overlap). The repertoire of network states was estimated from the temporal variance of all-pairwise correlation coefficients of voxel time courses across the sliding windows. Correlation-time plots showed that the magnitude of voxel correlations within each network changed dynamically over time. The temporal dynamics was different at the two anesthetic levels. There was a greater proportion of high correlations at the higher dose, suggesting overall hyper-synchronization. The ReHo data suggested that networks became larger, consolidated, and less differentiated in deeper anesthesia. The temporal ReHo variance of networks with high ReHo values was also reduced suggesting a diminished repertoire by approximately 37%. In conclusion, the repertoire of brain states can be estimated from the temporal variance of resting state network correlations with changes consistent with loss of consciousness during propofol anesthesia.

P25 • Genome-wide expression profiling of brain areas involved in pain processing and depression in a mouse model of inflammatory bowel disease

William Lariviere*, Erin Young, David Benhayon, Margaret Kirshner, Matthew Coates, Brian Davis, Eva Szigethy

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by chronic relapsing inflammation of the gastrointestinal tract. Abdominal pain is a prevalent and disabling symptom of IBD, and appears to occur in the absence of active inflammation in a third of patients with UC and more than half of patients with CD. The relative dissociation of pain complaints from peripheral inflammatory events suggests that the CNS has a significant contribution. The current study examines gene expression changes in two brain areas, the prefrontal cortex (PFC) and the hippocampus (HC), which have been implicated in the pathogenesis of IBD by brain imaging studies. Gene expression profiles were determined in naïve mice and in mice that drank dextran sulfate sodium (DSS) water for seven days, an established model of bowel inflammation with similarities to UC. Illumina's genome-wide bead array (mouse WG6 V2) was used to assess changes in RNA expression levels induced by DSS. The expression of 167 and 176 genes were significantly affected in the PFC and HC, respectively. Of particular interest were fourfold increases in expression of genes for calcium-binding proteins, S100a5, S100a8, and S100a9, recently shown to have a role in pain processing, and a reduction in expression of Ttr (transthyretin or prealbumin) to half the levels seen in naïve mice that could contribute to the depressive phenotype observed in DSS animals and UC. Also of interest are observed changes in Egr1 and Sgk1 which, via transcriptional regulation and a variety of downstream events with known roles in nociception, could affect pain processing via CNS mechanisms. These results increase the priority of these targets for follow up studies of mechanisms in rodents and genetic association in human patients planned or in progress. This research was supported in part by the NIH and the University of Pittsburgh Office of the Senior Vice Chancellor for Health Sciences.

P26 • Examination of gene expression over time using tissue microarrays provides insight into the progressive compensatory responses within the nigrostriatal tract following intrastriatal 6-hydroxydopamine in the rat

Jack Lipton*, Nicholas Kanaan, Allyson Cole-Strauss, Kathy Steece-Collier, Caryl Sortwell, Brian Daley, Timothy Collier

The 6-hydroxydopamine (6OHDA) rat model of parkinsonism is among the first, and most commonly used, animal models of Parkinson's disease (PD). It provides insight into the compensatory changes that occur in the brain after DA neuron degeneration. We previously characterized the loss of substantia nigra (SN) DA neurons following intrastriatal 6OHDA injection in young adult male Sprague-Dawley rats. These data demonstrated a progressive loss of SN DA neurons over 6 weeks that then stabilizes. In order to better define the consequences of SN DA neuron loss on the neural and glial populations during and following nigrostriatal degeneration, tissue was collected from the striatum and SN from 6OHDA or vehicle treated, or naïve rats at 1, 2, 4, 6, and 16 weeks. Comprehensive gene-expression analysis using the Affymetrix Rat Gene 1.0ST array was conducted followed by analysis using Arraystar 5 (DNAStar) to detect significant differences in gene expression. Comparisons were conducted within the same treatment groups over time as well as across treatments within the same posttreatment interval. Longitudinal expression patterns were parsed using a k-means clustering algorithm as a method for finding patterns indicative of neuronal loss, upregulation in response to lesion or surgical damage exclusive of lesion. K-means clustering identified several previously unknown genes as potential pro-survival candidates. Comprehensive gene expression data from this 6OHDA model, when overlaid with experimental treatments shown to improve outcome, should enable a better understanding of their mechanistic underpinnings.

P27 • Deletion of PTEN in brain leads to autism-like behavioral deficits and learning and memory deficits

Joaquin Lugo*, Erin Arbuckle, Gregory Smith, Crina Floruta, Jessica Morrison, Obi Okonkwo, Nowrin Ahmed, Andy Holley

Rationale: Recent studies have shown that genetic deletion of genes that modulate the mTOR signaling pathway result in an autistic phenotype. Here, we evaluated the behavioral consequences of mTOR hyperactivation by using neuron subset-specific (NS-Pten) conditional knockout mice. *Methods:* Multiple cohorts of NS-Pten knockouts (KO), heterozygous, and wildtype mice were examined through a battery of behavioral tests. We first examined isolation-induced ultrasonic vocalizations in postnatal day 6, 8, 10, and 12

pups. We then examined their locomotion and anxiety in an open field test and in the elevated-plus maze test. We examined their social behavior in a three-chamber test and a social partition test. We examined their repetitive behavior in a marble-burying test and in the hole-board test. We examined their learning and memory through a standard fear conditioning test. *Results:* The KO mice displayed hyperactivity in the open field test compared to controls, $p < 0.001$; and spent significantly less time in the center of the open field, $p < 0.05$; exhibited less anxiety in the elevated-plus maze test, $p < 0.05$. They showed deficits in social behavior in the social chamber test, $p < 0.05$; and in the social partition test, $p < 0.05$. The KO pups did not show a change in the number or duration of ultrasonic vocalizations. The KO mice demonstrate alterations in both behavioral tests for repetitive behavior, both at $p < 0.01$. In addition to deficits in the behavioral features that describe autism, they have learning and memory deficits in contextual learning in the conditioned fear test, $p < 0.01$. *Conclusions:* These findings demonstrate that hyperactivation due to genetic deletion of Pten results in long-term alterations in social behavior, anxiety, repetitive behavior, and learning and memory. Our data demonstrates that NS-Pten mice are a valuable tool to examine the behavioral consequences due to mTOR hyperactivation.

P28 • Intoxicating concentrations of alcohol enhance GABAA slow synaptic inhibition

Bruce MacIver*, Edmund Posadas, Melis Sunay

Despite its widespread use and long history of research into the effects produced by alcohol, we still have only a poor understanding of the cellular and molecular actions produced by this small molecule. The most recent research indicates that ethanol acts on extrasynaptic "delta" subunit containing GABA receptors that generate "tonic" chloride currents in neurons. This effect would result in a general depression of neuronal excitability, since increasing tonic chloride currents would hyperpolarize neurons and decrease their ability to discharge action potentials. We tested this hypothesis, and also asked if ethanol acts on "non-tonic" GABAA synaptic receptors, by measuring field potential recordings from rat hippocampal brain slices. Glass microelectrodes were placed near the hippocampal CA1 cell body layer in brain slices prepared from 25- to 30-day- old male rats. Population spikes were evoked by stimulating Schaffer-collateral fibers with a bipolar tungsten electrode. Low concentrations of ethanol (0.1 vol % = 24 mM) enhanced GABAA "slow" receptor-mediated synaptic inhibition in hippocampus, seen as increased paired- pulse depression of population spikes, at 100 ms, but not at earlier paired-pulse time intervals. This indicates selective enhancement of GABAA "slow" receptors, but not the commonly measured "fast" receptor-mediated inhibition. No evidence for effects on GABAA "tonic" receptors was seen, since first pulse population spike

responses were not depressed by these same low concentrations, in fact, first pulse responses were slightly increased in amplitude. The lack of ethanol effect on tonic inhibition is likely due to the relatively low expression of delta subunit containing GABAA receptors in CA1 neurons. The small increase in amplitudes seen could come about by disinhibition of CA1 neurons from depressed fast inhibition, secondary to increased slow inhibition of fast interneurons.

P29 • Taste reward circuitry related brain structures characterize ill and recovered anorexia nervosa and bulimia nervosa

Guido K.W. Frank*, Megan E. Shott, Jennifer O. Hagman, Vijay A. Mittal

The pathophysiology of the eating disorder anorexia nervosa remains obscure, but structural brain alterations could be functionally important biomarkers. Here we assessed taste pleasantness and reward sensitivity in relation to brain structure, which might be related to food avoidance commonly seen in eating disorders. We applied VBM8/DARTEL brain analysis methods in individuals with restricting type currently ill (n = 19) or recovered-anorexia nervosa (n = 24), bulimia nervosa (n= 19) and healthy control women (n=24). All eating disorder groups showed increased ($p<0.05$ FWE corrected) gray matter volume of the medial orbitofrontal cortex (gyrus rectus). Manually tracing confirmed larger gyrus rectus volume, and predicted taste pleasantness across all groups ($R2=0.07$, $p<0.017$). The analyses also indicated other morphological differences between diagnostic categories ($p<0.05$ FWE corrected): Ill and recovered-anorexia nervosa had increased right, while bulimia nervosa had increased left antero-ventral insula gray matter volumes compared to controls. Furthermore, dorsal striatum volumes were reduced in recovered-anorexia and bulimia nervosa, and predicted sensitivity to reward in the eating disorder groups. The eating disorder groups showed reduced white matter in temporal and parietal areas. Notably, the results held when controlling for a range of covariates (e.g., age, depression, anxiety, medications). Brain structure in medial orbitofrontal cortex, insula and striatum is altered in eating disorders and suggests altered brain circuitry that has been associated with taste pleasantness and reward value.

P30 • Prenatal nicotine exposure augments the trigeminocardiac reflex via 5-HT2A/C–receptor activation

David Mendelowitz*, Christopher Gorini

The trigeminocardiac reflex is the most powerful autonomic reflex. Activation of trigeminal sensory fibers, by airborne irritants or water, evokes an increase in parasympathetic cardiac activity resulting in a pronounced bradycardia,

accompanied by peripheral vasoconstriction and apnea. While normally cardioprotective, exaggeration of this response can be fatal and has been implicated in various cardiorespiratory diseases such as sudden infant death syndrome (SIDS). Parasympathetic cardiac vagal neurons (CVNs) in the nucleus ambiguus (NA) play an integral role in mediating this reflex. Stimulation of trigeminal sensory afferents elicits a polysynaptic excitatory glutamatergic neurotransmission to CVNs. Previous work has shown this neurotransmission is facilitated by application of the 5-HT2A/C-receptor antagonist ketanserin (10μm). Prenatal nicotine (PNN) exposure is a major risk factor for SIDS and has been known to interfere with normal autoresuscitation. Additionally, PNN exposure induces an increase in endogenous 5-HT levels as well as 5-HT–receptor function abnormalities. In this study we examined the effects of PNN exposure on trigeminally evoked neurotransmission to CVNs. In contrast to control animals, those that have been prenatally exposed to nicotine have a significant decrease in glutamatergic neurotransmission upon application of the 5-HT2A/C–receptor antagonist kentanserin (10μm), indicating PNN elicits a change in brainstem 5-HT2A/C–receptor function within the trigeminalcardiac reflex. *Support:* NIH grants HL 59895, HL 72006, HL 49965 to DM and American Heart Association predoctoral fellowship to CG.

P31 • The dopamine receptor–interacting protein S100B: D2-receptor site of interaction and functional consequences

Kim Neve*, Hun-Joo Lee, David Buck, Yong Liu

S100B is a calcium-binding protein that participates in both extracellular and intracellular regulatory activities in the mammalian brain. We used a bacterial two-hybrid assay to identify a novel interaction between of S100B and the third cytoplasmic loop of the dopamine D2 receptor (D2-IC3). The binding of S100B to D2-IC3 was confirmed using polyHis pull-down and FLAG co-immunoprecipitation (co-IP) assays, and was highly sensitive to the presence of Ca2+ in the assay. In addition, the binding of heterologous S100B to full-length D2 receptor in HEK293 cells, and of endogenous S100B to endogenous D2 receptor in the rat neostriatum, was demonstrated by co-IP. Although sequence analysis suggested the presence of a putative S100B binding motif near the N-terminus of D2-IC3, additional FLAG co-IP assays identified binding determinants outside of that motif. S100B is thought of as a glial protein, but S100B-like immunoreactivity was detected in microtubule-associated protein-2 (MAP2) expressing cells in neostriatal neuronal cultures. Expression of S100B in HEK293 cells also stably expressing the D2 receptor significantly increased D2 receptor stimulation of extracellular signal-regulated kinases (ERKs), while causing little change in NGF-stimulated activation

of ERKs, and enhanced D2 receptor inhibition of adenylate cyclase. Taken together, these findings suggest that the interaction of S100B with the D2 dopamine receptor enhances D2-receptor function. (MH045372 and VA Merit Review)

P32 • Long-term behavioral and biochemical consequences of neonatal overexposure to NRG1 and NRG3 in mice

Clare Paterson*, Amanda Law

The bioactive domain of Neuregulin 1 (NRG1) crosses the murine blood–brain barrier (BBB) and overexposure in neonatal mice has long-term effects on adult behavior and neurotransmission. NRG3 (10q22-q23), a paralog of NRG1, is genetically associated with several neurodevelopmental and cognitive disorders. Cortical NRG3 expression is increased in schizophrenia patients and in association with risk polymorphisms. NRG3 is abundant in the human brain, is developmentally regulated and enriched during fetal life, but its biological role remains unknown. We sought to determine the consequences of developmental overexposure of NRG3 (vs. NRG1) using a peripheral injection paradigm in mice. We synthesized bioactive NRG3-EGF and demonstrate that the peptide crosses the neonatal BBB and activates ErbB signaling cascades. Male C57BL6 mice were injected with NRG3 or NRG1β (1mg/kg) from postnatal day 2–10 and assessed for general health, neurodevelopmental milestones, and adult behaviors related to schizophrenia. As previously reported, overexposure to NRG1 resulted in developmental abnormalities, including premature eye opening and tooth eruption and impairments in sensorimotor gating as measured by prepulse inhibition of startle (PPI). In comparison, NRG3 mice have intact sensorimotor gating, but do exhibit increased freezing behavior in response to restraint during the no stimulus portion of the task. General health screening revealed no effect of NRG1/3 on motoric and reflex abilities. NRG3 mice displayed increased grooming, suggestive of an obsessive compulsive phenotype. NRG1/3 exposure did not impact open field locomotor activity. Adult brain tissue from neonatally treated mice showed a persistent impact on the activity of the NRG-ErbB signaling pathway. These preliminary data suggest that albeit close family members, NRG1 and NRG3 have different neurodevelopmental functions. Studies are ongoing to determine the role of NRG3 as it relates to cognition and schizophrenia.

P33 • Analysis of putative stem and neural progenitor cell populations following CNS injury in the adult zebrafish

Jeffery Plunkett*, Lisandra Yut, Alejandra Cartagena, Fran Shabazz, Katarina Vajn, Alexis Tapanes-Castillo, Martin Oudega

Although postembryonic neurogenesis is limited in the mammalian brain, zebrafish *(Danio rerio)* retain multiple proliferative neurogenic and stem cell niches throughout adult life. The focus of our research is to study how injury to the central nervous system (CNS) affects the induction of neurogenic progenitor cell fates in the adult zebrafish brain. It has been well documented that in contrast to mammals, adult zebrafish recover functionally from a complete spinal cord transection injury. Damaged axons deriving from neurons within brainstem motor nuclei are able to regenerate across and beyond a spinal cord transection site. This ability is not characteristic for all brainstem neurons; different descending populations exhibit distinct regenerative responses, including failure to regenerate beyond the lesion site. We hypothesize that spinal cord injury will induce an endogenous, quiescent population of brainstem progenitor cells that act to integrate and enable the regenerative response seen following spinal cord injury in the fish. We are currently examining regenerative brainstem regions for stem cell marker expression pre- and post-injury. Prior to injury, Nestin and Sox 2 immunoreactivity were observed near ventricular areas, as well as in ventral brainstem regions, which contain nuclei from descending cerebrospinal projection neurons. These markers were also detected in similar brainstem regions following focal brainstem injury, as well as spinal cord injury. In addition, we have established an adult brainstem cell culture system which can be used to study CNS stem cells in vitro, as well as their effects on neurite outgrowth mechanisms in relation to permissive and nonpermissive environments.

P34 • Increased oxidative stress and loss of synaptic proteins in preclinical Alzheimer's disease

Stephen Scheff*, Mubeen Ansari

Alzheimer's disease (AD) manifests severe pathological changes in the central nervous system (CNS), including increased levels of amyloid, hyperphosphorylated tau, and synaptic loss. Synaptic dysfunction is a hallmark of the disease that associates with cognitive ability and level of dementia during the progression AD. Relatively recent imaging studies, coupled with neuropathology, suggest a long asymptomatic (preclinical) phase to AD, with cognitive function largely maintained despite substantial AD-type amyloid and tau pathology. Previous work from this laboratory reported a loss of synapses in the hippocampus of individuals with amnestic mild cognitive impairment (aMCI), which is believed to be an early stage of transition in AD. In the

present study, to test whether or not synapses were affected in the preclinical stage of the disease, we evaluated the hippocampal formation harvested from short postmortem autopsy samples obtained from three different cohorts: (1) individuals with no cognitive impairment (NCI) and low or no AD-type pathology (LP-NCI), (2) NCI individuals with high levels of AD-type pathology (HP-NCI), and (3) individuals with aMCI. Changes in several different key synaptic proteins were analyzed, along with possible changes in markers of oxidative stress. Compared to the age-matched LP-NCI cohort, individuals with HP-NCI and aMCI showed significant increases in numerous markers of oxidative stress. The hippocampal analysis of the HP-NCI and aMCI groups also revealed significant declines in key synaptic proteins. These results support the idea that in the preclinical stage of the disease, there already appears to be a defect in synaptic structure that may be related to levels of oxidative stress. The fact that the HP-NCI group continues to manifest adequate cognitive ability may be evidence for the use of cognitive reserve in this cohort. *Support:* AG27219; AG14449; AG028383

P35 • Escalation patterns of opioids used for pain treatment

Carrie Wade*, Leandro Vendruscolo, Joel Schlosburg, George Koob

Chronic pain is and continues to be a public health concern, costing approximately $600 billion annually in lost wages and health care costs. While opioids remain a first line of therapy in the treatment of severe chronic pain, practitioners remain cautious due to the potential for development of addiction. In fact, the current epidemic associated with oxycodone addiction has caused concern in the medical practice regarding appropriate pain therapy. This potential for abuse has led to formulations and altered routes of administration to decrease such risks. One such solution is the development of opioids with longer duration of action and half-life either through intrinsic properties of the ligand or through novel delivery systems. This type of pharmacokinetic profile is also thought to allow for slowed development of analgesic tolerance and an overall need for less drug. Opioids such as heroin and morphine are considered to be rewarding and reinforcing in animals by measures of conditioned place preference, escalation of self-administration, and increased progressive ratio breakpoints. All the aforementioned measures are dose-dependent, particularly by an IV route of administration. In this study we seek to examine the potential for escalation of self-administration of commonly used opioids for chronic pain therapy: oxycodone, which has a longer half-life; fentanyl which is commonly delivered by transdermal patch; and buprenorphine. In the first experiment we examined a dose response function of self-administration for each of the drugs.

The second experiment compared self-administration patterns of equivocal doses of heroin, oxycodone, fentanyl, and buprenorphine in both short and long access sessions. In the third experiment we examined naloxone-precipitated withdrawal at equivalent doses of the opioids tested. Overall, each drug produced similar self-administration patterns and withdrawal profiles with the exception of buprenorphine.

P36 • The role of glyoxalase 1 and methyglyoxal in diabetic neuropathy

Douglas Wright*, Megan Jack, Natalie Wilson, Janelle Ryals

Diabetes leads to the accelerated production of advanced glycation end products (AGEs) that alter proteins, thereby leading to neuronal dysfunction and diabetic neuropathy. The glyoxalase enzyme system, specifically glyoxalase I (GLO1), is responsible for detoxifying precursors of AGEs, such as methylglyoxal and other reactive dicarbonyls that are now known to affect important sodium channels. The purpose of our studies was to determine if expression differences of GLO1 within substrains of inbred mice play a role in the development of diabetic sensory neuropathy. BALB/cJ mice naturally express low levels of GLO1, while BALB/cByJ expressed approximately 10-fold higher levels of GLO1 on a similar genetic background due to increased copy numbers of GLO1. Accordingly, BALB/cByJ mice had elevated glyoxalase activity in the DRG levels compared to BALB/cJ mice. Five weeks following STZ injection, diabetic BALB/cJ mice developed a 68% increase in mechanical thresholds, characteristic of insensate neuropathy or loss of mechanical sensitivity. This behavior change correlated with a 38% reduction in intraepidermal nerve fiber density (IENFD). Diabetic BALB/cJ mice also had reduced expression of mitochondrial oxidative phosphorylation proteins in Complex I and V by 83% and 47%, respectively. Conversely, diabetic BALB/cByJ mice did not develop signs of neuropathy, changes in IENFD, or alterations in mitochondrial protein expression. These results suggest that alterations the levels of GLO1 expression and activity may strongly impact the levels of reactive dicarbonyls, which then may act to modify crucial proteins involved in sensory neuron function. These changes may play a role in the development of hyperglycemia-induced axonopathy in diabetic neuropathy. Together, these studies suggest a protective role for GLO1 in preventing reactive dicarbonyl-mediated alterations of neural complications associated with diabetes and the development of insensate neuropathy.

P37 • Assessing the effects of cocaine use on different forms of value-based behavior and learning

Heather Wied*, Nisha Cooch, Joshua Jones, Guillermo Esber, Federica Lucantonio, Will Johnson, Geoffrey Schoenbaum

Cocaine addiction is characterized by impaired decision-making as demonstrated by deficits in behaviors that rely on accurate value assessments. Evidence suggests that cocaine-induced changes in the orbitofrontal cortex may lead to difficulty with flexible and adaptive model-based behavior. We set out to test the hypothesis that exposure to cocaine through self-administration will disrupt the ability of animals to use inferred value to adequately guide behavior and new learning. Rats were taught to self-administer cocaine or sucrose for 14 days. After a four-week withdrawal period, we tested our hypothesis using sensory preconditioning and blocking, a behavioral task that can assess the contribution of different types of value signals to behavior and learning. Our data suggests that previous exposure to cocaine self-administration appears to disrupt both the expression of behavior and learning that is contingent upon inferred values; however, prior cocaine exposure does not appear to affect behavior or learning when normal behavior can be supported by cache values. These results are similar to the effects observed when the orbitofrontal cortex is inactivated during the critical sensory preconditioning probe test and during blocking. These results are consistent with the idea that dysfunction in decision making that arises in drug addiction is potentially mediated through neural deficits within the orbitofrontal cortex.

P38 • Mesolimbic dopamine signaling during decisions between options of differing utility

Monica Arnold*, Nick Hollon, Gerylin Gan, Mark Walton, Paul Phillips

Dopaminergic signaling in response to a reward-predictive cue scales with the value of the upcoming expected reward, suggesting phasic DA conveys quantitative information that might be useful for making cost/benefit decisions. However, a discrepancy remains regarding what cue-evoked DA encodes during decisions between options of differing utility. The present study evaluated cue-evoked phasic DA in the nucleus accumbens core using fast-scan cyclic voltammetry while rats preformed a mixed-contingency decision-making task. Each behavioral session included blocks of single-option "Forced" trials interleaved with blocks of two-option "Choice" trials. In the Moderate Cost condition, rats preferred a large reward obtained with moderate effort (4 food pellets/8 lever presses) over a small reward at low effort (1 pellet/4 presses).

Peak cue-evoked DA was greater for the large-reward compared to the small-reward option in Forced trials, suggesting cue-evoked DA encodes future reward value when the larger reward is preferred, a result we and others showed previously. In separate High Cost behavioral sessions, the small reward was preferred when the large reward was obtained with high effort (32+ presses) and peak cue-evoked DA levels were similar across trial type. However, DA concentration during high-reward Forced trials remained elevated longer after cue onset compared to the small-reward option, an effect also observed in Moderate Cost sessions. In both session types, DA release during choices for the preferred option was comparable to that in corresponding Forced trials. This demonstrates that DA release at Choice trial onset encodes the subsequently chosen outcome, even when it is the less valuable reward, a conclusion not confounded by the assessment of trials where animals choose the non-preferred reward. Our findings indicate that valuation of potential outcomes by DA release during concurrent choices take place after the subject has selected one of those options.

P39 • The medial prefrontal cortex inversely regulates toluene-induced alterations in excitatory synaptic transmission of mesolimbic dopamine neurons

Jacob Beckley*, Caitlin Evins, Hleb Fedarovich, Meghin Gilstrap, John Woodward

Toluene is an organic solvent that is voluntarily used by adolescents and adults for its intoxicating effects. Despite evidence showing that inhalants like toluene have abuse potential, little is known regarding toluene's actions on brain reward circuitry. To address this issue, adolescent rats were briefly exposed to either toluene vapor or air and whole-cell patch clamp electrophysiology was used to record excitatory postsynaptic currents (EPSCs) from retrogradely labeled subpopulations of ventral tegmental area (VTA) dopamine (DA) neurons. Two 10-minute exposures to toluene vapor (5700 ppm) enhanced the AMPA/NMDA (A/N) ratio of mesolimbic core DA neurons for up to three days while the same exposure protocol enhanced the A/N ratio of mesolimbic medial shell DA neurons for at least 21 days. In contrast, toluene had no effect on DA neurons projecting to the prefrontal cortex (PFC). In a separate experiment, subjects received an infusion of the GABAA modulators picrotoxin or baclofen/muscimol into the PFC just prior to toluene exposure in order to enhance or inhibit neuronal output from this region, respectively. Picrotoxin blocked toluene's enhancement of the A/N ratio of mesolimbic DA neurons, while the A/N ratio in baclofen/muscimol–treated animals was increased by a low dose of toluene that by itself had no effect. Preliminary results from optogenetics experiments show that selectively activating PFC-derived

glutamatergic terminals in a midbrain slice greatly enhances tonic firing of GABA neurons, while having little effect on mesolimbic DA neuron activity. Overall, these findings show that a brief exposure to toluene vapor causes a sustained and selective enhancement of mesolimbic but not mesocortical DA neuron excitatory synaptic strength and suggest that neurons in the mPFC actively oppose toluene-induced changes in synaptic plasticity of mesolimbic DA neurons, possibly by driving VTA GABAergic activity.

P40 • Central orexin2-receptor signalling regulates alcohol taking but not alcohol seeking in rats

Robyn Brown*, Shaun Khoo, Andrew Lawrence

Orexins are hypothalamic neuropeptides which bind to two GPCRs, orexin1 (OX1)- and orexin2 (OX2)-receptors. While a role for the OX1 receptor has been established in both alcohol reinforcement and alcohol-seeking behavior, the role of OX2 in these behavior is relatively less-studied. The aim of this study was to determine the role of OX2 receptors in alcohol-taking and alcohol-seeking behavior. Indiana alcohol-preferring rats (iP) rats were trained to self-administer ethanol (10% w/v) or sucrose (0.7–1% w/v) in the presence of reward-associated cues before being implanted with indwelling guide cannulae. The selective OX2-receptor antagonist TCS OX2 29 was administered intracerebroventricularly (ICV) to assess its effects on operant self-administration of alcohol and cue-induced reinstatement of alcohol seeking following extinction. ICV administration TCS OX2 29 at multiple doses (100, 300μg, n = 9 and 6, respectively) reduced self-administration of alcohol but had no impact on cue-induced alcohol seeking (0, 100, 300μg, n = 5, 6 and 6 respectively). In addition, ICV administration of TCS OX2 29 (100μg) was found to have no impact on self-administration of the natural reinforcer sucrose (n = 9). To determine where OX2 receptors were acting to regulate alcohol reinforcement, TCS OX2 29 (100μg) was microinjected into either the shell (n = 12) or core (n = 7) of the nucleus accumbens (NAc). Intra-NAc core but not shell infusions of TCS OX2 29 were found to decrease responding for alcohol. Collectively, these findings implicate OX2 receptors in the NAc core in mediating the reinforcing effects of alcohol. This effect appears to be drug-specific, as antagonism of central OX2 receptors had no impact on self-administration of the natural reinforcer sucrose. In addition, no impact of OX2-receptor antagonism was observed on cue-induced reinstatement of alcohol-seeking, suggesting that, unlike OX1 receptors, the role for OX2 does not extend to alcohol-seeking behavior.

P41 • Functional analysis of the schizophrenia-associated gene TCF4

Brady Maher*, Matthew Rannals, Aaron Briley

Schizophrenia (SZ) is a neurodevelopmental disorder with unknown pathophysiology. Genome-wide association studies (GWAS) have identified a number of loci associated with increased risk for SZ. One such locus is within an intron of the Transcription Factor 4 (TCF4) gene and mutations of TCF4 are known to cause Pitt Hopkins syndrome (PTHS), a rare neurodevelopmental disorder characterized by severe motor and mental retardation. Currently, the molecular mechanisms and underlying pathophysiology responsible for PTHS is unknown. Because TCF4 is associated with these two neurodevelopmental disorders, we are trying to identify its function during cortical development. To examine the function of TCF4 in the developing neocortex, we are using in utero electroporation to genetically manipulate layer 2/3 pyramidal cells of the rat medial prefrontal. We have designed two different shRNA constructs that target independent sequences within the TCF4 transcript and a recombinant TCF4 construct that expresses a human isoform of TCF4. Whole-cell electrophysiology experiments in acute brain slices from transfected rats show that knockdown of TCF4 results in a depolarized resting membrane potential compared to neurons expressing a control hairpin. In addition, TCF4 knockdown significantly decreases action potential output and results in the emergence of depolarization block not observed in control recordings. These results suggest a potential pathophysiology that may underlie the behavioral deficits observed in SZ and PTHS patients.

P42 • DREADDed drug seeking: Isolating the contribution of corticostriatal projections in motivation for cocaine self-administration

Susan Ferguson*, Kerry Kerstetter, John Neumaier

The cortico-basal ganglia system is a complex neural network involved in motivation and reward, and dysfunction of this circuitry has been implicated in drug addiction. Studies have found that the nucleus accumbens shell (NAcsh) regulates motivation for self-administration of cocaine. Although glutamate signaling within the NAcsh regulates striatal neuron plasticity, the primary source of glutamatergic drive has not been well-established. For example, cortical pyramidal neurons provide a major excitatory input into the NAcsh, but the NAcsh also receives glutamatergic inputs from other brain regions, such as

the thalamus, and the cortex projects to other areas of the basal ganglia circuit, as well as to structures that feed into the NAcsh. How cortical inputs into the NAcsh in particular regulate drug seeking has not been well-characterized. To address this, we used a Cre recombinase-dependent viral vector based flip-excision (FLEX) switch system to express engineered Gi/o-coupled DREADD (Designer Receptor Exclusively Activated by a Designer Drug; hM4Di) receptors selectively in prelimbic cortical (PLC) neurons that project to the NAcsh. Activation of hM4Di receptors by clozapine-N-oxide leads to a transient reduction of neuronal excitability. Following IV catheter surgery and viral expression of hM4Di receptors in PLC neurons, male Long Evans rats were given cocaine self-administration (0.75/mg/kg/infusion) training under a fixed-interval 20-s schedule followed by a progressive ratio (PR) schedule of reinforcement. We found that increasing Gi/o signaling selectively in PCL projections to NACsh significantly increases active lever responding for cocaine, as well as break point and cocaine intake. These data demonstrate that reducing excitability of PCL neurons increases motivation for cocaine and supports the idea that drug exposure leads to a loss of top-down control in cortical inputs that contribute to behaviors that are associated with a transition to addiction.

P43 • The behavioral profile of the BDNF knockout rat

Melissa Glenn*, Robyn St. Laurent, Sam Helm

Brain-derived neurotrophic factor (BDNF) is an essential growth factor for the neural plastic changes that occur in response to learning and enrichment. Diminished expression of it is linked to psychological disorders, including depression, addiction, and schizophrenia. The aim of this study was to characterize emotion and reward in rats with one copy of the gene. To do this, a battery of behavioral tests were conducted on adult male and female Sprague Dawley rats that were heterozygous for the gene (BDNF+/–; SAGE Labs) or intact (WT): emotional reactivity was assessed using the open field, elevated plus maze, and forced swimming tests; drug reward and relapse was assessed using conditioned place preference for cocaine; and learning and memory was assessed using a spatial reference memory task in a water maze. The behavioral findings were compelling and consistent: compared to WT, BDNF+/– rats were more anxious in the open field and on the elevated plus maze, exhibited increased despair in the forced swimming test, and displayed diminished responses to cocaine. Overall, spatial learning was only mildly affected by the deletion. Plasma BDNF levels were confirmed to be significantly lowered in BDNF+/– rats compared to WT and were used to analyze the relation of individual BDNF levels to behavioral profiles. The results from the battery of behavioral tests highlight a central role for BDNF in behaviors that are

affected in depression and addiction and lay the foundation for future work on neuroprotection via this system. Work on neural and epigenomic outcomes is ongoing and will shed light on the hypotheses that these processes are excellent targets for mechanisms of neuroprotection. Based on this work, we also underscore the use of these rats as a preferred model system for psychological constructs that are pathological in humans. *Support:* NCRR 5P20RR016463-12; NIGMS 8P20GM103423-12 from NIH to MJG.

P44 • Posttraining optogenetic manipulations of basolateral amygdala activity modulate the consolidation of inhibitory avoidance memory in rats

Ryan LaLumiere*, Mary Huff, Rachel Miller, Karl Deisseroth, David Moorman

Memory consolidation studies, including those examining the role of the basolateral amygdala (BLA), have traditionally used techniques limited in their temporal and spatial precision. The development of optogenetics provides increased precision in the control of neuronal activity that can be used to address the temporal nature of the modulation of memory consolidation. The present experiments, therefore, investigated whether optogenetically stimulating and inhibiting BLA activity immediately after training on an inhibitory avoidance (IA) task enhances and impairs retention, respectively. The BLA of male Sprague-Dawley rats was transduced to express either channelrhodopsin-2 (ChR2) or ArchT. Immediately after IA training, rats received optical stimulation or inhibition of the BLA, and two days later, rats' retention was tested. The results indicate that stimulation of ChR2-expressing neurons in the BLA, using trains of 40 Hz light pulses, enhanced retention, consistent with recording studies suggesting the importance of BLA activity at this frequency. Identical stimulation given to the BLA of rats that did not receive a footshock during training had no effect on retention. Inhibition of ArchT-expressing neurons in the BLA for 15 min, but not 1 min, significantly impaired retention. Control experiments found that illumination alone of the BLA, following the same illumination parameters of each experiment, had no effect on retention. In addition, 15 min of BLA inhibition given 3 h after IA training had no effect on retention. These findings provide critical evidence of the importance of specific patterns of activity in the BLA during consolidation and the temporal window in which BLA activity is necessary for normal consolidation. Moreover, the present results indicate that optogenetic manipulations can be used to alter activity after a learning event to investigate the processes underlying memory consolidation.

P45 • NMDA modulates adult prefrontal cortical interneurons

Eastman Lewis*, Patricio O'Donnell

Disinhibited cortical circuits are a central element in current views of schizophrenia pathophysiology. Noncompeting NMDA-receptor antagonists, known to be psychotomimetic in adults, have been proposed to exert their effect primarily by blocking receptors in fast-spiking (FS) interneurons yielding increased pyramidal cell activity. Reductions in NMDA signaling early in development, either globally using pharmacological approaches or specifically in parvalbumin (PV) positive interneurons have been shown to lead to behavioral and electrophysiological phenotypes resembling phenomena observed in schizophrenia patients (Belforte et al, 2010). However, it has been recently demonstrated that the contribution of NMDA-receptor activation to excitatory postsynaptic potentials (EPSP) and currents (EPSC) is minimal compared to that of pyramidal cells (Rotaru et al, 2011), calling into question the role NMDA receptors play in FS cells within the adult cortex. Interestingly, cortical FS interneurons show a significant tonic NMDA current in vitro (Povysheva and Johnson, 2012), suggesting that while synaptic events onto FS cells might not have a substantial NMDA component, NMDA activation could regulate FS cell activity via extrasynaptic NMDA receptors. We tested this possibility with whole-cell recordings in brain slices to measure changes in FS cell excitability in the rat medial prefrontal cortex (mPFC) in response to bath application of NMDA. We have found that bath application of NMDA leads to an increase in FS interneuron excitability which is accompanied by a slight depolarization. These responses were not due to activation of other cell types and glutamate release, as AMPA receptors were blocked by CNQX throughout each recording. Our results suggest that even in the absence of a significant synaptic NMDA component, extrasynaptic NDMA activation could play a meaningful role in regulating the activity of FS interneurons.

P46 • The development of high-affinity inhibitors toward the allosteric binding site in the serotonin transporter

Claus Løland*, Per Plenge, Benny Bang-Andersen, Jacob Andersen, Ulrik Gether, Kristian Stroemgaard, Anders Kristensen, Klaus Bøgesø

The serotonin transporter (SERT) plays a key role in regulating serotonin (5-HT) homeostasis and is the major pharmacological target for antidepressants (ADs) such as S-citalopram (S-CIT) in the treatment of depression and anxiety disorders. Data have supported the existence in SERT of a allosteric binding site for inhibitors such as S-CIT. Binding of S-CIT to the allosteric site (S2) modulates ligand binding properties of the primary

high-affinity binding site (S1) and has been suggested to cause the faster onset of action of S-CIT. We have recently localized the allosteric site to the extracellular vestibule (S2) of SERT. Thus, we hypothesized that a selective high-affinity allosteric inhibitor could possess a new clinical potential compared to the current ADs either as separate entities or as an adjuvant therapy improving the clinical efficacy of existing drugs targeting S1. Here, we present a new compound, Lu AE56461, that binds to the allosteric binding site with a potency of 110[100,120] nM (mean[SE interval]). This is a 50-fold higher affinity than found for S-CIT, the most potent allosteric modulator found so far. In addition, Lu AE56461 has a 10-fold selectivity for the S2 site relative to the S1, which makes it the first compound reported to posses S2 selectivity. Finally, Lu AE56461 inhibited [3H]5-HT uptake with a potency equal to its S2 affinity, suggesting that binding to the allosteric binding site has functional implications for substance transport in SERT.

P47 • Cocaine, but not morphine, self-administration impairs overexpectation-induced extinction learning

Federica Lucantonio*, Yavin Shaham, Geoffrey Schoenbaum

The OFC has been implicated in adaptive responding and aspects of addiction may be due to drug-induced changes in OFC (Lucantonio et al, *Nature Neuroscience,* 2012). Consistent with this hypothesis, we have shown that cocaine-experienced rats failed to show extinction in response to overexpectation but exhibited normal extinction in response to reward omission in a Pavlovian overexpectation task (Lucantonio et al., *SFN Abstracts,* 2010). Learning in this task is dependent on OFC, likely due to real-time integration of the cue-evoked expectations for reward in OFC during the critical learning phase (Takahashi et al, *Neuron,* 2009).We have demonstrated that cocaine disrupts this normal ability of OFC to signal estimates about future outcomes (Lucantonio et al., *SFN Abstracts,* 2011). Here, we explored if similar impairments might be observed in rats trained to self-administer the opiate drug morphine. Rats were trained to self-administer morphine or sucrose for 3 hours/day for 14 daily sessions. After morphine or sucrose self-administration training and a three-week withdrawal period, rats were trained in the Pavlovian overexpectation task. In the first stage, three cues were separately trained as signals for reward. In the second stage, two of the three cues were presented in compound followed by the same reward. Subsequent test trials with the cues by themselves typically demonstrate a reduction in conditioned responding to the compounded cues. This effect is thought to reflect extinction induced by violation of summed expectations for reward during compound training. We found that morphine-experienced rats showed normal extinction in response to overexpectation and reward omission. This lack of effect contrasts with the

performance of cocaine-experience rats. The differences between the long-term effects of morphine and cocaine may have implications for understanding how particular brain circuits are modified by exposure to opiate versus psychostimulant drugs.

P48 • Cross-modal plasticity of excitatory synapses in auditory cortex following visual deprivation

Emily Petrus*, Hey-Kyoung Lee

Loss of vision triggers sensory compensation in the remaining senses. This is evident in blind individuals who show enhanced tone discrimination (Gougoux et al, 2004) and sound localization (Roder et al, 1999). Cross-modal plasticity can be rapidly recruited in adults, with only a few days of blindfolding resulting in enhanced Braille reading capacity and activation of visual cortex during these tasks (Merabet, 2008). We previously reported that 1 week of dark exposure (DE) in mice produces both unimodal and cross-modal changes in AMPA receptor–mediated miniature excitatory postsynaptic current (mEPSC) amplitudes in visual cortex (V1) and other primary sensory cortices, including auditory cortex (A1) (Goel et al, 2006). We hypothesize that these synaptic changes are the mechanism underlying sensory compensation reported in human cross-modal studies. The polarity of DE-induced unimodal changes in V1 is lamina-dependent, as mEPSC amplitude increases in layer 2/3 (L2/3) (Goel et al, 2006), and decreases in L6 (Petrus et al, 2011). The present study examines whether cross-modal plasticity in DE mice is lamina specific, and if a specific input drives the postsynaptic changes. We found that in A1, 1 week of DE decreases L2/3 mEPSC amplitude, but increases those of L4. The L2/3 and L4 changes are recruited through adulthood (postnatal age 90 days, p90). An increase in L4 mEPSC amplitude suggests that there might be an increase in signal-to-noise ratio for enhanced auditory processing following the loss of vision. We are currently examining whether the increase in L4 mEPSCs reflects changes in thalamic inputs onto these neurons by expressing channel rhodopsin in the auditory thalamus.

P49 • Ovarian steroids increase dendritic spine–dependent PSD-95 in the serotonergic dorsal raphe nucleus of macaques

Heidi Rivera*, Cynthia L. Bethea

Rhesus macaques have a reproductive cycle that is identical to women. They also express estrogen and progestin receptors in serotonin neurons, unlike rodents. Thus, they provide an optimal animal model to study the action of ovarian steroids on serotonin neurons. Dendritic spines are the basic structural

units of neuronal plasticity. Intracellular signaling cascades that promote spinogenesis are centered on RhoGTPases. We recently found that ovarian steroids increase gene and protein expression of the RhoGTPases, RhoA and Cdc42, in serotonin neurons (PMIDs: 19687787, 22342969). In the present study, we determined whether an anatomical increase in spines occurs in the dorsal raphe via detection of the spine marker protein, postsynaptic density 95 (PSD-95). PSD-95 is a major scaffolding protein located at the postsynaptic density of excitatory synapses. Adult ovariectomized (Ovx) monkeys were treated with Silastic implants filled with estradiol (E), progesterone (P), or a combination of E and P (E + P) for 1 month (n = 3/group). Sections through the dorsal raphe first underwent protease pretreatment and then were immunostained with immunogold silver staining for PSD-95. Gold particles were counted with StereoInvestigator (Microbrightfield) on a Zeiss Axioplan. The total number of PSD-95-positive puncta was determined with stereology across 4 levels of the dorsal raphe. There was a significant difference between groups in the total number of puncta (ANOVA, $P = 0.0438$). E, P, and E+P increased the total number of puncta relative to the Ovx group (Newman-Keul's posthoc $P < 0.05$ all). In summary, we have shown in macaques that ovarian steroids act to increase gene and protein expression of RhoGTPases involved in spinogenesis, and that an increased number of spines and/or synapses result from this action. Increased spinogenesis on serotonin dendrites would facilitate excitatory glutamatergic input and in turn, increase serotonin neuronal activity throughout the brain.

P50 • Imaging the motility of inositol trisphosphate receptors in intact mammalian cells using single-particle-tracking photoactivated localization microscopy (sptPALM)

Ian Smith*, Divya Swaminathan, Ian Parker

Inositol trisphosphate receptors (IP3Rs) are calcium-permeable channels in the membrane of the endoplasmic reticulum (ER) that liberate calcium to generate cytosolic calcium signals that control diverse cellular functions, including gene expression, secretion, and synaptic plasticity. The spatial distribution of these channels is crucial in determining the patterning of intracellular calcium signals. The mechanisms underlying the aggregation and maintenance of IP3Rs in clusters are controversial. Local calcium signals arise at just a few, fixed locations within a cell, suggesting clusters are stable entities; and calcium blips generated by 'lone' IP3Rs are also immotile. In contrast, GFP-tagged or immunostained IP3Rs show a dense distribution throughout a cell. Moreover, the majority IP3Rs can diffuse freely within the ER membrane, and aggregate into clusters following sustained activation of IP3 signaling

and/or cytosolic calcium elevation. These apparently different behaviors may be explained because calcium imaging studies detect only functional IP3Rs, whereas imaging studies utilizing immunostaining or GFP-tagged IP3Rs report on the entire population of IP3R proteins. We therefore hypothesize that a majority of IP3Rs are motile, but functionally unresponsive. Local calcium signals arise, instead, from a small subset of IP3Rs that are anchored, individually or in clusters, by association with static cytoskeletal structures and possibly as a consequence of this anchoring, display high sensitivity to IP3 to calcium signals. To test this hypothesis, we have utilized the new generation of photoactivatable genetically encoded proteins to track the motility of thousands of individual IP3R molecules with nanoscale spatial resolution and millisecond temporal resolution (sptPALM). We find that IP3Rs can be distinguished into two groups with relatively high or low/zero motility and that the apparently immotile IP3Rs are preferentially grouped within tight clusters.

P51 • Cognition-enhancing actions of psychostimulants are dependent on noradrenergic α2- and dopamine D1-receptors within the prefrontal cortex

Robert Spencer*, Craig Berridge

Psychostimulants, including methylphenidate (MPH, Ritalin), enhance a variety of cognitive/behavioral functions dependent on the prefrontal cortex (PFC) and extended frontostriatal circuitry. These actions are seen in individuals with and without Attention Deficit Hyperactivity Disorder (ADHD) as well as normal animal subjects. Despite widespread use of these drugs, the brain regions/receptor mechanisms involved in their cognition-enhancing and therapeutic effects are poorly understood. The current studies examined the degree to which MPH acts within distinct frontostriatal subfields to improve PFC-dependent cognition as measured in a delayed-response test of spatial working memory. Additionally, these studies investigated the receptor mechanisms involved in the cognition-enhancing actions of intra-PFC infused MPH. We observed that MPH (0.03-8.0 μg/500 nl) infused into the dorsomedial PFC (dorsal prelimbic and anterior cingulate cortex), but not ventromedial PFC (infralimbic) or dorsomedial striatum, elicited an inverted-U shaped facilitation of PFC-dependent cognition as measured in this task. Furthermore, this improvement was blocked with the concurrent infusion of either a NE α2 (Atipamezole; 1.25 μg/500 nl) or DA D1 (Sch23390; 0.5 μg/500nl) receptor antagonist at doses that did not alter performance when given alone. These observations provide the first definitive evidence that psychostimulants act at NE α2 and DA D1 receptors directly within the PFC to enhance cognition.

P52 • Optogenetic manipulations of relapse neurocircuitry during cue-induced reinstatement of cocaine seeking

Michael Stefanik*, Peter Kalivas

With repeated drug use, environmental stimuli become conditioned cues which can elicit craving and trigger relapse to drug seeking. Animal models of drug seeking have implicated the basolateral amygdala (BLA) and its afferent projections in conditioned reward. One of the outputs thought to be involved is to the nucleus accumbens (NAc). The NAc receives a diverse number of projections and is responsible in part for optimizing reactions to an ever-changing environment as well as solidifying these responses into well-learned behaviors. Exposure to cocaine is thought to cause a dysregulation in NAc-related circuitry and is hypothesized to underlie persistent, maladaptive drug seeking. Recent work utilizing optogenetics has provided evidence that projection-specific inhibition may produce different effects on motivated behaviors than previously used, less specific, nuclei-centric inhibition of neural activity. Current work uses optogenetics to study the role of the BLA and its afferents to the NAc during cue-induced relapse to cocaine seeking. Male Sprague-Dawley rats underwent surgeries for viral microinjections of adeno-associated virus (AAV) containing the coding sequence for the proton pump archaerhodopsin (ArchT) with a CAG promoter into the BLA, implantation of bilateral guide cannulae aimed at the BLA or NAc, and implantation of intra-jugular venous catheters. The combination of injection and cannula sites allowed for targeting of cell bodies or their terminal fields in other regions. Animals then went through 12 days each of cocaine self-administration followed by extinction training (2 hr/day). Following extinction, animals underwent cue-primed reinstatement of lever pressing along with the presence/absence of optical inhibition. Initial work confirms that BLA inactivation is sufficient to block cue-induced reinstatement. Current studies are underway to assess the influence of BLA projections to the NAc and other regions during drug seeking.

P53 • Noncompeting NMDA-receptor antagonists alter auditory event-related potentials (ERP) in the rat

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

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

the intact skull in several locations in order to measure signals from multiple regions simultaneously in a manner similar to the way EEG signals are acquired in humans. In addition, we unilaterally implanted deep electrodes into the auditory cortex and the hippocampus to measure local field potentials (LFP) concurrent with surface EEG signals. In this study we recorded EEG and LFP in response to a battery of auditory stimulation paradigms, including auditory steady state responses (ASSR) to click trains, pitch oddball, and paired-click sensory gating. We were able to elicit mismatch negativity (MMN) during oddball stimuli, entrainment to the steady-state click trains and sensory gating to the paired clicks. We also have begun to examine the effects of acute and chronic NMDA receptor antagonist administration (MK-801; 0.1 mg/kg i.p.) on these ERP and EEG signals. We have found that acute MK-801 significantly increases power in gamma and high gamma bands ($p = 0.012$ and $p = 0.015$, respectively). Additionally, acute MK-801 significantly increases intertrial coherence (ITC) during the 20 Hz ASSR task ($p = 0.012$). No significant effects of chronic MK-801 were found, suggesting that the action of acute MK-801 may be different from that of chronic exposure. This study illustrates the feasibility of ERP measures in freely moving rodents, and demonstrates that these signals are affected by NMDAR antagonism in a way similar to human subjects.

P54 • Basolateral amygdala-evoked heterosynaptic suppression of inputs from other temporal cortical structures in the prefrontal cortex

Hugo Tejeda*, Patricio O'Donnell

The prefrontal cortex is critical for executive control, flexible behavior, and working memory. Prefrontal function is dependent on interconnected circuits, including limbic substrates (i.e., amygdala and hippocampus), and other cortices. Afferents from the amygdala are likely providing information related to emotional states and may adjust PFC function and the impact of other inputs. It is conceivable that strong amygdala activation reduces PFC synaptic responses to other afferents. The present study was aimed at examining the interactions between the basolateral amygdala (BLA) and other temporal cortical nuclei including the ventral hippocampus (VH) and the amygdalopiriform transition area (APiri), an associative cortical structure, using in vivo intracellular recordings. Medial PFC (mPFC) neurons were recorded, and synaptic responses were generated by electrical stimulation of the BLA and fimbria (ventral hippocampal fiber bundle innervating the forebrain) or APiri. A baseline pulse (S1) was applied to the fimbria or APiri followed by conditioning burst stimulation of the BLA (10 pulses; 10, 20, or 50 Hz). A test synaptic response (S2) was evoked at varying delays after the last BLA pulse

in the train. BLA burst stimulation attenuated fimbria- and APiri-evoked S2 EPSP amplitudes in a time- and frequency-dependent manner. These effects were also observed using optical stimulation of the fimbria in rats expressing channelrhodopsin-2 in ventral hippocampal neurons. This effect is activity-dependent as single pulse BLA stimulation is without effect on fimbria- or APiri-evoked S2 responses at all delays. Heterosynaptic suppression of temporal cortical inputs is unidirectional as fimbria and APiri train stimulation did not alter BLA-evoked responses. BLA-evoked heterosynaptic suppression of temporal cortical inputs could be critical for the selection of the appropriate behavioral response to stimuli that activate the amygdala.

P55 • The effects of hESC-derived motor neuron transplantation on respiratory function in the SMNdelta7 mouse model of SMA

Tanya Wyatt*, Monica Siegenthaler, Gabriel Nistor, Tatiana Hernandez, Rockelle Robles, Bita Alaghebandan, Chris Airriess, Hans S Keirstead

Background: Infantile spinal muscular atrophy (SMA) is the most common and severe hereditary neurological disease in childhood. The disease ultimately becomes fatal due to the progressive loss of lower motor neurons. Currently, there is no treatment that can change the course of the disease; however, stem cells are garnering attention as a potential treatment for SMA. Advances in stem cell technology represent a foreseeable alternative in alleviating the deficits seen in SMA. We have devised protocols to produce hESC derived-motor neuron progenitors (hMNPs) in a clinically compliant manner. hMNPs secrete multiple growth factors that have several beneficial effects, including enhanced neurite outgrowth, neuronal protection, prevention of muscle atrophy, and improved motor performance. Here we investigate the effects of hMNP transplantation on respiration in the SMNdelta7 mouse model of SMA. *Results:* SMNdelta7 pups transplanted with hMNPs demonstrate improvements in respiratory parameters as measured by pulse oximetry and in neuromuscular junction (NMJ) pathology of the intercostal muscles as indicated with IHC. Treated mice demonstrate improved arterial oxygen saturation, breathing rate, and heart rate as compared to untreated mice. Treated mice have significantly more fully innervated NMJs as compared to untreated mice, whereas untreated mice have significantly more denervated and partially denervated NMJs. Furthermore, treated mice have significantly more mature NMJ morphology as compared to untreated mice. *Conclusions:* Transplantation of hMNPs in the SMNdelta7 mouse provides evidence for benefit to muscle function, and preservation of

muscle integrity and connectivity. Previous studies that demonstrate functional and histological benefits in other animal models of motor neuron loss support these findings. In conclusion, hMNP transplantation has great potential as a therapy for SMA in which quality of life and respiratory function can be improved.

P56 • The relationship between circadian and cognitive dysfunction in bipolar disorder

Raphael Braga*, Anil Malhotra, Katherine Burdick

A considerable cognitive heterogeneity has been found in bipolar disorder (BPD). Although at the group level neurocognitive deficits are present in euthymic BPD patients, 30–50% of BPD patients present with performance comparable to healthy controls.

WITHDRAWN

Several clinical factors appear to increase cognitive impairment. Sleep dysfunction is a cardinal feature of BPD, and it has been associated with reduced quality of life and poor functional outcomes. The relationship between sleep quality and neurocognition seems intuitive. One study showed an association between circadian disruption and executive functioning impairment. However, no other studies have systematically addressed this question.

In the present report we describe the prevalence of sleep dysfunction and its possible relationship with cognition in BPD. We evaluated a subset data from an R03 on cognitive and clinical correlates of suicide. Forty-two BPD euthymic patients were included. Sleep quality was inferred from HRSD scores. Data collection is still ongoing for the current project. Additional data will be presented at the meeting.

Despite affective remission, 43% of patients had insomnia; 40% had psychomotor retardation; and 76% reported anergia, suggesting a high rate of trait-like sleep and activity-based abnormalities during remission. To directly test the relationship between sleep quality and cognition in BPD, (Table 1) depicts correlational data from a sample of 15 euthymic patients who completed the MATRICS Consensus Cognitive Battery (MCCB), Sleep Disturbance (Pittsburgh Sleep Quality Scale; PSQ), and Daytime Wakefulness (Epworth Sleepiness Scale; ESS) ratings. These data provide compelling support for a relationship between circadian function and neurocognition in patients with BPD and suggest the potential utility in targeting sleep quality to influence cognitive performance and quality of life.

P57 • Selective reduction of anxiety by alcohol: Psychophysiological evidence from laboratory manipulations of threat uncertainty

John Curtin*, Kathryn Hefner, Christine Moberg, Daniel Bradford

Accumulating evidence suggests that anxiety and fear are distinct affective processes with separable neurobiological substrates. Recent research has used uncertain vs. certain threats to elicit anxiety vs. fear, respectively. Basic affective neuroscience research in animals indicates that CRF-sensitive pathways through the lateral division of the bed nucleus of the stria terminalis may be involved selectively in the response to uncertain threat. We present data from four experiments in humans that used novel manipulations of threat uncertainty to test for selective effects of alcohol on anxiety but not fear. Across experiments, threat uncertainty was manipulated via unpredictable (vs. predictable) shock administration, low (vs. high) probability shock, temporally uncertain (vs. certain) shock, and uncertain magnitude (vs. certain/low and certain/high magnitude) shock. Three of the four experiments used a moderate dose of alcohol (target BAC of 0.08%). The final experiment examined alcohol dose response across a range of BACs from 0.00% to 0.12%. Startle potentiation served as the primary measure of negative affective response in all experiments. The use of startle potentiation provides an important translational bridge to similar research on the neurocircuitry of anxiety and fear in rodents and nonhuman primates. Across experiments, alcohol produced consistent, robust, and significantly greater reduction in startle potentiation during uncertain than certain threat. Individual differences analyses provided some evidence that alcohol effects moderated by trait-negative emotionality. These results help clarify the reinforcing effects of alcohol and may partially explain the pattern of comorbitiy between alcoholism and anxiety disorders. Furthermore, they provide a foundation to examine putative stress neuroadaptations that may result from chronic alcohol or other drug use.

P58 • A triple dissociation between delay, trace and contextual fear conditioning in glutaminase-deficient mice

Inna Gaisler-Salomon*, Liran Hazan

Fear conditioning (FC) paradigms are commonly used to measure associative learning in rodents. Glutaminase-deficient mice (GLS1 hets), with reduced glutamate recycling and release, were previously reported to display reduced hippocampal function and memory of contextual cues in a delay FC paradigm, where a tone (conditioned stimulus; CS) coterminates by a foot-shock (unconditioned stimulus; US). We hypothesized that this deficit in GLS1 hets reflects an inability to acquire or integrate non-salient cues, rather than

contextual information per se. We therefore tested contextual FC in the absence of a CS, and found that GLS1 hets indeed performed normally in this task. Surprisingly, when we used a trace FC paradigm, where a 20-sec delay separated CS from US, GLS1 hets displayed enhanced cued FC, and continued to show reduced memory of contextual cues. Others have shown that a delay between CS and US alters the relative salience of tone and context; thus, this latter finding suggests that glutaminase deficiency leads to preferential processing of a salient CS at the expense of contextual information. It also implies that other brain regions are involved in trace FC, and may compensate for lost hippocampal function in GLS1 hets. We measured the expression of the immediate early gene Arc in the hippocampus and medial prefrontal cortex of GLS1 hets at baseline and following trace fear conditioning. Our findings confirm previous fMRI findings of decreased baseline hippocampal activity, and point to aberrant activation of prefrontal cortex in GLS1 hets following trace and contextual FC. Taken together, these findings indicate that brain glutaminase deficiency leads to pattern integration deficits, which result in deficient processing of contextual cues in delay and trace FC, and that an adequate balance between salient and non-salient cues requires intact hippocampal and mPFC function.

P59 • Thermal hyposensitivity in novel knockout rat models for pain research

Kevin Gamber*, Rachel Henry, Lara Little, Andre Chambers, Aaron McCoy, Guojun Zhao, Diana Ji, Xiaoxia Cui, Edward Weinstein

For pain research, rats, rather than mice, have been the preferred historical model. Rats are less sensitive to stress-induced analgesia, and behavioral assays of nociception were first developed in the rat. The larger size of the rat makes it more amenable for surgeries (such as those required for assays of neuropathic pain) and allows larger tissue collection. Until very recently, investigations of nociception in genetically modified animal models have been limited to mice, and the associated behavioral assays have had to be adapted for use in mouse. Very recently, genomic modification in species other than mouse has been made possible through new genomic editing tools, most notably zinc finger nucleases. Here, we describe the creation of the first ZFN-mediated knockout rats for pain research. Using zinc finger nucleases, we disrupted the function of transient receptor potential cation channel subfamily V member 1 (TRPV1), nerve growth factor receptor (p75NGFR), and fatty acid amide hydrolase (FAAH). Amongst other functions, all three of these proteins mediate nociception.

Sequencing was performed to demonstrate gene disruption at the genomic level. Loss of protein was demonstrated in all three lines by western blot. At the phenotypic level, these lines show increased foot lick latency on the hot plate test. Lastly, via Irwin battery, p75NGFR knockout rats showed increased reactivity to touch, while FAAH knockout rats showed increased fear/startle response.

P60 • Mild and moderate traumatic brain injury (mTBI) disrupts the diurnal glucocorticoid rise and fear-conditioning behaviors

Robert Handa*, Sibyl Swift, Stephen Shannon, David Carbone, T. John Wu

Traumatic brain injuries are known to cause disturbances in the HPA axis that manifest as a blunted ACTH or corticosterone (CORT) response to stress. Depression and anxiety disorders including posttraumatic stress disorder (PTSD), are linked to HPA-axis dysregulation. However, little is known about the impact of graded levels of TBI on normal HPA-axis function. In these studies, we used a novel high-intensity, focused ultrasound (HIFU) method to deliver a nonimpact blast type TBI to explore this relationship. Adult male C57Bl/6 mice were subjected to mild (LOW) and moderate (MOD) HiFU exposure (400 mV for 1 ms and 5 ms, equivalent to 100 kPa and 250 kPa, respectively). Animals were euthanized 24h and 10 days post-injury to examine the diurnal CORT rise across the light:dark transition. We additionally asked whether glucocorticoid negative feedback was appropriate by examining the response to the synthetic glucocorticoid, dexamethasone. Results show that there were significant elevations ($p < 0.05$) in CORT in the SHAM group with a peak at time of lights out. After LOW and MOD TBI there was no significant afternoon CORT rise and there was no discernable peak. Treatment with DEX suppressed CORT in all groups (SHAM, LOW, and MOD) at both 1 and 10 days after TBI indicating normal negative feedback responses were in place. Fear conditioning tests revealed that SHAM, LOW, and MOD mice increase ($p < 0.05$) freezing during fear conditioning. However, during the extinction phase, levels of freezing remained elevated in mTBI mice compared to shams ($p < 0.05$). These data show that mild TBI can disrupt normal HPA axis function and fear conditioning. Further, we also show that CORT can regulate circadian genes such as Per2 in many tissues including the brain. Thus, these results showing altered neuroendocrine and behavioral function after mild TBI have important ramifications for physiology and health. *Funding:* DMRDP, DoD.

P61 • Disruption of Arp2/3 models progressive synaptic and behavioral abnormalities of psychiatric disorders

Il Hwan Kim*, Bence Racz, Hong Wang, Lauren Burianek, Richard Weinberg, Ryohei Yasuda, William Wetsel, Scott Soderling

Despite evidence for a strong genetic contribution to several major psychiatric disorders, individual candidate genes explain only a small fraction of these diseases, leading to the suggestion that multigenetic pathways may be involved. Several known genetic factors contributing to psychiatric disease are related to the regulation of actin polymerization, which plays a key role in synaptic plasticity. We have prepared a conditional knockout to gain new insight into the possible pathogenetic role of this pathway, targeting the Arp2/3 complex, a conserved final output that orchestrates de novo actin polymerization. Here we report that loss of Arp2/3 in mice leads to a progressive development of synaptic abnormalities, beginning with impaired structural plasticity followed by progressive synapse loss. This progression of synaptic deficits corresponds with an evolution of distinct cognitive, psychomotor, and social disturbances as the mice age. Together these results point to the dysfunction of actin signaling, specifically that which converges to regulate Arp2/3, as an important cellular pathway that may contribute to the etiology of complex psychiatric disorders.

P62 • Neural control of intake by the medial prefrontal cortex

Mark Laubach*, Marc Parent, Marcelo Caetano, Linda Harenberg, Nicole Horst, Benjamine Liu

In a recent study using a delayed-response task, we found that major sources of neuronal variability in the medial prefrontal cortex (mPFC) are associated with processing behavioral outcomes and monitoring reward consumption. Here, we report several new studies that were done to better understand the role of mPFC in outcome/reward processing. Using electrical stimulation methods, we found that stimulation of mPFC disrupts ongoing ingestive behavior but does not alter goal-directed locomotion or lever pressing. Two simple behavioral procedures were then used to study the role of the mPFC in the control of intake: (i) an operant variable interval procedure with fluid delivered from a contact-sensitive spout and (ii) a consummatory successive negative-contrast (SNC) procedure using relatively high and low concentrations of liquid sucrose. Recordings in both tasks found that rhythmic spike and field potential activity was coupled to bouts of licking and tracked changes in lick microstructure. Reversible inactivations of mPFC (muscimol) in during SNC reduced intake

of the better option (high conc.), reduced the duration of persistent "bouts" of licking, and had no effect on licking for the worse option (low conc.). Based on known aging-related changes in rhythmic brain activity associated with the muscarinic system, we tested rats with mPFC infusions of scopolamine, a muscarinic antagonist, and physostigmine, an AChE inhibitor. Similar to muscimol, scopolamine reduced intake of the better option, and physostigmine led to increases in response vigor. Our results suggest that the mPFC is a crucial brain structure for the motivational control of intake and has an enabling, not inhibitory, role in the control of consummatory behaviors.

P63 • Adrenergic and serotonergic effects on the duration of the laryngeal chemoreflex—Implications for SIDS

James Leiter*, William Donnelly, Donald Bartlett, Jr.

The sudden infant death syndrome (SIDS) occurs when a sleeping infant experiences a challenge to cardiorespiratory homeostasis to which it fails to mount an effective response. Babies who died of SIDS have abnormalities in serotonergic nuclei known to be important in cardiorespiratory control, such as the nucleus of the solitary tract (NTS). The NTS mediates a variety of inhibitory reflexes, including the laryngeal chemoreflex (LCR). The LCR is initiated when water or other solutions activate chemoreceptors in the laryngeal mucosa. In neonatal mammals the reflex inhibits breathing (apnea) and causes bradycardia. Activity of second order neurons in the NTS mediating the LCR is controlled or altered by TRPV1 receptor activation, glutamate, GABA and adenosine (working through adenosine A2a–receptors), which enhance apnea duration. We tested the hypothesis that augmenting levels of serotonergic signaling in the NTS of immature rats would shorten the duration or blunt the intensity of LCR apnea. Methods: Rat pups aged P5 to P20 were anesthetized and EKG and intercostal EMG activity were recorded. Distilled water was delivered to the larynx to elicit the LCR. Apnea duration resulting from the LCR was compared pre- and posttreatment with serotonin, serotonergic agonists, or antagonists. *Results:* Microinjections of serotonin shortened apnea duration. Specific agonists of 5-HT3 microinjected into the NTS also shortened the LCR. Glutamatergic excitation of the caudal raphe, a serotonergic nucleus, also shortened the LCR. *Conclusion:* GABA and adenosine in the NTS tend to prolong the LCR, and serotonin tends to shorten the LCR. The inhibitory neurotransmitters tend to initiate and sustain the LCR, and serotonin, which may be released as part of an arousal response, seems to curtail the LCR.

P64 • A hierarchy of pathogenesis revealed by full-length and fragment models of Huntington's disease in Drosophila

J. Lawrence Marsh*, Douglas Bornemann, Brett Barbaro, Namita Agrawal, John Burke, Tamas Lukacsovich, Judy M. Purcell

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by expansion of CAG repeats located near the N-terminus of the 3144 amino acid Huntingtin (Htt) protein. Various proteolytic processing events give rise to several N-terminal fragments that have been identified in patient material and in mice and these are associated with intracellular aggregates. Central questions in the field of misfolded protein–induced neurodegeneration are whether there is a single toxic species or whether many fragments, as well as the full-length protein, contribute to pathogenesis and what the role of misfolded protein aggregates in the disease process is. In HD, it remains unclear what the pathogenic implications of these fragments are and how they affect the aggregation process.

Drosophila expressing full-length mHtt do not display processing of Htt but do display multiple defects consistent with disruption of signaling pathways implicated in HD, including disruptions of the JNK-signaling pathway. The proteolytic fragments also display this common theme of JNK-related phenotypes and shortened life span. On the other hand, animals expressing exon1-like fragments exhibit additional defects in later stages, including overt degeneration of neurons that is not seen with full-length Htt constructs. These studies shed light on the role of aggregate formation and the severity of the phenotype, since the constructs that generate both the strongest and the weakest phenotypes produce abundant aggregates, while many intermediate-severity constructs produce little or no aggregation but nonetheless display robust phenotypes. Further, we find that co-expression of a nontoxic but aggregating species suppresses the pathology of a toxic but non-aggregating full-length protein. These results suggest that expanded polyQ can have core effects (e.g., on JNK signaling) independent of proteolytic processing or aggregation, while other pathologic events may require Htt processing.

P65 • GAT1 expression during normal human brain development and in schizophrenia

Michelle Mighdoll*, Thomas Hyde, Barbara Lipska, Ali Towhid, Amanda Law, Mary Herman, Daniel Weinberger, Joel Kleinman

The GABA signaling system undergoes well-characterized changes during brain development. Abnormal GABA-mediated neurotransmission is one of the more consistent postmortem findings in schizophrenia. Both genetic variation in the GABA signaling system and abnormal brain development are thought

to contribute to the neuropathology of schizophrenia. An essential component of this system is the neuronal GABA transporter GAT1, which regulates inhibitory neurotransmission by the uptake of GABA released at synapses. We have tested both genetic and neurodevelopment hypotheses by measuring GAT1 expression in a normal developmental series (n = 240) and patients with schizophrenia (n = 31) and age matched controls in prefrontal cortex (PFC) (schizophrenic cohort, n = 31; control cohort, n = 73) and hippopcampus (schizophrenic cohort, n = 30; control cohort, n = 62) using microchip arrays and qRtPCR.

Results. 1. Prefrontal GAT1 expression follows an inverted U-shaped trajectory across the lifespan, but is more stably expressed in late adulthood in the hippocampus. Prefrontal GAT1 follows the expression trajectories of KCC2, NKCC1, and GAD67, but unlike other GABA signaling elements, declines in later life. GAT1 levels rose less robustly in the hippocampal formation than the DLPFC. 2. We found that patients with schizophrenia tend to show an immature expression pattern in the hippocampus, with decreased expression of GAT1 ($p < 0.004$). Additionally, we examined the association between GAT1 expression and allelic variation in another gene in the GABA pathway, GAD1, at rs3749034. In the combined cohort of schizophrenia and normal control subjects, homozygotes for the risk allele had a significantly decreased expression of GAT1 mRNA ($p < 0.012$).

Conclusions. In summary, the persistence of an immature GABA signaling system and its relationship to a risk-associated SNP in GAD1 suggest a mechanism of the association of GABA markers with schizophrenia involving abnormal GABA neurotransmission.

P66 • Gene-expression profiling and pathway analyses reveal molecular signatures and relationships underlying enhanced methamphetamine neurotoxicity caused by protracted corticosterone exposure

James O'Callaghan*, Diane Miller, John Bowyer, Kimberly Kelly

Enhanced expression of proinflammatory mediators often accompanies injury-induced glial activation, including glial responses to neurotoxic insults. Previously, we documented a striatal neuroinflammatory response following nerve terminal damage due to acute exposure of mice to the dopaminergic neurotoxicant methamphetamine (METH). When we pretreated mice with the classic antiinflammatory stress hormone, corticosterone (CORT), with the intent of suppressing neuroinflammation, we instead found a markedly exaggerated neuroinflammatory response to METH. METH-induced astrogliosis (GFAP), microglial activation (Isolectin B), and dopaminergic

neurotoxicity (Tyrosine Hydroxylase (TH)) also were enhanced by pretreatment with CORT. To identify molecular changes associated with chronic CORT (1 week in drinking water) pretreatment, we compared expression profiles in striatum at 12 and 24 hours after METH exposure of C57Bl6/J male mice (20 mg/kg, s.c.) with and without chronic CORT (400 mg/L). Tissue was analyzed by Expression Analysis, Inc. using an Illumina MouseRef-8 BeadChip by Expression Analysis to assess gene expression after CORT and METH treatment. Interrogation of the data set by Ingenuity Pathway Analysis revealed changes consistent with our previous findings. The top networks for chronic CORT- and METH-treated mice were inflammatory response, cell death, endocrine system development and function at 12h; and inflammatory response, cell-to-cell signaling and interaction and cell death at 24h. Focus molecules included GFAP, LIF, suppressor of cytokine signaling 3 (SOCS3), S100 calcium-binding protein B (S100B), signal transducer and activator of transcription 3 (STAT3) and TH, i.e., molecules related to astrogliosis, neuroinflammation, and dopaminergic neurotoxicity. These data will inform further investigation of the mechanisms of METH-induced dopaminergic neurotoxicity and provide the earliest biomarkers of neuroinflammation and glial activation responses.

P67 • Subarachnoid hemorrhage (SAH)–linked brain inflammation contributes to arteriolar dilating dysfunction and neuropathology in rats

Dale Pelligrino*, Hao-liang Xu, Chanannait Paisansathan, Francesco Vetri

Rats were subjected to SAH, via suture perforation of the anterior cerebral artery. In pilot experiments, we detected marked elevations in CSF expression of the astrocytic protein, S100B, at 48h post-SAH. Since S100B is a ligand for the pro-inflammatory receptor, RAGE (the receptor for advanced glycation end products), we tested the hypothesis that brain inflammation leads to impairment of arteriolar dilating function and contributes to brain damage. In rats prepared with closed cranial windows at 1–3 days post-SAH, pial arteriolar dilation assessments were performed using intravital microscopy/videometry. To evaluate the role of S100B and RAGE, rats were given the following treatments at 30 min post SAH: (1) ONO 2506 (10 mg/kg, ip), a novel S100B inhibitor; or (2) sRAGE (icv via osmotic pump), a soluble RAGE decoy. After SAH, we observed diminished pial arteriolar responses to hypercapnia, and topically applied adenosine, acetylcholine, and S-nitroso-N-acetyl penicillamine, with maximum attenuation seen at 48 h post SAH. The applications of both ONO 2506 and sRAGE significantly prevented the impaired pial arteriolar dilating responses. Neuropathology at 48h post-SAH was evaluated using FluoroJade B (FJB) staining, which detects

damaged neurons. The high-level FJB reactivity seen in the ipsilateral cortex, hippocampus, and striatum in vehicle controls was markedly diminished in ONO 2506- and sRAGE-treated rats. These results indicate that the activation of the S100B/RAGE pathway plays a key role in SAH-associated cerebral vascular dysfunction. Blockade of the enhanced S100B and RAGE interaction may provide a promising treatment against SAH-associated brain damage. *Support:* NS63279; HL88259

P68 • CHRNA5-promoter polymorphisms are associated with cognitive outcome after mild traumatic brain injury

C. Harker Rhodes*, Laura Flashman, Gregory Tsongalis, Jason Moore, Brenna McDonald, Andrew Saykin, Thomas McAllister

Cognitive deficits, particularly in the domains of memory, attention, executive function, and speed of information processing, are a common long-term consequence of traumatic brain injury (TBI). Although cognitive outcome varies according to the severity of the initial injury, individuals who suffer seemingly similar degrees of injury can have very different outcomes. Previous work in this and other labs has identified genetic factors which account for a small fraction of this individual variability, but many other factors presumably remain to be identified. The nicotinic receptor α5 subunit is expressed in the pyramidal neurons of layer VI of frontal cortex, plays a key role in these processes, and has common functionally significant genetic polymorphisms. To test the hypothesis that genetic variation in CHRNA5 affects cognitive outcome after mild TBI (mTBI), we examined CHRNA5 polymorphisms in a previously described cohort of well-characterized mTBI patients and normal controls. Analysis of the haplotype structure of the region reveals that in Caucasian populations, three polymorphisms (rs16969968, rs578776, and rs905740) capture most of the significant genetic variation at this locus. Measures of memory, including the short-delay and long-delay conditions of the California Verbal Learning Test, were associated with rs578776, but only in mTBI patients and not in controls. This study adds CHRNA5 to the growing list of genes with polymorphisms associated cognitive performance after mTBI and may have implications for pharmacological therapies in these individuals.

P69 • Identification of a novel dopaminergic agonist that selectively activates the D2 dopamine receptor in a biased fashion

David Sibley*, R. Benjamin Free, Jennie Conroy, Kyle Emmitte

In order to develop novel, small-molecule scaffolds for the D2 dopamine receptor (D2R), we used high-throughput screening to identify ligands with unique functional characteristics and selectivity among dopamine receptor

(DAR) subtypes. Using a beta-arrestin recruitment assay to compare activity at all DAR subtypes, we identified a ligand, MLS001163508 (compound 3508), that selectively activates the D2R but not other DAR subtypes. Compound 3508 is an antagonist at the D3R for beta-arrestin recruitment and has no activity at the D4R or D1-like DARs (D1R and D5R). Compound 3508 exhibits full agonist activity with EC50 values ranging from 100 nM–1 μM in three different functional assays for the D2R: beta-arrestin recruitment, Ca2+ mobilization, and inhibition of cAMP accumulation. Using a Go BRET activation assay, we found that 3508 is a full agonist at the D2R but displays weak partial (< 20%) agonist activity at the D3R. Interestingly, 3508 is a full antagonist with no agonist activity on D2R-linked or D3R-linked GIRK channel activation, indicating that it is a biased agonist. This is most striking for the D2R, at which 3508 is a full agonist at all the other pathways evaluated. Consistent with our studies in heterologous cells, application of 3508 elicited a minimal, if any, response in D2R-activated, whole-cell GIRK-mediated currents measured in dopaminergic neurons in mouse midbrain slices, while it effectively blocked the response elicited by the full agonist quinpirole. Molecular modeling studies suggest subtle differences in 3508 binding poses to the D2R and D3R that may underlie its functional properties. In summary, 3508 is a full and selective agonist at both G-protein-linked and beta-arrestin-mediated D2R signaling pathways; however, it is an antagonist for D2R GIRK activation, indicating biased agonism. In contrast, because of its very low or lack of agonist efficacy, 3508 generally functions as a potent D3R antagonist.

P70 • Fasting-induced ghrelin activation of vasopressin neurons via retrograde transneuronal-glial stimulation of excitatory GABA circuits

Jeffrey Tasker*, Juhee Haam

Behavioral and physiological coupling between energy balance and fluid homeostasis is critical for an organism's survival. Previous studies have shown that the orexigenic hormone ghrelin activates the secretion of the osmoregulatory hormone vasopressin (VP), linking nutritional status to control of blood osmolality; however, the physiological mechanisms underlying this interaction are poorly understood. Here we show using brain-slice patch-clamp recordings that ghrelin stimulates VP neurons in the hypothalamic paraventricular nucleus (PVN) in a feeding status-dependent manner by activating an excitatory GABAergic synaptic input. Ghrelin increased the frequency of GABAergic postsynaptic currents (PSCs) in VP neurons from fasted rats (52.8 ± 16.4% increase, $p < 0.01$), but not in VP neurons from fed rats. The ghrelin-induced increase in GABAergic PSCs caused a two-fold

WITHDRAWN

increase in spiking activity (101.6 ± 33.6% increase) in VP neurons from fasted rats. The ghrelin effect on GABAergic PSCs was inhibited by blocking postsynaptic G protein activity, inhibiting vasopressin V1a receptors, and blocking action potentials, indicating that it was mediated by postsynaptic ghrelin receptor-dependent dendritic VP release and stimulation of presynaptic GABA neurons. Ghrelin also induced a calcium response in neighboring astrocytes, and the ghrelin-induced increase in GABAergic PSCs was blocked by pretreatment with the gliotoxin fluorocitrate and by blocking ATP P2X receptors. These findings suggest a model of retrograde signaling that involves ghrelin-induced dendritic VP release, VP activation of neighboring astrocytes, astrocytic ATP stimulation of upstream GABA neurons, and GABA excitation of the VP neurons. This retrograde trans-neuronal-glial signaling triggered by ghrelin represents a novel mechanism for the local circuit regulation of neurons, and provides a cellular mechanism for the integration of energy and fluid homeostasis. *Support:* NIH grant NS042081.

P71 • Mechanisms of regulation of mitochondrial length by neuronal activity

Ramon Trullas*, Joana Figueiro-Silva, Petar Podlesniy

In neurons, signals that have opposite effects on cell survival cause a comparable fragmentation of the mitochondrial network. On the one hand, apoptotic stimuli such as nitrosative stress, Amyloid Beta, or low neuronal activity all produce mitochondrial fragmentation before causing damage to cytoplasmic membranes. On the other hand, high neuronal activity or activation of membrane receptors linked with neuronal survival also induces mitochondrial fragmentation. In previous studies, we reported that Neuronal Pentraxin 1 contributes to the mitochondrial fragmentation evoked by low neuronal activity during apoptosis. We have now investigated the role of cytoplasmic membrane receptors and of Neuronal Pentraxin 1 (NP1) in the fragmentation of the mitochondrial network evoked by high neuronal activity or by oligomeric Amyloid Beta (Ab) (2uM). We found that treatment of cultured cortical neurons with a depolarizing concentration of K+ (50mM) or with Ab both reduce mitochondrial length. The mitochondrial fragmentation caused by Ab was prevented with either AMPA or NMDA glutamate receptor antagonists but not with Nimodipine (5uM) an L-type Ca2+ channel blocker. In contrast, mitochondrial fragmentation evoked by depolarization with high K+ did not depend on glutamate receptor activation. The reduction of mitochondrial length evoked by both depolarization and Ab are blocked by a DRP1 inhibitor and are associated with translocation of DRP1 from cytoplasm to mitochondria. Deletion or Knockdown of NP1 inhibited the translocation

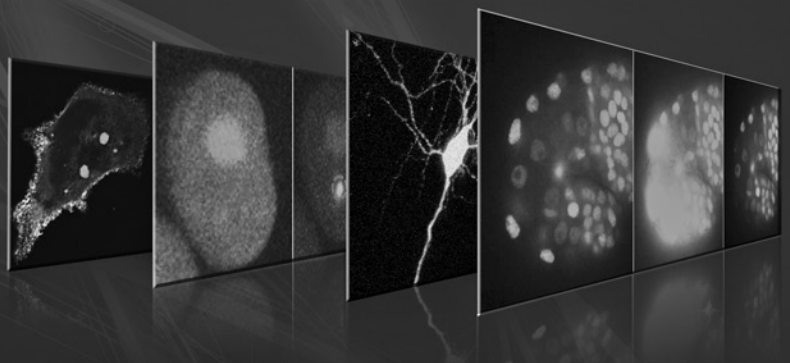
of DRP1 to mitochondria and mitochondrial fragmentation evoked by both treatments, indicating that NP1 is a key mechanism where different signal transduction pathways converge for the regulation of neuronal activity dependent mitochondrial dynamics. *Support:* SAF2011-23550 from Ministerio de Economia y Competitividad of Spain and CIBERNED.

P72 • Abnormal mTOR and ERK signaling in cortical dysplasia associated with epilepsy

Angus Wilfong*, Vinit Patil, Daniel Yoshor, Daniel Curry, Anne Anderson

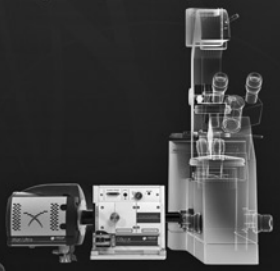
Cortical dysplasia (CD) and tuberous sclerosis (TSC) are commonly associated with drug-resistant epilepsy. There are two main types of isolated cortical dysplasia—type I (CD type I) and type II (CD type II). Both are characterized by cortical dyslamination with ectopic and dysplastic neurons, while only CD type II is associated with cytomegalic neurons. Cytomegalic neurons found in dysplastic tissue are hyperexcitable. Molecular studies performed to identify the cause of dysplasia and hyperexcitability have shown activation of mammalian target of rapamycin (mTOR) pathway, the cause of which is unknown. One potential explanation for hyperactivation of the mTOR pathway is phosphorylation of the upstream mTOR regulator, TSC2 at the S664 site by extracellular regulated kinase (ERK). Human brain tissue sections obtained after resection from epilepsy surgery were stained with antibodies against phosphorylated ERK (pERK), TSC2 (ERK phosphorylation site S664; pTSC2), S6K1 (phosphorylation site T389; pS6K1), and S6 (phosphorylation site S240/244; pS6). Tissue staining with these antibodies was correlated with the neuropathological and clinical history. IHC analysis of brain sections obtained from individuals with CD and TSC showed increased pS6K1 and pS6 labeling of dysplastic neurons and cytomegalic neurons. However, increased staining for pERK and pTSC2 was evident only in the cytomegalic neurons. Correlation studies confirmed previous reports of positive correlation between MRI lesion representative of CD type II and better surgical outcome with pERK staining. Our findings suggest that the mTOR pathway is aberrantly activated in CD type I and II and TSC, while the ERK pathway is activated only in CD type II and TSC. ERK and mTOR pathway cross-talk at the level of TSC2 in cytomegalic neurons in epilepsy, thereby identifying a potential mechanism for mTOR upregulation in CD type II.

ANDOR™
TECHNOLOGY



Andor's Microscopy Systems business provides solutions to address a broad range of optical microscopy techniques including optogenetics, laser spinning disk confocal microscopy, photo-bleaching, TIRF, white light spinning disk confocal.

Our microscopy portfolio includes:



- **Revolution XD**
  The world's fastest spinning disk confocal system
- **Revolution DSD**
  The personal confocal imaging unit

- **Active Illumination Portfolio**
  Hardware for dynamic light-based investigations

andor.com/microscopy

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

Save the Date!

47TH WINTER CONFERENCE ON BRAIN RESEARCH

JANUARY 25–30, 2014
STEAMBOAT SPRINGS, COLORADO