

43rd Annual

Winter Conference on Brain Research

January 23–29, 2010
Breckenridge, Colorado



Welcome to the 43rd Annual Winter Conference on Brain Research

To those of you who are returning to WCBR, a hearty welcome back! And to you first-timers, you're in for a treat! The Winter Conference on Brain Research (WCBR) was founded in 1968 to promote the exchange of information and ideas within neuroscience. The meeting allows both formal and informal interactions between clinical and laboratory neuroscientists, and provides a vehicle for scientists with common interests to discuss current issues in an informal setting. WCBR brings together approximately 500 neuroscientists and clinicians from around the world to share their science and experience in formal scientific sessions and to socialize, network, and brainstorm on the mountain slopes. The success of the meeting depends on the active participation of the attendees at panel presentations, workshops, and posters. We begin with a Saturday evening **Welcome Reception** where you will join up with friends and colleagues and welcome new attendees. The organization has a commitment to mentor the next generation of neuroscientists, and thus provides financial and collegial support for young scientists as **WCBR Travel Fellows**. Please welcome new attendees (blue badges) and Travel Fellows (badges with blue dots) into your scientific discussions, your ski/snowboard trips and meals throughout the week.

The **Opening Breakfast** on Sunday will feature our keynote speaker, **Zach Hall, PhD**. Dr. Hall, whose scientific work focused on the neuromuscular junction, was the first head of the Neuroscience Program at the University of California, San Francisco. He served as director of the National Institute of Neurological Disorders and Stroke (NINDS) and returned to UCSF as executive vice chancellor. He was later president of the California Institute of Regenerative Medicine (CIRM), the state agency for funding stem cell research in California. He is currently a board member of the New York Stem Cell Foundation. His talk will be entitled, "Recent Progress in Stem Cell Research: A Matter of Science, Politics, and Culture."

We have a full week of science and socializing planned. We will again host two activities that are designed to educate the lay public. On Monday night WCBR will hold a **Town Meeting Lecture**, organized by Karen Greif, to be held at Beaver Run Resort & Conference Center, in room Peak 9/10, Dr. James Joseph of Tufts University will speak on "Nuts, Berries, and Brain Health—Do the Forest Animals Actually Have It Right?" All WCBR attendees and their families are welcome to join the lay public at the lecture and reception. WCBR scientists also provide **School Outreach** sessions, organized by Frank Welsh, throughout the week in the local elementary, middle and high schools. You are all invited to the **Special Poster Session** on Tuesday evening, featuring top poster abstract

submissions from new investigators. Light refreshments will be provided. You are encouraged to engage in discussions with poster presenters, as well as corporate exhibitors. Exhibitors also sponsor the afternoon breaks; so please visit exhibitor booths throughout the week. Plan to join us at Wednesday's **Mountain Lunch** on Peak 8 at the Vista Haus. **The Smitty Stevens Memorial (NASTAR) Ski Race** will occur on Peak 9—Sundown Run. Please be sure to attend the **Business Meeting** on Wednesday following the afternoon sessions, as we will hold elections for Facilities Chair-Elect, Program Chair-Elect and board members. Additionally, we will discuss the program, budget and future meeting sites. Because board members are important for WCBR governance, we encourage you to nominate yourself or a colleague for open board positions in clinical, cell/molecular, or systems/behavioral neuroscience. We will close the week on Friday night with the **Annual Banquet**, wherein we will announce awards for the Special Poster Session and the Ski Race, as well as let our hair down dancing to live music.

WCBR is an all-volunteer organization. Please join me in thanking Barbara Lipska, program chair, and her committee members for an outstanding scientific program. We thank Janet Finlay, facilities chair for the meeting venue and organization. Thanks to Paula Dore-Duffy and John Mendelson who have solicited support from the many exhibitors at the conference and advertisers in the program. Behind the scenes, Gretchen Snyder and George Wilcox, as fellowship co-chairs, have worked hard to identify exceptional Travel Fellows and matched them with WCBR mentors. Jacqueline McGinty keeps us on solid financial ground as WCBR treasurer. Lastly, we thank the current members of the board of directors and past WCBR Conference Chair, Barry Levin, for guidance throughout the year, and Michelle Chappell at the University of Illinois for limitless energy, historical memory and professional meeting organization.

Enjoy the meeting, your colleagues, and the snow!

Kimberly Topp
Conference Chair

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Participants	151

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:

	<i>Morning</i>	<i>Afternoon</i>
Saturday 1/23	8:00–10:00 AM	3:30–9:00 PM
Sunday 1/24	7:00–10:00 AM	3:30–7:00 PM
Monday 1/25	7:00–9:45 AM	3:30–6:30 PM
Tuesday 1/26	7:00–9:45 AM	3:30–8:00 PM
Wednesday 1/27	7:00–9:45 AM	3:30–5:30 PM
Thursday 1/28	7:00–9:45 AM	3:30–6:30 PM
Friday 1/29	7:00–9:45 AM	

The WCBR telephone number for messages or information is 217-714-9479.

Registration packets containing a conference badge, registration receipt, tickets for breakfasts, mountain lunch and closing banquet, and program book should be picked up at the WCBR Information Desk.

Posters will be available for viewing in three different sessions during the week in Peak 1–4.

Poster Session 1, Sunday–Monday

Posters will be available for viewing at 3:30 PM on Sunday through 6:30 PM on Monday. Presenters will be with posters on Sunday and Monday from 3:30 to 4:30 PM.

Poster Session 2, Tuesday–Wednesday

This is a special session with 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 their posters on Tuesday, 3:30 to 4:30 PM, and returning for the special session 6:30 to 8:30 PM. Additionally, presenters will be with their posters Wednesday from 3:30 to 4:30 PM.*

Poster Session 3, Thursday

Posters will be available for viewing after 8:30 PM Wednesday through 6:30 PM on Thursday. Presenters will be with posters on Thursday from 3:30 to 4:30 PM.

Please refer to pages 22–27 for a listing of poster sessions.

All posters must be removed by 10:00 PM Thursday, January 28.

Exhibits and Lounge are in Peak 1-4. Exhibitor setup is Sunday, January 24, 12:00–3:00 PM. Refreshments are provided 3:30–4:30 PM, Sunday through Thursday. Exhibits close after 10:30 AM on Friday, January 29. Friday's afternoon break will be in the Colorado Ballroom Lobby.

Breakfast is served to all registrants on Sunday, 7:00–8:30 AM, in the Colorado Ballroom and Lobby. Tickets are not required. Monday through Friday breakfast will be available from 6:00–8:30 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 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 Friday 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.



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Tel 877-455-2687
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Travel Fellowship Program

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Karen Greif

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Exhibitors

Abcam plc

330 Cambridge Science Park
Milton Road
Cambridge, Cambridgeshire, CB 1
3AB, UK

Contact: Katinka Vigh-Conrad
Tel 44 1223 696 000
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Association Book Exhibit

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Special Events

Saturday, January 23

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

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

Sunday, January 24

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

7:00–8:30 AM • Breakfast

8:00–9:30 AM • Plenary Address

The plenary keynote address is presented by:

Zach W. Hall, PhD, Member, Board of Directors, New York Stem Cell Foundation; Former President, California Institute of Regenerative Medicine; Former Director, NINDS; Emeritus Professor, UCSF

“Recent Progress in Stem Cell Research: A Matter of Science, Politics, and Culture”

Stem cell research has recently made dramatic advances, which have reconfigured the scientific, cultural and political terrain that it inhabits. This talk will briefly review the scientific and political history of stem cell research, give an update on recent advances, and discuss their implications for the ongoing ethical and political debates. Among the questions to be addressed are:

- What is the scientific and ethical significance of iPS cells?
- Why are they important for neurological disorders?
- Do we still need human stem cell lines generated by nuclear transfer or from embryos?
- What are the new NIH policies and what are the prospects for the future?
- Is there a continuing need for state and private foundation support for stem cell research?

Monday, January 25

First Meeting of the Board of Directors • 6:30–8:30 AM, Peak 9/10

Town Meeting • 7:30–9:30 PM, Peak 9/10

Attendance is open to all.

“Nuts, Berries, and Brain Health: Do the Forest Animals Actually Have it Right?”

James Joseph, PhD, Director, Neuroscience Lab, USDA Human Nutrition Research Center on Aging at Tufts University

Tuesday, January 26

Breakfast for Travel Fellows Meeting • 6:30–7:30 AM, Imperial Ballroom

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

The 30 top-ranked posters submitted by junior investigators will be on display, Tuesday from 6:30 to 8:30 pm in a special session with wine and cheese. Awards will be selected, including a “Best Poster” award made possible by a generous donation by Pfizer Pharmaceutical, Inc. 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 Friday, January 29.

Wednesday, January 27

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 AM, Peak 9, Sundown Run

NASTAR registration cards to be completed no later than Monday, January 25, 8:00 AM at the WCBR Information Desk or online at www.nastar.com.

Mountain Lunch • 11:30 AM–2:00 PM, Peak 8, Vista Haus

Non-skiers requiring transportation will need a foot pass ticket to ride the Colorado SuperChair from the base of Peak 8 up to the Vista Haus. Please sign up at the WCBR Information Desk by Monday, January 25.

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 PM, Peak 5

Attendees will elect a Program and Facilities Chair-Elect, and new board members. They will also discuss future meeting locations, along with other business items. All are welcome and encouraged to attend.

Friday, January 29

Second Meeting of the Board of Directors • 6:30–8:30 AM, Peak 9/10

Banquet and Dance • 7:30 PM, Colorado Ballroom (Peak 1–5)

Required ticket is in your registration packet. Cash bar opens at 6:30 PM in the Colorado Ballroom Lobby.



Program

Preamble to the Program

The 2010 WCBR Program consists of panels, workshops, and posters. Please consult the program book and posted announcements for details regarding the scientific presentations as well as information regarding the School Outreach program and the Town Meeting.

Sunday, January 24

7:00 AM

Breakfast • Colorado Ballroom •
Peak 1–5

8:00 AM

Plenary Address • Colorado Ballroom •
Peak 1–5

Zach Hall, PhD

**Recent Progress in Stem Cell
Research: A Matter of Science,
Politics, and Culture**

3:30–4:30 PM

Exhibits and Posters • Peak 1–4

4:30–6:30 PM

1. Panel • Peak 5

**Making a Mountain Out of a
Mogul? Neural Assessment of
Effort during Decision Making**

Paul Phillips (Chair), Stan Floresco,
Mark Walton, Steven Kennerley,
Matthew Botvinick

2. Panel • Peak 17

**Do Tonic and Phasic Dopamine
Release Activate Distinct Receptor
Subtypes?**

Kim Neve (Chair), Anthony Grace,
Weixing Shen, Jeremy Seamans,
Christopher Ford

3. Panel • Peak 11/12

**Phosphodiesterase 10A
Modulation of Basal Ganglia
Function: Implications for
the Treatment of Psychiatric
Disorders**

Erik Charych (Chair), Gretchen
Snyder, Chris Schmidt, Anthony
West

4. Panel • Peak 14

**Developing Anti-Relapse
Medications for Drug Addiction:
Challenges and Promises**

George Koob, Janet Neisewander,
Ronald See (Chair), Thomas
Newton

5. **Panel • Peak 15/16**

**Circadian Influences on
Molecules, Signaling and Memory
Formation**

Karl Obrietan, Martha Gillette, **Jerry
Yin (Chair)**, Dan Storm

6. **Panel • Peak 6/7/8**

**Modulating Protein
Phosphorylation as a Therapeutic
Strategy for Neurodegenerative
Diseases**

Warren Hirst (Chair), Einar
Sigurdsson, John Anderson, Mark
Cookson

8:30-10:00 PM

7. **Panel • Peak 5**

**Novel Ligands and Approaches to
Analgesia, Tolerance and Reward**

James Zadina (Chair), Catherine
Cahill, Jay McLaughlin, Lawrence
Toll

8. **Panel • Peak 17**

**Neuro-Inflammation in Aging and
Disease**

Stephen C. Bondy, J. Steven
Richardson, Salah Fathy, **N. Eric
Naftchi (Chair)**

9. **Panel • Peak 11/12**

**Rehabilitation vs.
Neuroprotection: Use of Exercise,
Environmental and Dietary
Therapies to Reduce Brain
Damage**

Jennifer Thomas, **Anna Klintsova
(Chair)**, Tammy Ivanco, Tess
Briones

10. **Panel • Peak 14**

**Nutrition and the “Longevity
Dividend” in Neuroscience**

Erika Allen (Chair), James Joseph,
Jane Cavanaugh, Amanda Smith,
Henirette van Praag

11. **Panel • Peak 15/16**

**Innate Immune Genes and Brain
Health**

Fulton Crews, Thomas Kuhn, Nigel
Greig, **Susanna Rosi (Chair)**



Monday, January 25

7:30-9:30 AM

12. **Panel • Peak 5**

SNPs and Chips

Meeta Mistry, Michael Oldham,
Mark Cookson, **Barbara Lipska
(Chair)**

13. **Panel • Peak 17**

**Genetic Vulnerability of Striatal
Circuits in Addiction**

Yasmin Hurd, John Wang, John
Neumaier, **Jacqueline McGinty
(Chair)**

Monday, January 25, continued

14. Panel • Peak 11/12

Cell Renaissance in the Damaged CNS: Gliogenic Versus Neurogenic Niches

Vittorio Gallo, Philip Horner,
Friederike Klempin (Chair)

15. Panel • Peak 14

Cerebrovascular Perfusion Confusion: Function and Dysfunction

Charles Leffler (Chair), Dale Pelligrino, Jonathan Jaggar, David Busija

16. Panel • Peak 15/16

Phosphodiesterases 8-11: The New Kids on the Block

Christopher Schmitd (Chair), Joseph Beavo, Jos Prickaerts, Gretchen Snyder, Erik Charych

17. Panel • Peak 6/7/8

Is It Really Worth It? Prefrontal Cortex Contributions to Valuation and Control of Choice Behavior

Mark Walton (Chair), Matthew Roesch, Peter Rudebeck, Lesley Fellows, Todd Hare

3:30-4:30 PM

Exhibits and Posters • Peak 1-4

4:30-6:30 PM

18. Panel • Peak 5

Genetic Risk Factors, Fetal Transcripts, Brain Development, and Schizophrenia

Joel Kleinman (Chair), Daniel Weinberger, Thomas Hyde, Amanda Law, Kristin Bigos

19. Panel • Peak 17

Impact of the Mesolimbic “Addiction” Circuitry on Food Intake and Food Seeking

Jeffrey Grimm (Chair), Gary Aston-Jones, Bart Hoebel, Stephen Benoit

20. Panel • Peak 11/12

Molecular Mechanisms of Axon Formation and Guidance

Tom Soderling (Chair), Katherine Kalil, Gianluca Gallo, James Bamburg

21. Panel • Peak 14

When Drug Abuse Becomes Compulsive: Unraveling the Role of Ventral and Dorsal Striatal Circuits in Addiction

Erik Oleson, Friedbert Weiss, **Ingo Willuhn (Chair)**, Amanda Gabriele

22. Panel • Peak 15/16

Skiing Moguls: How the Brain Navigates the Steep Slope of Motor Learning

Peter Fox, Charles Larson, Julien Doyon, **Donald Robin (Chair)**

23. Panel • Peak 6/7/8

Dopamine Signaling and Disease: Wormholes, Flytraps, Organic Farmers and Mouseketeers in the Pursuit of New Medications

Randy D. Blakely (Chair), David Krantz, Amy Newman, Aurelio Galli

7:30-9:30 PM

Town Meeting • Peak 9/10

8:30-10:00 PM

24. Panel • Peak 5

Making Sense of Multisensory Integration

Michael Beauchamp (Chair),
Stephen LaConte, Paul Laurienti

25. Panel • Peak 17

Inhibition in Striatum

Anatol Kreitzer, Stefano Taverna,
Tibor Koos, **Stefano Vicini (Chair)**

26. Panel • Peak 11/12

Synaptic Basis of Circuit Function and Behavior

A. Villu Maricq, Grae Davis, **John Isaac (Chair)**, Anatole Krietzner

27. Panel • Peak 14

Non-Invasive CNS Repair: The Double Diamond Run

Victor Rafuse, Brian Kaspar, **Isabelle Aubert (Chair)**, Henriette van Praag

28. Minicourse • Peak 15/16

Synergistic Merge of Operant Conditioning and Chronic Pain Models

Carolyn Fairbanks (Chair), S. Steve Negus, T. Jeff Martin, Andrea Hohmann

29. Panel • Peak 6/7/8

Synapses and Circuitry of the Retina

Catherine Morgans (Chair), Stephen Massey, Wei Li, Ron Gregg, Lane Brown



Tuesday, January 26

7:30-9:30 AM

30. Panel • Peak 5

Photoreceptors and Mechanosensory Hair Cells in Development, Disease, and Regeneration

Teresa Nicolson, David Raible, Brian Perkins, **Monte Westerfield (Chair)**

31. Panel • Peak 17

Glutamate's Roles in Opiate Addiction

Jerry Frankenheim (Chair), Ryan LaLumiere, Ronald See, Virginia Pickel, Elena Chartoff

32. Panel • Peak 11/12

Transcriptional Regulation in the Brain: How to Accessorize Your Genes

Thomas Hyde (Chair), Michael Dean, Reini Luco, Iris Cheung, Erin Newburn

33. Panel • Peak 14

Last but Not Least: Delayed Onset of Reward-Related Frontal Cortical Function in Adolescence

Julie Markham, Frances Leslie, Kyle Frantz, **Kuei Y. Tseng (Chair)**

Tuesday, January 26, continued

34. Panel • Peak 15/16

Regulation of Ionotropic Glutamate Receptors

Richard Hugarir, A. Villu Maricq,
Katherine Roche (Chair), Roger
Nicoll

35. Panel • Peak 6/7/8

Why Wait? Rapid-Acting Antidepressant Strategies and Mechanisms of Action

Steven Potkin (Chair), William
Bunney, Ruth Benca, Fritz Henn

3:30-4:30 PM

Exhibits and Posters • Peak 1-4

4:30-6:30 PM

36. Panel • Peak 5

Here We Come To Save The Day: Finding The Mighty Mouse Model of Schizophrenia

Amanda Law, Karoly Mirnics,
Toshifumi Tomoda, **Paul Glineburg
(Chair)**

37. Panel • Peak 17

Probing the Glial Hypothesis of Epilepsy

Tom Swanson (Chair), Detlav
Boison, Dave Poulsen, Bruce
Ransom

38. Panel • Peak 11/12

Different Tokes for Different Folks: Individual Differences in Responses to Abused Drugs

Nancy Zahniser, **Joshua Gulley
(Chair)**, Marilyn Carroll,
Harriet de Wit

39. Panel • Peak 14

Revealing Elusive Neural Circuits Using Comparative Approaches

Cathy Wolkow, Yonathan Zohar,
Donald Ingram, **Mary Ann Ottinger
(Chair)**

40. Panel • Peak 15/16

Life and Death Decisions in the Oligodendrocyte Lineage: Novel Receptors and Immune Signaling

James Connor, Guillermina
Almazan, Robert Skoff, **Pamela
Knapp (Chair)**

41. Panel • Peak 6/7/8

NMDA Receptor from Biophysics to Disease

Stephen F. Traynelis, Jon W. Johnson,
Stefano Vicini (Chair), Lynn A.
Raymond

6:30-8:30 PM

Special Poster Session • Peak 1-4

Wednesday, January 27

7:30–9:30 AM

42. Panel • Peak 5

Translational Challenges for Developing Cognition Drugs in Schizophrenia

David Michelson, Mark Geyer, John Sweeney, Michael Egan (Chair)

43. Panel • Peak 17

A Newly Discovered Collection of GABA Neurons in the Brainstem Tegmentum that Projects Strongly to Midbrain Dopamine Cells and Influences Aversive Behavior

Daniel S. Zahm, Susan Sesack (Chair), Michel Barrot, Thomas Jhou

44. Panel • Peak 11/12

NMDA Receptor Trafficking in Synaptic Plasticity and Synaptogenesis

R. Suzanne Zukin (Chair), June Liu, Graham Collingridge

45. Panel • Peak 14

Classical and Non-Classical Neuropeptides in Brain: From Opioids to Peptide Endocannabinoids

Lloyd Fricker (Chair), Lakshmi Devi, Iris Lindberg

46. Panel • Peak 15/16

Understanding the Neurobiology of Suicide: Translational Approaches

Stephen H. Koslow (Chair), Victoria Arango, Gregory Ordway, Gustavo Turecki, John Keilp

47. Panel • Peak 6/7/8

Exercise and Brain Health

Justin Rhodes (Chair), Kirk Erickson, Monika Fleshner, Joanna Gill-Mohapel

10:00–11:30 AM

Smitty Stevens Memorial Ski Race •

Peak 9—Sundown Run

11:30 AM–2:00 PM

Mountain Lunch • Peak 8, Vista Haus

3:30–4:30 PM

Exhibits and Posters • Peak 1–4

4:30–6:30 PM

48. Panel • Peak 5

Integrating the Pleomorphic Roles of Hypocretin/Orexin

Barry Levin (Chair), Louis de Lecea, Gary Ashton-Jones, Masashi Yanagisawa, Catherine Kotz

49. Panel • Peak 17

Neuroprotection Revisited: Bridging the Chasm Between Pre-Clinical and Clinical Trials in TBI

Edward Hall (Chair), Stephen Scheff, Don Stein, Alan Faden

50. Panel • Peak 11/12

Post-GWAS in Psychiatry: Extending the Phenotype

Katherine Burdick (Chair), Steven Potkin, John Kelsoe, Anil Malhotra

Wednesday, January 27, continued

51. Minicourse • Peak 14

Modes of Mind: Intrinsic Coherent Networks (ICN) in Brain Function and Structure

Peter Fox (Chair), Stephen Smith, Simon Eickoff, David Glahn

52. Panel • Peak 15/16

Novel Approaches to the Treatment and the Etiology of Alzheimers Disease

Steve Richardson (Chair), Xin-Min Li, Weihong Song, Peter Yu, Charles Etienne Benoit

53. Panel • Peak 6/7/8

The Surprising Role of the Amygdala in Uncertainty and Attention

Paul Whalen, Dan Salzman, **Geoffrey Schoenbaum (Chair)**, David Bucci

6:30 PM

Business Meeting • Peak 5



Thursday, January 28

7:30–9:30 AM

54. Panel • Peak 5

Taking It All In: Functional Properties of Distinct Inputs to VTA Dopamine Neurons

Paul Shepard, **Carl Lupica (Chair)**, Hitoshi Morikawa, Cameron Good

55. Panel • Peak 17

Reelin' and Rockin': Role of the Extracellular Matrix Protein from Development to Cognition

André Goffinet, Gabriella D'Arcangelo, **Pascale Chavis (Chair)**, Edwin Weeber

56. Panel • Peak 11/12

Behavioral Correlates of Neurological Dysfunction and Recovery: Assessments for Translational Research

Kimberly Topp (Chair), Gail Widener, Diane Allen, David Brown, Carolyn Patten

57. Panel • Peak 14

Hypoxia—The Good, Bad and the Ugly: Clinical Relevance and Rationale for Using “Therapeutic Angiogenesis” as a Treatment Paradigm

Sami Harik, **Christian Kreipke (Chair)**, Paula Dore-Duffy, Joseph LaManna

58. Panel • Peak 15/16

Web Collaborations in Neuroscience

Hakon Heimer (Chair), June Kinoshita, Tim Clark, Matt McQueen

59. Panel • Peak 6/7/8

**Recent Advances in
Neuromodulation of Neural
Plasticity**

Nelson Spruston, Ricardo Araneda,
Scott Thompson, **Alfredo Kirkwood**
(Chair)

3:30-4:30 PM

Exhibits and Posters • Peak 1-4

4:30-6:30 PM

60. Panel • Peak 5

**Seize The Day: Novel Therapies for
Epilepsy**

Susan Masino, Nathaniel Hartman,
Janice Naegele (Chair), Frances
Jensen

61. Workshop • Peak 17

**Who is the “Hemichannel” and
What Does It Do?**

David Spray (Chair), Michael
Bennett, Eliana Scemes, Roger
Thompson, Gerhard Dahl

62. Panel • Peak 11/12

**The Genetics of Pain from Rodent
and Human Studies**

Jeffrey Mogil, **William Lariviere**
(Chair), William Maixner

63. Panel • Peak 14

**Cannabinoid Receptor
Signaling and Modulation of
Monoaminergic Circuits**

Elizabeth Van Bockstaele (Chair),
Ken Mackie, Mary Abood, Eleni
Tzavara, Ana Carvalho

64. Panel • Peak 15/16

**Identification of Functional
Variation across the Genome:
Insights from Preclinical and
Clinical Studies**

Wolfgang Sadec, David Goldman,
Harriet de Wit, Anil Malhotra
(Chair)

65. Panel • Peak 6/7/8

**Functional Relevance of
Hippocampal-Prefrontal
Synchrony**

Joshua Gordon (Chair), Yukiori
Goto, Hidehiko Takahashi, Patricio
O'Donnell, Avishek Adhikari

8:30-10:00 PM

66. Panel • Peak 5

**Gap Junctions and Plasticity in the
CNS**

Michael Bennett (Chair), Martin
Theis, Alberto Pereda, Rolf
Dermietzel, John O'Brien

67. Panel • Peak 17

**Poring over Ion Channel Pores:
Gating and Modulation of Central
and Novel Gating Pores of Ion
Channels**

Todd Scheuer (Chair), Baron
Chanda, Michael Sanguinetti

68. Panel • Peak 11/12

**The Immune System and CNS
Function in Health and Disease**

Klas Blomgren (Chair), Lena
Brundin, Steven Levison, Marcela
Pekna, Alan Faden

Thursday, January 28, continued

69. Panel • Peak 14

The Aging Brain on Super Foods and Supplements: Hope or Hype

Donald Ingram (Chair), Barbara Shukitt-Hale, Paula Bickford, Richard Hartman, Michael Forster

70. Panel • Peak 15/16

Time to Hit the Gym? Improvements in Diabetic Neuropathy via Exercise and Lifestyle Intervention

Gordon Smith, J. Robinson Singleton, Patricia Kluding, **Doug Wright (Chair)**

71. Panel • Peak 6/7/8

Do In Vitro Models Shed Light on Neural Disease?

Rosemary Schuh (Chair), Samir Jafri, Jean Harry, Hey-Kyoung Lee



Friday, January 29

7:30–9:30 AM

72. Panel • Peak 5

The More We Learn, the Less We Know about Axonal Plasticity and Regeneration in the Nervous System

W. Marie Campana, George M. Smith, **Mark H. Tuszynski (Chair)**

73. Panel • Peak 17

Cell Migration and Its Control in the Nervous System

Harold Cremer, **James Fawcett (Chair)**, Joel Levine, Francis Szele

74. Panel • Peak 11/12

Taking STEPs to Improve Cognition

Susan Goebel-Goody, **Paul Lombroso (Chair)**, Aaron Gloster, Michael Browning

75. Panel • Peak 14

Astrocyte Intermediate Filament (Nanofilament) System and Its Role in Adult Neurogenesis, Regeneration and CNS Pathologies

Milos Pekny (Chair), Michael Brenner, Yang (Ted) Teng, Albee Messing

76. Panel • Peak 15/16

New Vistas in Understanding and Treating Alcohol Abuse

Bart Hooebel (Chair), Charles O'Brien, Sarah Leibowitz, Friedbert Weiss, Philippe DeWitte

77. Panel • Peak 6/7/8

DISC1 and the Gang: How DISC1 Acts in Concert with Other Mental Illness Candidate Proteins

Atsushi Kamiya, Qi Wang, Carsten Korth (Chair), Josef Kittler

4:30-6:30 PM

78. Panel • Peak 5

Structure and Function of the Cerebellar Cortex and Nuclei

Detlef Heck (Chair), Dieter Jaeger, Ray Turner, Chris De Zeeuw, Robert Sachdev

79. Panel • Peak 17

Signaling Interaction and Transcriptional Regulation during Hypothalamic Pituitary Adrenal Axis Adaptation to Stress

Stoney Simons, Greti Aguilera (Chair), Stafford Lightman, Arshad Khan

80. Panel • Peak 11/12

Mitochondria in Synaptic Plasticity

George Spirou, Jennifer Morgan, J. Marie Hardwick, Elizabeth Jonas (Chair)

81. Panel • Peak 14

NMDAR Hypofunction Induced Deficits in Psychiatric Illness—It's Not All about Changes in Long Term Plasticity!

Robert Greene (Chair), Margarita Behrens, Janet Finlay, Terrence Sejnowski, Craig Powell

82. Panel • Peak 15/16

DA-Mediated Reward Processing: Interactions with Opioids and Sex Differences

Charles O'Brien, Tiffany Love (Chair), Jill Becker

83. Panel • Peak 6/7/8

Neural Substrates of Social Cognition: New Frontiers for Nonhuman Primate Studies

Ludise Malkova (Chair), Christopher Machado, Michael Platt

7:30 PM

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

Poster Session 1

Sunday–Monday • Peak 1–4

Posters will be available for viewing at 3:30 pm on Sunday through 6:30 PM on Monday. Presenters will be with posters on Sunday and Monday from 3:30 to 4:30 PM.

- P1. Self-Administration of Heroin and Incubation of Heroin-Seeking in Adolescent vs. Adult Male Rats
James Doherty
- P2. Dysregulation of Genes that Control Dopaminergic Activity in the Clock Mutant Mice, a Model of Mania
Sade M. Spencer
- P3. Neurocognitive Improvement among Alcohol-Dependent Individuals Treated with a Combination of Flumazenil and Gabapentin
Joseph P. Schacht
- P4. Synthetic Triterpenoids Induce a Cytoprotective Pathway in Astrocytes and Attenuate Immunological Activation in Microglia
Brent T. Harris
- P5. Role of Dopamine Receptors, but not $\alpha 2$ Adrenoceptors, in Yohimbine-Induced Reinstatement of High-Fat Food Seeking
Brittany Navarre
- P6. Fluoxetine (Prozac) Potentiates Methylphenidate (Ritalin)-Induced Gene Regulation in Addiction-Related Brain Regions
Vincent Van Waes
- P7. Cerebrovascular Reactivity after Intracisternal Blood Injection in Insulin Resistant Rats
Adam Institoris
- P8. MRI and Histological Analysis of Beta-Amyloid Plaques in Both Human Alzheimer's Disease and APP/PS1 Transgenic Mice
Mark D. Meadowcroft
- P9. Receptor Kinetic Computational Model Distinguishes mEPSC Contributions of NR2A and NR2B Subunit-Containing NMDA Receptors during Status Epilepticus
David E. Naylor
- P10. Dopamine Transporter Coding Variant Ala559Val Associated with Attention Deficit Hyperactivity Disorder Impairs AMPH-Induced DAT Internalization and DAT-Mediated DA Efflux
Erica Bowton
- P11. The Western Diet Alters Blood-Brain Barrier and Microglial Activation in Middle-Aged Rats
Lotta Granholm
- P12. BDNF Signaling to the Jak/STAT Pathway via the P75 Neurotrophin Receptor
Amy Brooks-Kayal

- P13. Axonal Microdomains of PI3K Activity Drive the Formation of Axonal F-Actin Patches That Serve As Precursors to the Formation of Filopodia
Gianluca Gallo
- P14. Synaptotagmin 1 Overexpression Increases Cell Process Complexity in Developing Embryonic Chicken Forebrain Neurons In Vitro
Karen F. Greif
- P15. Neuronal Pentraxin 1 Regulates the Neuronal Activity-Dependent Intrinsic Program of Apoptosis by Facilitating Bax Translocation to Mitochondria
Ramon Trullas
- P16. Differential Expression of Myostatin in the Brain of Genetically-Modified Mice
Sonsoles de Lacalle
- P17. Molecular Determinants of Antidepressant Selectivity at the Human Serotonin and Norepinephrine Transporters
Anders Kristensen
- P18. Sub-Second Measures of Glutamate Dynamics in Non-Human Primates: A Step Towards Clinical Application
Francois Pomerleau
- P19. Exercise and Time-Dependent Benefits to Learning and Memory
Nicole Berchtold
- P20. Role of V2a Interneurons in the Mouse Spinal Locomotor Network
Ronald Harris-Warrick
- P21. Methamphetamine-Induced Neurotoxicity in Dorsal Striatum Affects Phasic Dopamine Release, Striatonigral Neuron Function, and Striatum-Dependent Learning and Memory
Kristen A. Keefe
- P22. Synaptic Modulation by Glutamate and Dopamine is Altered in Striatal Medium Spiny Neurons Lacking the NR2A Subunit
John G. Partridge
- P23. Advances in Microelectrode Arrays: A Novel Turnkey Probe for In Vivo Neurochemical Recordings
Peter Huettl
- P24. Role of Dopamine, Ca²⁺ and α -Synuclein in Vulnerability of SN Neurons in PD
Eugene V. Mosharov
- P25. Power Spectral Analyses of Sleep EEG in Abstinent MDMA Users Suggest Non-Restorative Sleep
Una D. McCann
- P26. Determination of the Amnestic Concentration of Midazolam and its Metabolites in Brain Tissue: Implications for In Vitro Studies
Robert Pearce
- P27. Predictors of Buprenorphine-Naloxone Dosing in Opioid-Addicted Youth
George Woody
- P28. Effect of Repeated Nicotine and Cocaine on Changes in Synaptoneurosomal Neurofilaments and Receptors
Henry Sershen
- P29. Characterization of PREPL, a Brain-Enriched Serine Oligopeptidase Deleted in Patients with Hypotonia-Cystinuria Syndrome
John Creemers
- P30. Network Structure and the Collapse of Consciousness during Anesthesia
Anthony G. Hudetz

Poster Session 2

Tuesday–Wednesday • Peak 1–4

This is a special session with 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 their posters on Tuesday, 3:30 to 4:30 PM, and returning for the special session 6:30 to 8:30 PM. Additionally, presenters will be with their posters Wednesday from 3:30 to 4:30 PM.

- P31. Identifying Molecular Neuroadaptations in Cocaine-Activated Rat Striatal Neuronal Ensembles Using Fluorescence Activated Cell Sorting (FACS)

Danielle Guez-Barber

- P32. Defining a Sensitive Period for Iron in the Development of Hippocampal CA1 Dendritic Structure and Spatial Memory Behavior

Stephanie Fretham

- P33. Glutamate Evoked Calcium Signal in Individual Spines in D1-Dopamine Receptor Containing Medium Spiny Neurons in the Nucleus Accumbens after Chronic Cocaine Treatment

Veronica A. Alvarez

- P34. Genetic Variation in GRIK4 is Associated with Serotonin Transporter Binding Potential in the Cingulate Cortex

Gonzalo Laje

- P35. Replication of Association of the NTRK2 Gene with Lithium Response in Bipolar Disorder in a Prospective Sample

Susan Leckband

- P36. Linking Food and Mood: Insulin Regulation of the Norepinephrine Transporter (NET) via Akt

Sabrina Robertson

- P37. Lithium Treatment Selectively Restores Dopamine Cell Size, Excitability and Mood-Related Behavior in the Clock Mouse

Laurent F. Coque

- P38. Neural Activity in Central Nucleus Drives Increased CS and US Processing in Response to Decrements, but Not Increments, in Reward Value

Donna J. Calu

- P39. New Insights to Trafficking of the Neurokinin 3 Receptor to the Nucleus of Hypothalamic Neurons

Dane D. Jensen

- P40. Locus Coeruleus Stimulation and Norepinephrine Application Produce Opposite Effects on Accumbens-Projecting Neurons in the Ventral Subiculum

Witold Lipski

- P41. A Reduction of miR-17 Family Expression in Cultured Neuroblasts as a Hallmark of Their Transition through Differentiation

Natalie Beveridge

- P42. An Inducible, Reversible Strategy to Regulate Klf-9 Expression in the Developing Dentate Gyrus and during Adult Hippocampal Neurogenesis.

Kimberly Scobie

- P43. Adult Mouse Subventricular Zone Stem and Progenitor Cells are Sessile and Epidermal Growth

- Factor Receptor Negatively
Regulates Neuroblast Migration
Yongsoo Kim
- P44. Alterations in Dopamine
Neurotransmitter Dynamics in
Brain-Derived Neurotrophic Factor
Deficient Mice
T. A. Mathews
- P45. Regulation of CB1 Cannabinoid
Receptor Expression in the Cortex
during Postnatal Development
Heinz Steiner
- P46. Neonatal Habenula Lesion as a
Novel Animal Model of ADHD
Young-A Lee
- P47. Post-Depolarization Potentiation
of GABA-A Receptors: A Novel
Mechanism Regulating Tonic
Inhibition in Hippocampal
Neurons
Christopher Ransom
- P48. High Purity Human Cell
Populations from Human
Embryonic Stem Cells: Their
Utility in Screening and
Therapeutic Development
Monica Siegenthaler
- P49. Aberrant Activation and
Localization of Mammalian Target
of Rapamycin (mTOR) Pathway
Targets in Hippocampus following
Prolonged Limbic Seizures
Amy Brewster
- P50. Effect of the Cannabinoid
CBII Receptor Partial Agonist
Gw405833 on Neurological
Damage Caused by Hypoxia
Ischemia in Rats
Jack Rivers
- P51. Altered Neuroligin Expression
is Involved in Social Deficits in
a Mouse Model of the Fragile X
Syndrome
Regina Dahlhaus
- P52. On the Role of Clock in Cocaine
Reward-Related Behaviors:
Region-Specific Influence?
Edgardo Falcon
- P53. Long-Lasting Effects of Alcohol on
Glutamatergic Transmission in the
Nucleus Accumbens
Vincent Marty
- P54. Absence of NMDA Receptors in
Dopamine Neurons Attenuates
Dopamine Release but Not
Pavlovian Conditioned Approach
Jones Parker
- P55. Sleep Dysfunction and the Effects
of Extended-Release Zolpidem
during Cannabis Withdrawal
Ryan Vandrey
- P56. Novel NMDA Receptor
Antagonists Identified Using a
Cell-Based Screening Assay for
Allosteric Modulators of NR2D-
Containing NMDA Receptors
Kasper B. Hansen
- P57. Phasic Striatal Dopamine Release
to Cues and Rewards with
Escalating Costs
Matthew J. Wanat
- P58. Structural Basis for Subunit-
Specific Activation of NMDA
Receptors
Kasper B. Hansen
- P59. Corticotropin Releasing Factor
(CRF) Increases Accumbal
Dopamine Release in Naïve, but
Not Stressor Exposed Mice
Julia Lemos
- P60. Alcohol Use during Adolescence
Alters Future Reinforcement
Learning: Behavioral Evidence for
the Aberrant Learning Theory of
Addiction
Nicholas A. Nasrallah

Poster Session 3

Wednesday–Thursday • Peak 1–4

Posters will be available for viewing after 8:30 PM on Wednesday through 6:30 PM on Thursday. Presenters will be with their posters on Thursday from 3:30 to 4:30 PM.

P61. A Single Episode of Early Life Seizures Results in Long-Lasting Changes to the Expression Mechanisms of Long Term Depression

Paul Bernard

P62. Acquisition and Extinction of Fear Memory in a NR2C Knockout Mice

Shashank Dravid

P63. Stress-Enhanced Fear Learning Increases Voluntary Alcohol Consumption and Preference

Edward Meyer

P64. Attenuation of Morphine-Induced Astrocyte Activation and Tolerance Development by Ultra-Low Dose Naltrexone

Catherine Cahill

P65. Lucid Dreaming and Prefrontal Task Performance

Peter Morgan

P66. Opioid Self-Administration in Inflammatory and Neuropathic Chronic Pain Conditions

Carrie L Wade

P67. Analysis of Epileptic Seizures via Nonlinear Computational Tools

Matin Daneshyari

P68. Effects of Nigella Sativa on the Neuronal Alterations of the Striatum and Parkinsonism Induced by Haloperidol

Tafheem Malik

P69. Ipsilateral Orbitofrontal Lesions Alter Signaling of Reward Prediction Errors by Dopamine Neurons in Rat Ventral Tegmental Area

Yuji K. Takahashi

P70. Sequential Ion Pair Formation during Activation of a Sodium Channel Voltage Sensor

William A. Catterall

P71. Knock-Down of CLOCK in the VTA Modifies Dopaminergic Activity and Mood-Related Behavior in Mice

S. Mukherjee

P72. Control of Glutamate Spillover by Transporters in the Hippocampus

Michael Kavanaugh

P73. Mechanical Conflict System (MCS): A Novel Operant Method for Assessing Acute and Chronic Nociception

Thomas Morrow

P74. Rapid Optimization of AMPA Receptor Kinetics and Role of Subunit Independence

Tim Benke

P75. Opioid and Cannabinoid Actions within the Amygdala-Striatal Systems Differentially Contribute to Palatability-Driven Feeding Behaviors

Matthew Will

- P76. Subthalamic Neurons Recorded in Humans Exhibit Agent Selective Responses to Sedatives
M. Bruce MacIver
- P77. Opioid Reward and Withdrawal in Methadone Maintained Patients: Modulation by a Neurokinin 1 (NK1) Receptor Antagonist
Malcolm S. Reid
- P78. Status Epilepticus: Therapeutic Implications of the Receptor Trafficking Hypothesis
Claude Wasterlain
- P79. Blocking PSD95 Interactions Provides Neuroprotection by Maintaining Cortical Function and Neurotrophic Signalling
Michelle Aarts
- P80. A Novel Biomarker for Parkinson's Disease: The Purine Connection
Peter LeWitt
- P81. Pre- and Postsynaptic Regulation of Proopiomelanocortin Neurons via Multiple Opioid Receptor Subtypes
Shane T. Hentges
- P82. Glial Fibrillary Acidic Protein and Vimentin are Negative Regulators of the Neurogenic Niche
Tulen Pekny
- P83. Analysis of the Role of Trace Amine Associated Receptor 1 (TAAR1) in the Movement Control in Parkinson's Disease Models
Tatyana D. Sotnikova
- P84. GLP-1 Receptor Stimulation Reduces Amyloid- β Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease
Harold Holloway
- P85. Antisocial Substance-Dependent Boys' Processing of Rewards and Punishments after Risky Behaviors
Thomas Crowley
- P86. Looking BAC Carefully: Altered Dopaminergic Signaling in BAC D2-GFP Transgenic Mice
Paul F. Kramer
- P87. Constitutively Active Mu Opioid Receptors: A Novel Therapeutic Target for Pain?
Christopher Evans
- P88. Pseudo-Bayesian Analysis of Alzheimer's Disease Genetic Association Data
C. Harker Rhodes

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Session Abstracts

Panel • Sunday 4:30-6:30 PM • Peak 5

1. Making a Mountain Out of a Mogul? Neural Assessment of Effort during Decision Making

Chair: Paul Phillips

Presenters: Stan Floresco, Mark Walton, Steven Kennerley, Matthew Botvinick

To survive in the wild or in society, decisions need to approach optimality in maximizing benefits while minimizing costs. One of those costs that we are faced with in assessing future actions is the amount of energy utilization that is required to achieve the goal. These energetic costs can come in the form of physical or cognitive effort. Appropriate effort-based decision making can be critical for life and death. For foraging animals, the choice to harvest a barren resource could result in energy expenditure that outweighs the energetic gains resulting in net energy loss that is incompatible with survival. Even in environments that have a rich food supply, deficits in the economics of energy management are manifested in traits such as anergia and lethargy that span diagnostic categories of psychiatric disease. Thus, understanding the neural basis of the assessment of effortful decisions is important to understand normal cognitive function and mental illness. This session will discuss the neural basis of effort-based decision making. First, Stan Floresco will present behavioral neuropharmacology approaches to identify the anatomical and chemical substrates of effort processing. Next, Mark Walton will discuss subsecond dopamine signaling in the nucleus accumbens during the assessment of future effort in action selection. Steven Kennerley will present the results from neurophysiological studies that address the encoding of effort in cortical brain regions. Finally, Matthew Botvinick will present functional magnetic resonance imaging data showing the neural representation of effort in the nucleus accumbens when humans are faced with tasks manipulating cognitive demand.

Panel • Sunday 4:30-6:30 PM • Peak 17

2. Do Tonic and Phasic Dopamine Release Activate Distinct Receptor Subtypes?

Chair: Kim Neve

Presenters: Anthony Grace, Weixing Shen, Jeremy Seamans, Christopher Ford

The concentration of dopamine at dopamine receptors depends on both their distance from dopaminergic terminals and the pattern of dopamine release.

Tonic low concentrations of dopamine resulting from spontaneous single unit firing and/or from diffusion out of the synapse might be expected to preferentially activate receptors that have higher affinity for dopamine, whereas phasic high concentrations produced by burst firing or by psychostimulant drugs might be required to activate receptors that have lower affinity for dopamine. Kim Neve will briefly introduce the topic by summarizing biochemical data that have been used to support a model in which, in the basal forebrain, tonic dopamine activates high affinity D2 receptors while phasic dopamine activates lower affinity D1 receptors. Tony Grace will show electrophysiological data to support the model and discuss its implications, Weixing Shen will demonstrate how lesion studies can differentiate between tonic and phasic effects of dopamine, and Jeremy Seamans will present his work indicating that, in the prefrontal cortex, D1 receptors respond to lower concentrations of dopamine than D2 receptors. Chris Ford will conclude with evidence that a high concentration of dopamine is required to activate D2 receptors in the midbrain that mediate phasic dopamine transmission. In this panel/workshop hybrid, the speakers will be encouraged to keep their formal presentations short to allow time for members of the audience to contribute. Any "volunteer speakers" should send a slide or two to the panel organizer by Sunday morning of the conference. Contrarian views are welcome!

Panel • Sunday 4:30-6:30 PM • Peak 11/12

3. Phosphodiesterase 10A Modulation of Basal Ganglia Function: Implications for the Treatment of Psychiatric Disorders

Chair: Erik Charych

Presenters: Erik Charych, Gretchen Snyder, Chris Schmidt, Anthony West

The cyclic nucleotide phosphodiesterase 10A (PDE10A) is highly expressed in basal ganglia circuits and plays a critical role in the metabolism of both cAMP and cGMP. Disruption of PDE10A activity produces effects that potentially modulate basal ganglia output. Furthermore, recent studies support the utility of PDE10A inhibitors for the treatment of brain disorders such as schizophrenia. This panel will provide an update on the molecular, cellular, and systems level effects of PDE10A manipulations and discuss the relevance of these observations for the pathophysiology and treatment of psychiatric disorders. Erik Charych (Wyeth Inc) will summarize recent developments in the cell biology and signaling of PDE10A. Gretchen Snyder (Intra-Cellular Therapies Inc) will discuss the functional role of PDE10A in the regulation of dopamine signal transduction in the striatum, focusing on biochemical cascades involving DARPP-32. She will also summarize biochemical evidence supporting

a preferential role of PDE10A in the modulation of signaling within the D2 receptor-enriched striatopallidal neurons. Tony West (Rosalind Franklin University) will discuss recent work examining how inhibition of PDE10A activity modulates the membrane excitability of striatal MSNs to enhance corticostriatal transmission and striatal output. Chris Schmidt (Pfizer Inc) will review the current state of drug development efforts aimed at manipulating the activity of PDE subtypes as they pertain to psychiatric disorders such as schizophrenia. Discussions generated by this panel are expected to shed light on the many complexities of PDE10A signaling which hold the key for the development of novel treatment strategies for disorders associated with aberrant basal ganglia function.

Panel • Sunday 4:30-6:30 PM • Peak 14

4. Developing Anti-Relapse Medications for Drug Addiction: Challenges and Promises

Chair: Ronald See

Presenters: George Koob, Janet Neisewander, Ronald See, Thomas Newton

The establishment of viable animal models of addiction and relapse has led to increasing attempts to develop pharmacotherapies addiction treatment. However, while promising targets abound, multiple issues face the field in terms of the proper approach to testing putative anti-relapse medications. Among these are the measurement of appropriate endpoints, generation of false positives, and the relationship of basic neuroscience findings to relevant clinical measures of addiction and relapse. This panel brings together four key areas of research focusing on the development of viable anti-relapse treatments. Dr. George Koob (Scripps Institute) will describe medication development strategies for targeting the “dark” side of addiction and relapse, with a particular focus on neuropeptide receptor targets that modulate negative emotional states and the loss of reward function. Dr. Janet Neisewander (Arizona State University) will present findings on the effects of selective monoamine receptor agents observed with animal models in relation to their validity as a screen for anti-relapse medications. Dr. Ronald See (Medical University of South Carolina) will discuss studies that have compared acute vs. chronic dosing strategies with several novel compounds found to attenuate drug-seeking in animal models of relapse. Dr. Thomas Newton (Baylor College of Medicine) will provide a clinical perspective on recent human laboratory studies and controlled clinical trials that have been conducted with novel pharmacotherapies for psychostimulant addiction and relapse and the relationship of these findings to animal model data. The panel will present a novel and integrated perspective on the key issues facing this critical area of addiction research.

5. Circadian Influences on Molecules, Signaling and Memory Formation

Chair: Jerry Yin

Presenters: Karl Obrietan, Martha Gillette, Jerry Yin, Dan Storm

There is a growing appreciation for the widespread influence that circadian rhythms have on many aspects of neurobiology, including complex processes such as learning and memory formation. Animals show “time-of-day” effects on memory formation, with optimal performance occurring at particular times of training and/or testing. How these processes occur at the organismal level, how they might be linked together between cells, and how molecular mechanisms within cells might interpret and use these signals is the topic of this panel. Karl Obrietan will describe the important role of the MAPK/ERK signaling pathway in central clock cycling, and in photic-responsive re-setting of the central clock. This kinase sits near the top of a cascade that communicates with “downstream” effectors (such as mTOR and microRNAs) to help regulate and adjust the clock. Martha Gillette will discuss recent progress on a total peptidomic display of the suprachiasmatic nucleus (the central clock in mammals), and the search for intercellular signaling peptides that could regulate the clock and/or be involved in “synchronizing” different cellular clocks. Jerry Yin will discuss recent progress on time-of-day effects in *Drosophila* memory formation, and how these converge on signaling pathways that affect dCREB2 transcriptional activity. Dan Storm will discuss time-of-day effects on mouse memory persistence, and how this depends upon circadian ERK/MAPK cycling and calcium-stimulated adenylyl cyclase. Collectively, these presentations will describe the current state of the field and contemporary experimental approaches.

6. Modulating Protein Phosphorylation as a Therapeutic Strategy for Neurodegenerative Diseases

Chair: Warren Hirst

Presenters: Warren Hirst, Einar Sigurdsson, John Anderson, Mark Cookson

Phosphorylation is a key regulatory mechanism controlling multiple aspects of normal cellular function. However, aberrant phosphorylation is thought to underlie the pathophysiological state of multiple neurodegenerative disorders including Alzheimer’s disease and Parkinson’s disease. Warren Hirst (Wyeth

Research) will present data on the c-Jun N-terminal kinase (JNK) pathway that potentially links the three major pathological hallmarks of Alzheimer's disease: the development of amyloid plaques, neurofibrillary tangles consisting of hyperphosphorylated tau protein, and neuronal degeneration leading to brain atrophy. Einar Sigurdsson (NYU School of Medicine) will describe immunotherapy targeting phosphorylated tau. This approach, in transgenic mouse models over-expressing human tau, reduces aggregated tau in the brain and slows/inhibits their behavioral phenotype, including the prevention of cognitive impairments. John Anderson (Elan Pharmaceuticals) will present on phosphorylation of α -synuclein at serine 129, a defining feature of the pathology of synucleinopathies such as Parkinson's disease; he will focus on the role of polo-like kinase 2 (PLK2). Mark Cookson (NIH) will discuss kinases that are involved in inherited forms of Parkinson's disease. He will present data suggesting that recessive mutations in PINK1, a mitochondrial serine threonine kinase, negatively influence mitochondrial turnover by loss of function. In contrast, mutations in the cytosolic leucine-rich repeat kinase 2 (LRRK2) cause dominantly inherited Parkinson's disease because of an as yet unclear gain of function. Overall, this panel will provide insights on how modulating phosphorylation of key proteins in neurodegenerative disorders may provide future therapies for these debilitating diseases.

Panel • Sunday 8:30–10:00 PM • Peak 5

7. Novel Ligands and Approaches to Analgesia, Tolerance and Reward

Chair: James Zadina

Presenters: James Zadina, Catherine Cahill, Jay McLaughlin, Lawrence Toll

The four branches of the opioid family play distinct but often interacting roles in the regulation of pain, loss in responsiveness to analgesics, and reward. The mu opioid receptor is the target of most clinically used opioids, but the effectiveness of these agonists is limited by side effects, including reward that is associated with abuse potential, and loss of effectiveness, requiring increasing doses to maintain analgesia. Approaches for achieving a desired effect (analgesia) while limiting side effects include: (1) targeting other opioid receptors (delta, kappa or the opioid-related receptor ORL-1), each of which is also prone to adverse side effects, (2) developing novel ligands that may reflect new concepts of functional selectivity, to improve therapeutic/side effect ratios through a given receptor, (3) elucidating interactions between opioid systems, such as mu and delta interactions in the development of tolerance, and (4) refinement of behavioral methods to better assess the relative effectiveness of novel agonists at

producing wanted vs. unwanted effects. These issues will be discussed from the perspective of mu agonists (James Zadina), delta agonists and delta/mu receptor interactions (Catherine Cahill) the kappa opioid system (Jay McLaughlin) and the nociceptin/orphanin-ORL1 system (Larry Toll).

Panel • Sunday 8:30-10:00 PM • Peak 17

8. Neuro-Inflammation in Aging and Disease

Chair: N. Eric Naftchi

Presenters: Stephen C. Bondy, J. Steven Richardson, Salah Fathy, N. Eric Naftchi

Basal inflammation characterizes the normal aging of the brain that becomes exaggerated or excessive in many neurodegenerative diseases. This unprovoked chronic reactivity, can account for much of the damage to the aging brain. Retarding the degenerative process, may attenuate, delay, or possibly ameliorate some of the progressive neurological diseases. Muscular dystrophies (MD) are a diverse group of inherited diseases, primarily affecting muscles. Disorders result from a constant breakdown of the muscle due to an absence of a crucial protein, dystrophin required for maintaining muscle stability and strength. The muscle is gradually replaced by fibrous (scar) and fatty tissue. Treating with a copper nicotinate complex, improved the muscle power in patients with Duchene muscle dystrophy (DMD). EM revealed increased fibrous tissue in interstitial compartment and mild degenerative changes in muscle fibers accompanied by a decrease in the size and number of the pores in plasma membrane. Mitochondria in the majority of fibers were mostly localized in focal collections of variable size organelles just beneath the plasma membrane. There was an increase in the number and size of the mitochondria coinciding with clinically observed increase in muscle power. Thus, sub-sarcolemmal collections of the mitochondria may contribute more energy to the motility apparatus, governed by the dystrophin, and its related proteins concerning energy production. Bondy will discuss relationship of immunity to disease process and the possibility that melatonin may have utility in inhibition of irrelevant inflammatory responses without compromising immune function. Richardson will illustrate the role of free radicals in neurodegeneration, disease, and aging. Salah will talk about the clinical aspect of Duchene Muscular Dystrophy (DMD), treatment, efficacy and ameliorative changes brought about by a copper nicotinate complex. Naftchi will cover the treatment of DMD with copper nicotinate complex and the effects on the cellular level.

9. Rehabilitation vs. Neuroprotection: Use of Exercise, Environmental and Dietary Therapies to Reduce Brain Damage

Chair: Anna Klintsova

Presenters: Jennifer Thomas, Anna Klintsova, Tammy Ivanco, Tess Briones

Brain injury inflicted by oxygen deprivation (during development or in adulthood) or by developmental exposure to alcohol results in long-term functional and structural abnormalities. Although the mechanisms of damage to the main cell types in the nervous system are reasonably well understood, the main goal remains to be rehabilitation or/and protection from such insult. The goal of the participants in this session is to present the most recent approaches to therapeutic and pharmacological treatment after hypoxia- or developmental alcohol exposure-induced brain damage. J. Thomas will discuss whether perinatal choline, an essential nutrient, can improve outcome following developmental alcohol exposure. She will present exciting data on the effect of choline supplementation during postnatal development on reduction of the severity of learning deficits on a variety of tasks that depend on the functional integrity of the hippocampus and prefrontal cortex. A. Klintsova will talk about the new studies testing the hypothesis that environmental enrichment is necessary to enhance the survival of newly generated neurons in adult hippocampus since exercise alone is not sufficient to rescue reduced cell proliferation and neurogenesis in alcohol-exposed brain. T. Ivanco will report on short term, but chronic, perinatal hypoxia that influences brain and body development and novel approaches, integrating diet and environment, to produce better functional outcome. T. Briones will present findings on the neuroprotective effects of environmental and dietary therapies through modulation of excitotoxicity, inflammatory response, and oxidative stress after transient global cerebral ischemia.

10. Nutrition and the “Longevity Dividend” in Neuroscience

Chair: Erika Allen

Presenters: James Joseph, Jane Cavanaugh, Amanda Smith, Henirette van Praag

Aging is associated with a decrease in motor coordination and balance, as well as, an increase in age related diseases, such as Alzheimer’s and Parkinson’s disease. There are currently no treatments for age-related deficits that are not

associated with a disease state. Therefore, as aging becomes a bigger concern, because of the lack of Medicare and Social Security funds and an increasing population of people aged 65 and older, finding a way to deter the negative effects of aging becomes more imperative. There are different schools of thought on how to decrease the effects of aging without traditional medications, including exercise, diet, and environmental enrichment. This panel will discuss the impact of these alternative treatments on age-related motor decline and neurodegeneration. Jim Joseph will present the effects of blueberry and walnut diets on increasing memory performance with age. Jane Cavanaugh will discuss research data on the effects of resveratrol on kinase signaling and neuroprotection with age. Amanda Smith will discuss the effects of chronic exercise on neurotrophic factors. Henriette van Praag will present data on the effects of exercise, neurogenesis, and aging. Together the panel members will provide evidence that non-traditional treatments may be a valuable asset to aging gracefully and a cohesive overview of alternative ways to deter some of the negative effects of aging.

Panel • Sunday 8:30–10:00 PM • Peak 15/16

11. Innate Immune Genes and Brain Health

Chair: Susanna Rosi

Presenters: Fulton Crews, Thomas Kuhn, Nigel Greig, Susanna Rosi

Neurons respond to biological mediators produced by glial cells and are able to control glia activity and modulate neuron-glia or neuron-neuron communications (cross-talk) by releasing proinflammatory factors. This complex interplay is guided by transcription and translation of innate immune genes. Innate immune gene products can negatively affect neuronal activity and contribute to the various disorders including the potential for alterations in immune function. This session will discuss the innate immune gene-mediated response in the brain during infection, injury, disease and aging and various therapeutic approaches as well as nutritional intervention to restore brain health. Fulton Crews will discuss the persistent activation of innate immune genes and age related neurodegeneration. Dr. Crews will present studies on proinflammatory gene induction in brain through NFkB-NOX-ROS-NFkB positive loops. Tom Kuhn will talk about the neuronal NADPH oxidase—forgotten culprit in the progression of neuroinflammation and healthy diets likely to diminish NADPH oxidases activity. The prototype proinflammatory cytokine most studied as a component of innate immune genes is tumor necrosis factor-alpha (TNF- α). Nigel Greig and Susanna Rosi will present data demonstrating that thalidomide-based TNF- α protein synthesis inhibitors, synthesized in the Greig laboratory,

ameliorate aberrant neuronal functions measured with molecular and behavioral endpoints in animal models of peripheral and central administration of lipopolysaccharide (LPS) and other brain insults. Together these studies will provide a provocative discussion on the crucial role of the innate immune genes as a contributor to neurodegenerative disease and will provide information on novel therapeutic approaches able to modify the gene expression.

Panel • Monday 7:30-9:30 AM • Peak 5

12. SNPs and Chips

Chair: Barbara Lipska

Presenters: Meeta Mistry, Michael Oldham, Mark Cookson, Barbara Lipska

We will present data from genome wide gene expression and genome wide SNP genotyping studies in human brain, and show how gene expression is determined by sex, race, age, brain region and genotype. Meeta Mistry will show the results of a large meta-analysis of genome-wide expression studies of normal human cortex and discuss the effects of age, sex, postmortem interval and brain pH, yielding a “meta-signature” of gene expression changes for each factor. Michael Oldham, by analyzing gene co-expression relationships in microarray data generated from human cerebral cortex, caudate nucleus, and cerebellum, will show that the transcriptomes of human brain regions are robustly organized into co-expression modules that reflect the cellular heterogeneity of brain tissue. This approach reveals that cell type-specific information can be recovered from whole brain tissue without isolating homogenous populations of cells. Mark Cookson will show how the normal human genetic variation influences gene expression in brain. He will present the data from several brain regions and from small groups of identified neurons captured from specific brain regions to show how the heterogeneity of the brain influences our ability to detect genetic influences. Barbara Lipska will present data from the prefrontal cortex of ~270 individuals across the lifespan, including the 2nd trimester of fetal life, and show how genetic variability, sex and factors related to race affect transcript expression dynamics in the developing brain and across the lifespan. Understanding determinants of variability in gene expression in normal individuals will help assessing lifetime risk of common brain disorders.

13. Genetic Vulnerability of Striatal Circuits in Addiction

Chair: Jacqueline McGinty

Presenters: Yasmin Hurd, John Wang, John Neumaier, Jacqueline McGinty

Changes in gene/protein expression in the striatum underlie many longterm neuroadaptations induced by abused drugs. The goal of this panel is to discuss the genetic/molecular vulnerability of striatal circuits leading to addiction. Yasmin Hurd will discuss the contribution of genetic polymorphisms aligned to the striatonigral and striatopallidal pathways in relation to heroin abuse and gene expression levels in the human brain. Viral-mediated manipulations of discrete striatal cell populations will be discussed in relation to heroin self-administration vulnerability. John Wang will discuss the sensitivity of Homer1a expression in striatal neurons in response to dopamine stimulation. His evidence shows that D1 stimulation induces a rapid and transient Homer1a expression which serves as a negative feedback mechanism to suppress group I mGluR signaling in rats. John Neumaier will discuss experiments using new molecular tools—designer receptors activated by synthetic ligands—that can selectively activate or silence neurons with temporal and spatial precision. These were introduced into direct or indirect pathway medium spiny neurons of rats using phenotype-specific viral vectors, and the results indicate that the indirect pathway interferes with, while the direct pathway facilitates, the development of sensitization to amphetamine. Jackie McGinty will discuss evidence that intrastriatal phosphoinositide 3 kinase (PI3K) inhibition and viral vector-mediated regulator of G protein signaling (RGS) 4 overexpression both enhance locomotor activity while inhibiting vertical activity after acute amphetamine. The relationship to phospho-ERK and phospho-Akt induction in striatal neurons will be described. These studies strengthen the evidence that discrete striatal neuroadaptations underlie drug-induced dysfunctions leading to addiction.

14. Cell Renaissance in the Damaged CNS: Gliogenic Versus Neurogenic Niches

Chair: Friederike Klempin

Presenters: Vittorio Gallo, Philip Horner, Friederike Klempin

In the adult brain, neural stem cells reside in regional niches formed by a microenvironment that dictates the rate and type of neural cells developed. In models of neurodegeneration, neurogenic niches are shown to exhibit an injury-induced increase in adult neurogenesis. However, in typically gliogenic areas, such as the entorhinal cortex (ECX) no neuronal rebirth program of local endogenous

precursor cells occurs. In order to better understand how cell replacement can be achieved, this panel will review neural stem cells within their various niches in the intact adult CNS and after injury in the context of regenerative responses. Vittorio Gallo will give an overview about multipotency of neural stem cells in the intact brain, and will discuss molecular and cellular cues that regulate neural progenitor fate decision during early postnatal development. Philip Horner will examine the injury signals in non-neurogenic regions that limit cell genesis, create glial fate restriction and lead to scar formation in traumatic injury of the spinal cord, and will particularly focus on blood-derived signals. Friederike Klempin will illustrate the regenerative potential of the non-neurogenic adult ECX where neuronal loss occurs early in AD, and present data of how the instructive niche can be stimulated with appropriate neurogenic signals (BDNF), and how to direct cell fate (Olig2). Together, this session will look for parallels and differences between regenerative regions and non-regenerative regions of the adult CNS in order to define potential new strategies for improved nerve cell replacement in injury and degenerative diseases.

Panel • Monday 7:30-9:30 AM • Peak 14

15. Cerebrovascular Perfusion Confusion: Function and Dysfunction

Chair: Charles Leffler

Presenters: Charles Leffler, Dale Pelligrino, Jonathan Jaggar, David Busija

The cerebrovascular circulation is regulated to precisely match blood flow to neuronal activity. This regulation is complex, incompletely understood, but critically important to any resemblance of normal brain function from cognition to central control of vegetative functions. Unlike the systemic circulation where arteries and large arterioles play little role in controlling blood flow, arteries from the Circle of Willis to pial arteries and arterioles are major resistance vessels and are critical for control of blood flow. In the cerebrovascular circulation, signals to vascular smooth muscle come from endothelium, nerves, astrocytes, and pericytes, which form a neurovascular unit. Control of cerebrovascular circulation is easily impaired by pathological conditions such as ischemia/reperfusion, hemorrhage, traumatic head injury, hypertension, diabetes mellitus, atherosclerosis and eclampsia. The first three speakers will focus on mechanisms of physiological regulation and the last on a condition where this regulation may be impaired. I will discuss astrocytic communication of neuronal signals to the arteriolar vascular smooth muscle utilizing the gasotransmitter, carbon monoxide. Dale will talk about the central role of astrocytes in mediating both local and remote (upstream) vasodilation following increased neuronal activity (“In the realm of neurovascular coupling, the astrocyte is king”). Jonathan will discuss novel intracellular calcium and ion channel-mediated

signaling mechanisms that control cerebral artery contractility. Finally, David will discuss impairment of cerebrovascular function as a component of metabolic syndrome applicable to stroke, small vessel disease, and Alzheimer's disease.

Panel • Monday 7:30-9:30 AM • Peak 15/16

16. Phosphodiesterases 8-11: The New Kids on the Block

Chair: Christopher Schmidt

Presenters: Joseph Beavo, Jos Prickaerts, Gretchen Snyder, Erik Charych

Phosphodiesterases (PDE) are the only enzymes known to degrade cyclic nucleotides. To date, 11 families of PDEs have been identified. Most PDE families are expressed in the brain, but no two PDEs show the same regional/subcellular distribution, enabling exquisitely precise regulation of cyclic nucleotide signaling. Great attention has been paid in recent years to the potential of PDEs as therapeutic targets. As such, it is important to gain a full understanding of how each PDE family influences brain function. To this end, Joseph Beavo will describe the role of PDE8 in the regulation of the HPA axis and stress responses, focusing on work from PDE8B knockout mice. Jos Prickaerts will compare and contrast how PDE9A and PDE10A inhibitors alter behavioral domains relevant to psychiatric disease. Gretchen Snyder will then discuss the role of PDE10A in regulating protein phosphorylation cascades in medium spiny striatal neurons. She will compare and contrast the functional effect of PDE10 inhibition on motor activity with that of other striatal-enriched PDEs, like PDE1. Finally, Erik Charych will discuss the first characterization of PDE11A function in the brain. Sharing behavioral, anatomical, and biochemical data collected in PDE11A knockout mice, she will elucidate a role for PDE11A in ventral hippocampal functioning. Together, these talks will elucidate the differential role each PDE family plays in the regulation of brain function and will show that not all PDE families are created alike.

Panel • Monday 7:30-9:30 AM • Peak 6/7/8

17. Is It Really Worth It? Prefrontal Cortex Contributions to Valuation and Control of Choice Behavior

Chair: Mark Walton

Presenters: Matthew Roesch, Peter Rudebeck, Lesley Fellows, Todd Hare

Numerous studies have investigated how reward value is learned and encoded in the brain and how this guides decision-making. However, such decisions depend not only on anticipated outcomes but also on factors such as the context

of the available alternatives and the likelihood of the outcome occurring. Moreover, subjective value also needs to take into account the costs that would be incurred by choosing that option, and current motivational goals. The prefrontal cortex—particularly orbital and ventromedial prefrontal cortex—has long been implicated in flexible decision-making and subjective valuation, but there is little consensus as to each region's contribution and how each part interacts with connected structures. In this session, we will examine four diverse, complementary approaches to this issue from different methodological standpoints. First, Matthew Roesch will discuss electrophysiological recordings investigating how reward magnitude and delay-to-reward are encoded in rat orbitofrontal cortex and how this compares with other interconnected regions. Peter Rudebeck will then present data on how lesions to orbitofrontal cortex in monkeys affect flexible reward-guided decision-making and how outcome information is represented in different parts of region. Lesley Fellows will review a series of studies investigating how human patients with damage to orbital and ventromedial PFC learn about value and make judgements about the relative value of alternatives. Finally, Todd Hare will discuss human functional neuroimaging studies on the role of parts of orbital and ventromedial PFC in subjective valuation and how these signals may be used in self-control and decision-making.

Panel • Monday 4:30-6:30 PM • Peak 5

18. Genetic Risk Factors, Fetal Transcripts, Brain Development, and Schizophrenia

Chair: Joel Kleinman

Presenters: Daniel Weinberger, Thomas Hyde, Amanda Law, Kristin Bigos

Single nucleotide polymorphisms (SNPs) in genes associated with increased risk for schizophrenia and/or its related intermediate phenotypes may exert their effects by altering the levels of transcripts that are primarily expressed in the fetus. This hypothesis provides a mechanistic link between the neurodevelopmental hypothesis of schizophrenia and recently discovered SNPs in genes associated with increased liability towards this disorder. Dr. Daniel Weinberger will provide an overview of the neurodevelopmental hypothesis of schizophrenia focusing on the interaction between obstetrical complications and genes associated with increased risk for illness, including BDNF, AKT1, and GRM3. He will also discuss how the development of molecular genetic technologies have made it possible to test this hypothesis at the genetic and cellular level. Dr. Thomas Hyde will discuss maturational abnormalities in several GABA signaling genes, and the relationship of their expression to allelic variation in GAD1, the gene that encodes one of two primary synthetic enzymes for GABA. Dr.

Amanda Law will present data on the NRG-ERB signaling pathway that is critical for neurodevelopment and implicated in schizophrenia. She will focus on NRG3, a specific ligand for ErbB4, presenting evidence that the gene undergoes complex splicing and that clinically-associated polymorphisms in NRG3 regulate expression of specific isoforms in the human adult and developing brain and in schizophrenia. Dr. Kristin Bigos will show how glutamate-related genes, GRM7 and CACNA1C, associated with bipolar disorder, are also implicated in early brain development and schizophrenia. This panel will tie together current inquiries into genetic risk factors for schizophrenia with the longstanding supposition that abnormalities in brain development, occurring years before the onset of illness, are the underpinnings of this disorder.

Panel • Monday 4:30-6:30 PM • Peak 17

19. Impact of the Mesolimbic “Addiction” Circuitry on Food Intake and Food Seeking

Chair: Jeffrey Grimm

Presenters: Jeffrey Grimm, Gary Aston-Jones, Bart Hoebel, Stephen Benoit

Mesolimbic circuitry has been identified as the primary neurobiological substrate for the rewarding effects of both drugs and food. Addiction to drugs has been presented as a pathological adjustment of components of this system. More recently, the concept of food addiction, in particular related to sweet, high-fat, palatable foods has gained acceptance among some drug addiction researchers. The general hypothesis is that food addiction behaviors are mediated by changes in mesolimbic circuits in a manner similar to those by drugs of abuse. This panel will present findings on how mesolimbic circuits contribute to food addiction behaviors as examined in rat models of addiction frequently utilized for examining the primary and secondary rewarding effects of drugs of abuse. Jeffrey Grimm will present the results of systemic and nucleus accumbens core and shell site-specific antagonism of dopamine D1 receptors on responding for a cue previously associated with sucrose self-administration. Gary Aston-Jones will describe evidence for involvement of orexin (hypocretin) neurons in the lateral hypothalamus projecting to the ventral tegmental area (VTA) in conditioned food and drug seeking. Bart Hoebel will present evidence supporting a hypothesis of differential roles for dopamine and endogenous opioids in sugar vs. fat binge behaviors. Finally, Stephen Benoit will describe how prolonged exposure to a high-fat diet alters VTA and hypothalamic leptin-mediated responding for food as well as conditioned neuronal activation and accumbal dopamine responses in the expectation of food.

20. Molecular Mechanisms of Axon Formation and Guidance

Chair: Tom Soderling

Presenters: Tom Soderling, Katherine Kalil, Gianluca Gallo, James Bamburg

The functionality of neurons is dependent on their compartmentalized polarization of dendrites and an axon from initially immature neurites. The rapid and selective outgrowth of one neurite, relative to the others, to form the axon is critical in initiating neuronal polarity. Multiple signal transduction pathways that ultimately reorganize the cytoskeleton are essential to the initial polarization and subsequent extension and guidance of axons. Dr. Soderling will demonstrate a role for activation of membrane-associated Ca²⁺/CaM kinase I by Ca²⁺ permeable TRPC5 channels in the maturation of a neurite (Stage 2) into an axon (Stage 3) in cultured hippocampal neurons. Dr. Kalil will show that Wnt5a increases axon outgrowth while inducing repulsive guidance in cortical neurons. These effects are mediated by calcium signaling via IP₃ receptors or through TRP channels. These Ca²⁺ signaling pathways probably modulate the cytoskeleton. Dr. Gallo will present evidence that myosin II, whose interaction with the actin cytoskeleton generates intracellular force, does not have a role in specification of the axon, but rather regulates the timing of axonal specification. In addition, myosin II is a major determinant of the growth of minor processes, the precursors to formation of the axon. Finally, Dr. Bamburg will discuss cofilin-mediated actin dynamics, growth cone-like waves, and cofilin regulatory pathways that are part of the signaling to axon formation.

21. When Drug Abuse Becomes Compulsive: Unraveling the Role of Ventral and Dorsal Striatal Circuits in Addiction

Chair: Ingo Willuhn

Presenters: Erik Oleson, Friedbert Weiss, Ingo Willuhn, Amanda Gabriele

The transition from recreational drug use to compulsive drug abuse is a hallmark of drug addiction. This transition is accompanied by an escalation of drug consumption that can be modeled in rats self-administering cocaine when given extended access to the drug. Drug intake in early stages of addiction is strongly regulated by neurotransmission in the ventral striatum. Accumulating evidence suggests that increased drug seeking and taking during later stages of addiction may occur as progressive drug-induced recruitment of more dorsal areas of the striatum exert greater control over drug seeking. However, little is known

about the role of specific circuits and neurotransmitter systems during these later stages of addiction. Understanding the neural basis of the switch from recreational to compulsive drug taking is important to understand and develop better treatments for drug addiction. This session will discuss neural substrates underlying this transition. First, Erik Oleson will present data demonstrating that escalated drug consumption is associated with a decrease in the efficacy of cocaine to inhibit dopamine uptake in the ventral striatum. Next, Friedbert Weiss will discuss behavioral neuropharmacology approaches to identify the contribution of glutamate signaling in the ventral striatum to the development of compulsive drug taking. Ingo Willuhn will present electrochemical data showing changes in real-time dopamine signaling in the ventral and dorsolateral striatum over time during cocaine self-administration. Finally, Amanda Gabriele will present the results from studies that address the role of the dorsolateral striatum in relapse to drug taking following varied histories of cocaine self-administration and different periods of abstinence.

Panel • Monday 4:30-6:30 PM • Peak 15/16

22. Skiing Moguls: How the Brain Navigates the Steep Slope of Motor Learning

Chair: Donald Robin

Presenters: Peter Fox, Charles Larson, Julien Doyon, Donald Robin

Mastering complex motor skills requires extensive practice and experience. The goal of learning is to maximize performance while minimizing the expenditure of energy. The “slope” of learning is related to numerous factors including task complexity, the structure of practice and the nature of feedback. Audio-video recordings, EMG, reaction times and 3-D kinematics are typical measures of motor skill performance. Functional brain imaging allows for the study of the neurobiology of skill acquisition particularly when combined with one or more of the above measures. This session will provide a discussion of how fMRI, positron emission tomography (PET), and transcranial magnetic stimulation (TMS) can be used understand the basic and clinical neuroscience of the motor system. The session is organized and introduced by Donald A. Robin who will present the use of 3-D kinematics and audio recordings during TMS-induced performance alterations that inform models of normal and disordered motor control. Julien Doyon will describe the use of fMRI to study motor learning. Charles Larson will describe the combined use of fMRI, TMS and laryngeal EMG to investigate pathways underlying vocalization in non-human primates and humans. Peter T. Fox will describe the combined use of TMS, EMG, PET, fMRI, an image-guided robot, and structural equation modeling to model motor-system connectivity in humans and baboons.

23. Dopamine Signaling and Disease: Wormholes, Flytraps, Organic Farmers, and Mouseketeers in the Pursuit of New Medications

Chair: Randy D. Blakely

Presenters: Randy D. Blakely, David Krantz, Amy Newman, Aurelio Galli

Dopamine signaling is critical for motor function, response to novelty, reward, and executive function, among other actions. Compromised dopamine signaling is associated with Parkinson's disease, hypotonia, addiction, and Attention-Deficit Hyperactivity Disorder (ADHD). Penetration of the determinants of risk for these disorders, and surmounting the limitations with current dopamine-based therapeutics requires elucidation of DA-linked novel molecular targets and gene networks. The four speakers in this panel will illustrate examples of how their investigations of novel genetic models, gene networks and pharmaceuticals enrich our understanding of dopamine signaling and opportunities for medication development. Randy D. Blakely (Vanderbilt) will discuss how studies of dopamine signaling in the nematode *C. elegans* can provide new insights into a conserved network of genes that sustain dopamine signaling and how forward genetics can be applied to identify new targets for medication development. David Krantz (UCLA) will describe his lab's efforts to exploit the model system *Drosophila melanogaster* for insights into mechanisms of Parkinson's disease as well as how the nervous system adapts to reduced dopamine stores. Amy Newman (NIDA) will describe a novel class of molecules that target the dopamine transporter but which appear to be able to attenuate biochemical and behavioral actions of cocaine, providing a platform for the development of novel treatments for cocaine addiction and ADHD. Finally, Aurelio Galli will discuss findings from his group using rodent fMRI and transgenic mice that demonstrate a surprising role for insulin signaling in the actions of dopamine, norepinephrine and amphetamines in the CNS.

24. Making Sense of Multisensory Integration

Chair: Michael Beauchamp

Presenters: Michael Beauchamp, Stephen LaConte, Paul Laurienti

Most of our everyday activities require us to integrate information from multiple sensory modalities. However, little is known about the neural mechanisms

for this important cognitive operation. While blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) experiments in humans have identified dozens of brain areas that are multisensory, traditional fMRI analysis techniques of looking for active “blobs” in the brain have had limited success at moving beyond mere localization. In this panel, three speakers will discuss new methods that have the potential to make sense of multisensory integration. First, Michael Beauchamp will present new data on correlation analysis for understanding brain connectivity during visual-tactile and auditory-visual multisensory integration. Second, Stephen LaConte will show how real-time multivoxel pattern analysis (MVPA) can be used to train subjects during multisensory integration in a speech motor task. Third, Paul Laurienti will demonstrate that graph-theory based network analysis is a powerful new tool to understand brain dynamics during multisensory integration and other complex cognitive tasks.

Panel • Monday 8:30-10:00 PM • Peak 17

25. Inhibition in Striatum

Chair: Stefano Vicini

Presenters: Anatol Kreitzer, Stefano Taverna, Tibor Koos, Stefano Vicini

Striatum is a crucial brain structure implicated in devastating neurological disorders and is unique in the central nervous system as it contains mostly GABAergic neurons interspersed with very few large cholinergic interneurons. Recent development in mouse genetics have produced several mouse lines with neurons in the striatal circuitry labeled by fluorescent dyes that allows simultaneous patch-clamp recordings from identified neuronal elements. This panel will present different and complementary perspectives on the reciprocal connections and regulations between subtypes of medium spiny neurons and GABAergic interneurons, fundamental for our understanding of the role of striatum. First Dr. Anatol Kreitzer will define distinct microcircuit functions of striatal interneuron subtypes characterizing synaptic properties and their connectivity rules. Second, Dr. Stefano Taverna will compare the synaptic connectivity between pairs of striatonigral and striatopallidal medium spiny neurons, in both intact and dopamine depleted mice relevant for Parkinson's disease. Third, Dr. Tibor Koos will describe the physiological properties of local GABAergic circuits that are activated by cholinergic interneurons. Finally, Dr. Stefano Vicini will focus on the role of tonic activation of specific GABA_A receptors in regulating excitability of medium spiny neurons and interneurons acting as target to distinct dopaminergic receptor activation.

26. Synaptic Basis of Circuit Function and Behavior

Chair: John Isaac

Presenters: A. Villu Maricq, Grae Davis, John Isaac, Anatole Krietzler

This panel will discuss recent advances in understanding how synaptic mechanisms produce functional circuits that lead to behavior. In recent years the use of forward genetics combined with electrophysiological and behavioral assays in model organisms such as worms and flies has produced huge advances in identifying novel mechanisms essential for synaptic function that underlies circuits and behavior. In rodents, the development of high resolution imaging techniques combined with electrophysiology and genetic manipulations has enabled equally significant advances to be made in understanding synapses and circuits in the mammalian brain. This panel brings together experts in these diverse complementary areas to provide an overview and discuss recent new findings on this topic. Villu Maricq will present work on the mechanisms regulating glutamatergic synaptic function in *C.elegans* and the roles of these mechanisms in behavior in the worm. Grae Davis will discuss mechanisms regulating presynaptic function at the neuromuscular junction in *Drosophila* and how such mechanisms regulate synaptic homeostasis. John Isaac will present work on the mechanisms by which sensory experience drives the construction of functional circuits in mammalian neocortex focusing on layer 4 of barrel cortex. Anatole Krietzler will discuss the mechanisms by which spines regulate and integrate synaptic function in hippocampus and striatum.

27. Non-Invasive CNS Repair: The Double Diamond Run

Chair: Isabelle Aubert

Presenters: Victor Rafuse, Brian Kaspar, Isabelle Aubert, Henriette van Praag

The blood-brain barrier (BBB) is a protective network of blood vessels and cells that prevents many substances from entering the central nervous system (CNS). While the BBB remains an innate defender of brain health, it frustrates scientists developing cell, gene and drug therapies for treating the CNS. This panel will present non-invasive strategies to bypass the BBB for CNS repair in injury and disease. Dr. Rafuse (Dalhousie University) will discuss cell transplantation combined with electrical stimulation to restore contractile function and reverse muscle fiber atrophy of denervated myofibers. Dr. Kaspar (The Research Institute at Nationwide Childrens Hospital) will highlight the potential of adeno-associated virus administered in the bloodstream for gene delivery to neurons

and astrocytes of the brain and spinal cord. Dr. Aubert (Sunnybrook Research Institute) will present the application of focused ultrasound, guided by magnetic resonance imaging, to temporarily increase the permeability of the BBB, allowing the delivery of large therapeutic molecules (e.g. anti-amyloid-beta antibodies) to pass from the periphery through the BBB into the brain. Dr. van Praag (NIA) will review synergetic effects of diet and exercise on the stimulation of neurogenesis, cell survival, synaptic plasticity and vascular function. She will also describe a molecule present in flavanol-containing foods, which after ingestion is absorbed in the circulation, crosses the BBB, and may have direct effects on neuronal signaling. The optimal non-invasive approach to brain health may be found at the WCBR: learn, exercise, eat and sleep well.

Minicourse • Monday 8:30-10:00 PM • Peak 15/16

28. Synergistic Merge of Operant Conditioning and Chronic Pain Models

Chair: Carolyn Fairbanks

Presenters: Carolyn Fairbanks, S. Steve Negus, T. Jeff Martin, Andrea Hohmann

The recent epidemic in diversion of sustained release opioids prescribed for the treatment of chronic pain has highlighted multiple challenges of optimizing pain management approaches. It is important to clearly understand the biological bases for a number of factors related to opioid pharmacotherapy including, but not limited to, the effectiveness of opioid treatment under conditions of chronic pain, analgesic therapy, and the potential for escalation of extra-analgesic motivation for opioid-related reward beyond that required for pain relief. Applied separately, neither standard models of pain nor those of addiction will address these key questions. An approach that is increasingly used includes combining rodent models of chronic pain with those of self-administration and central administration. The merge of these techniques is accompanied by complex technical and experimental design challenges. This minicourse is intended to profile approaches that have been successfully applied in various forms by the panelists. Dr. Fairbanks will introduce the session and define the key challenges. Dr. Steven Negus will discuss the pharmacokinetic and pharmacodynamic aspects associated with delivery of reinforcing agents in merged models of analgesia and operant conditioning. Dr. T. Jeff Martin will describe his methods for study of centrally delivered analgesics in models of addiction. Dr. Andrea Hohmann will discuss the use of opioid and non-opioid reinforcing agonists in models of chronic pain. It is expected that through dialogue among the minicourse presenters and the audience members that new lines of investigation and/or approaches may arise to address the issues associated with chronic pain management and addiction.

29. Synapses and Circuitry of the Retina

Chair: Catherine Morgans

Presenters: Stephen Massey, Wei Li, Ron Gregg, Lane Brown

This panel will discuss new findings on the physiology and functional organization of retinal synapses and circuitry. Steve Massey will talk about the distribution of Cx36 in the mouse retina. A mouse line will be described in which cones are visualized by expression of the glycine transporter. Wei Li will discuss the photoreceptor ribbon synapse in the hibernating ground squirrel retina. In this species, photoreceptor synaptic ribbons undergo drastic morphological changes. Correlating the functional changes with the structural alterations of the ribbon synapse in the ground squirrel has yielded new insights into synaptic ribbon function in general. Ron Gregg will present findings demonstrating that mGluR6 mediated gating of a non-specific cation channel, identified as TrpM1, in retinal depolarizing bipolar cells requires the protein nyctalopin. Nyctalopin is an extracellular small leucine rich proteoglycan, and experiments examining its interaction and impact on expression of Trpm1 will be described. Lane Brown will present evidence that TRPM1 is the mGluR6-coupled cation channel in rod bipolar cells, and describe the kinetics and pharmacology of TRPM1 and the mGluR6-coupled current in rod bipolar cells and cone ON-bipolar cells.

30. Photoreceptors and Mechanosensory Hair Cells in Development, Disease, and Regeneration

Chair: Monte Westerfield

Presenters: Teresa Nicolson, David Raible, Brian Perkins, Monte Westerfield

Photoreceptors and mechanosensory hair cells are highly specialized sensory cells with ribbon synapses for sustained high frequency release of synaptic vesicles and actin or tubulin containing cilia. Mutations in components of these subcellular structures lead to deafness, blindness, or deafblindness. This panel will present new information about proteins required for development and function of these cells. Nicolson will present work on animal models for human deafness. Her laboratory has identified molecules required for hair-cell function and she will discuss defects in hair-cell synaptic transmission that underlie heritable deafness. Raible will present work from his laboratory on mechanisms underlying hair cell death using the zebrafish lateral line system. Because they are located on the surface of the body, lateral line hair cells are

accessible for visualization and manipulation. He will describe genetic and small molecule screens for modifiers of hair cell death. Perkins will present analysis of intraflagellar transport (IFT) function in photoreceptors. Although the role of anterograde IFT by kinesin-II in photoreceptor outer segment formation is well established, the function of retrograde IFT in vertebrate photoreceptors remains unclear. Using genetic analysis, the Perkins laboratory has identified cytoplasmic dynein-2 and components of the IFT particle in photoreceptor survival and function. Westerfield will present analysis of components of the Usher protein complex in photoreceptors and hair cells. Mutations in Usher genes lead to deafblindness. Analysis from the Westerfield laboratory of human patients and animal models has identified new components of the Usher complex that function in ciliary transport and synaptic transmission.

Panel • Tuesday 7:30-9:30 AM • Peak 17

31. Glutamate's Roles in Opiate Addiction

Chair: Jerry Frankenheim

Presenters: Ryan LaLumiere, Ronald See, Virginia Pickel, Elena Chartoff

Though roles for plasticity in brain glutamatergic systems have been well described in psychomotor stimulant addiction, roles for glutamate in opiate addiction are less established. However, recent findings indicate that glutamatergic plasticity plays critical roles in opiate addiction. Ryan Lalumiere will show that reinstatement of heroin-seeking (relapse model) is mediated by plasticity of glutamatergic afferents from prelimbic cortex to nucleus accumbens (NAc) core. His findings indicate that heroin self-administration produces long-term alterations in synaptic efficacy and metaplasticity in the prelimbic-accumbens core pathway. Heroin self-administration alters dendritic spine morphology, and a heroin reinstatement-priming injection produces rapid alterations in the spines. The neural circuitry underlying reinstatement of heroin-seeking, to be described by Ronald See, is more diffusely distributed than that for cocaine, likely because heroin indirectly stimulates dopamine (DA) release by activating mu-opioid receptors, while psychostimulants directly increase DA activity. In particular, recent data on cortical regulation of heroin-seeking will be described. Virginia Pickel will demonstrate that chronic morphine alters surface/synaptic availability of AMPA GluR1 subunits in mesolimbic DA neurons, many of which terminate in the NAc shell. In this region, she will demonstrate that prevalence of DA axons, and dendritic and axonal distributions of mu-opioid receptors, depend on expression of cannabinoid-type 1 receptors. Elena Chartoff will show that activation of AMPA receptors in the NAc is aversive and necessary for expression of morphine withdrawal-induced negative affect. Since alleviation of aversive states motivates relapse, these findings are consistent with the idea that morphine-induced neuroadaptations in glutamate transmission are critical for opiate addiction.

32. Transcriptional Regulation in the Brain: How to Accessorize Your Genes

Chair: Thomas Hyde

Presenters: Michael Dean, Reini Luco, Iris Cheung, Erin Newburn

Proper development in the brain depends upon the careful coordination gene expression in both the temporal and spatial domains. Mutation or abnormalities in the transcriptional regulatory elements may have serious implications for brain development, leading to developmentally based brain disorders such as mental retardation and schizophrenia. Critical elements regulating gene expression include methylation, histone acetylation, alternative splicing, and gene silencing. This session will highlight several examples of each of these processes, and their relationship to brain function and disease. Dr. Michael Dean will present data on strategies to comprehensively sequence all the human miRNA genes using human cancers as a model. Dr. Maria Reina Fernandez de Luco will explore the possibility that chromatin structure and epigenetic modifications also contribute to control of alternative splicing. Her work shows that she has identified a chromatin-binding adaptor protein which recruits regulators to nascent RNA. Dr. Iris Cheung will focus on profiling specific histone modifications across the neuronal genome in the developing prefrontal cortex. She will emphasize H3K4me3, a histone modification mark that is enriched around transcription start sites. Dr. Erin Newburn will discuss how the complexity of alternative splicing in the DISC1 gene has lead to alterations in protein-protein interactions. The panel will provide a look at how these processes are key regulatory phenomena in human brain and result in amazing diversity of the human genome.

33. Last but Not Least: Delayed Onset of Reward-Related Frontal Cortical Function in Adolescence

Chair: Kuei Y. Tseng

Presenters: Julie Markham, Frances Leslie, Kyle Frantz, Kuei Y. Tseng

Adolescence is a vulnerable period for onset of some major psychiatric disorders and substance abuse. However, we know very little about the neurodevelopmental processes that may contribute to this vulnerability. Here, we will discuss several mechanisms that may underlie increased susceptibility to drug addiction in adolescence. First, Julie Markham will present quantitative neuroanatomical data showing that volumetric changes occurring over periadolescence

in the rat prefrontal cortex are likely mediated by a combination of cellular events, including a late wave neuronal apoptosis as well as continued myelination and dendritic ramification. These processes follow sex-specific patterns that could contribute to sex differences in psychiatric illness. Next, Frances Leslie will describe the unique effects of brief, low dose nicotine treatment on the plasticity of reward pathways in adolescent rat brain. Integrated behavioral, neurochemical and neuroanatomical studies indicate that these effects are mediated by dopamine-serotonin interactions. Using the i.v. drug self-administration model, Kyle Frantz will discuss surprising data suggesting that rats self-administering drugs during periadolescence demonstrate lower rates of context- or cue-induced relapse after abstinence, and fail to show robust “incubation of drug craving” compared with older adults. Finally, Kuei Tseng will summarize data showing that a different form of neuroadaptation occurs in the adolescent vs. adult brain when exposed to cocaine, especially in the rostral frontal cortex. Several synaptic mechanisms underlying these changes will be presented. We will conclude by proposing a common mechanism that couples normative maturation of the mesocorticolimbic system with late adolescent onset of psychiatric and addiction-related syndromes.

Panel • Tuesday 7:30-9:30 AM • Peak 15/16

34. Regulation of Ionotropic Glutamate Receptors

Chair: Katherine Roche

Presenters: Richard Haganir, A. Villu Maricq, Katherine Roche, Roger Nicoll

Glutamate receptors mediate fast excitatory neurotransmission and are critical for neuronal development and synaptic plasticity. Over the past decade, significant progress has been made in elucidating the molecular mechanisms responsible for the functional regulation of glutamate receptors. In particular, many proteins have been identified that interact with glutamate receptors and regulate receptor trafficking and/or channel function. Rick Haganir will present recent findings on the protein 4.1N, which interacts with the AMPA receptor GluR1 and regulates expression of AMPA receptors on the surface of neurons. A. Villu Maricq will discuss the modulation of AMPA receptor function by CUB-domain transmembrane proteins. Katherine Roche will present findings showing that the trafficking of cerebellar NMDA receptors is facilitated by Akt/PKB phosphorylation of the NR2C subunit and interactions with 14-3-3 proteins. Finally, Roger Nicoll will discuss recent findings from his group demonstrating that the AMPA receptor auxiliary subunits known as TARPs interact and modulate AMPA receptor function with differing stoichiometry in different neuronal populations.

35. Why Wait? Rapid-Acting Antidepressant Strategies and Mechanisms of Action

Chair: Steven Potkin

Presenters: Steven Potkin, William Bunney, Ruth Benca, Fritz Henn

It takes 2 to 8 weeks for antidepressant medications to work, creating unnecessary suffering and increased risk of suicide. Sleep deprivation (SD) and ketamine infusion (KI) can each produce a robust and immediate (within 24 hours) resolution of depressive symptoms. This panel will discuss these treatments and their mechanisms of action (MOA). Steven Potkin will review the clinical efficacy and safety data of KI, including new data on sustained response with repeated KI. He will present data demonstrating that increased activity in the anterior cingulate (AnCg) predicts antidepressant response to both ketamine and sleep deprivation (SD). The AnCg is part of a proposed depression circuit involving four key structures: the AnCg, habenula, suprachiasmatic nucleus, and the paraventricular nucleus of the thalamus (PVT). Evidence suggests that these structures may play a role in rapid antidepressant actions. Ketamine blocks NMDA glutaminergic activity and may target these receptors in the PVT. William Bunney will present two relevant clinical studies: 1) Imaging biomarkers and genetic biomarkers that predict which patients respond to SD; and 2) new data on a strategy to sustain the rapid antidepressant response to SD. Ruth Benca will discuss the effects of slow wave sleep deprivation in depressed subjects that produce antidepressant response while maintaining relatively normal amounts of total sleep. She will also discuss the effects of SD on fear/anxiety, motivation, and impulsivity in animals. A well-studied animal model of depression is learned helplessness. Fritz Henn will discuss recent work on the circuits that mediate helplessness, identifying the final control point as the habenula. This has been verified in patients following tryptophan depletion. Glutamanergic overactivity, the suggested MOA, perhaps drives this response via decreased astrocytic uptake of glutamate. Studies aimed at increasing astrocytic glutamate uptake will be presented as a method to develop rapid and effective antidepressants.

36. Here We Come to Save the Day: Finding the Mighty Mouse Model of Schizophrenia

Chair: Paul Glineburg

Presenters: Amanda Law, Karoly Mirnics, Toshifumi Tomoda, Paul Glineburg

Most psychiatric disorders have complex and often human specific phenotypes that are difficult to model in rodents. However, certain biologic phenotypes associated with the human disorders have counterparts in rodents. This session will cover the behavioral and molecular features of disease risk-associated genetic models of schizophrenia in mice, with an emphasis on the advantages and disadvantages of single gene modeling. Dr. Amanda Law will describe recent findings from new genetically modified mice expressing the human NRG1 type IV transgene in a neuron-specific way and with temporal regulation. Dr. Karoly Mirnics will present a novel strategy for production of BAC-driven transgenic mice with cell specific miRNA gene regulation and results demonstrating NPY+ interneuron specific GAD1 transcriptional and protein downregulation in mice. Dr. Toshifumi Tomoda will focus on DISC1, a schizophrenia susceptibility gene involved in cell signaling and neuronal architecture, and its regulation of BDNF trafficking in a DISC1 knockout mouse model. Paul Glineburg will highlight gene regulation and unique behavioral differences observed in COMT knockout, knock-in, transgenic and COMT/dysbindin double knockout mice. The goal of this session is to bring together several of the most promising models available for schizophrenia research and discuss their efficacy for understanding human psychiatric disorders.

37. Probing the Glial Hypothesis of Epilepsy

Chair: Tom Swanson

Presenters: Detlav Boison, Dave Poulsen, Bruce Ransom

The vast wealth of the pharmaceutical industry has brought to market drugs that affect neuronal GABA or glutamate receptor systems in some way. After decades of pharmacology and electrophysiology research, 15–25% of all epilepsies in developed countries remain refractory to current drugs, VNS, and surgery. Receiving less corporate attention, but with an expanding body of supporting scientific evidence, is the idea that astrocytes participate in seizures and might be targeted in various ways to stop seizures. For example, these cells are involved in the synthesis and removal of synaptically released glutamate and GABA, and are key regulators of regional adenosine levels. This panel will focus on how the manipulation of mammalian astrocytes might regulate synaptic function, enhance inhibition, and treat epilepsy. Swanson will introduce the speakers, and

moderate discussion. Boison will demonstrate how rAAV vectors can manipulate astrocyte derived adenosine and cause inhibition in the hippocampus. Poulson will show how manipulating glutamate transporters with rAAV vectors in neurons and astrocytes alters EEG and clinical seizures in kainic acid injected rats. Ransom will discuss anatomic alterations of astrocytes seen in chronic seizure foci and consider how these changes might predispose to epileptic discharge. Enough provocative data are presently available to justify increased attention to astrocytes as possible therapeutic targets in epilepsy.

Panel • Tuesday 4:30–6:30 PM • Peak 11/12

38. Different Tokes for Different Folks: Individual Differences in Responses to Abused Drugs

Chair: Joshua Gulley

Presenters: Nancy Zahniser, Joshua Gulley, Marilyn Carroll, Harriet de Wit

Upon first exposure to drugs of abuse, humans and experimental animals exhibit markedly variable levels of responsiveness. Importantly, these differential initial responses are predictive of how these individuals will respond to repeated drug exposure. Thus, it is important to understand the basis of these individual differences and determine how they may be used to assess vulnerability to drug abuse and addiction in human populations. In this panel, we will discuss different approaches used to identify the neurobiological underpinnings of differential responsiveness to psychostimulant drugs, with an overall goal of bridging the gap between animal and human studies. Nancy Zahniser will talk about her work showing a role for differential function and regulation of striatal dopamine transporters in rats with disparate sensitivity to initial cocaine-induced hyperactivity. Josh Gulley will discuss a potential role for differential function of serotonin receptors in individual differences in cocaine-induced behavior and present data suggesting that drug-induced plasticity is enhanced in rats with reduced initial sensitivity to cocaine. Marilyn Carroll will discuss studies in which rats were selected or selectively bred for high (vs low) behavior maintained by nondrug rewards such as food, sweet tastes, or wheel running and how an avidity or impulsivity for a nondrug reward predicts greater drug seeking behavior over several critical phases of the addiction process. Lastly, Harriet de Wit will discuss sources of variability in responses to acute doses of amphetamine in human volunteers, with a particular focus on polymorphisms in the genes involved in the neural actions of the drug.

39. Revealing Elusive Neural Circuits Using Comparative Approaches

Chair: Mary Ann Ottinger

Presenters: Cathy Wolkow, Yonathan Zohar, Donald Ingram, Mary Ann Ottinger

The process of aging involves complex neural changes. The cascade of neural events involved in the biology of aging have parallels across vertebrate and invertebrate classes. Early developmental events and exposure to toxins and other environmental challenges have the capacity to influence these aging processes. Using a range of vertebrate and invertebrate models to ask specific research questions allows us to gain an understanding of both developmental and aging processes as well as begin to assess lifetime effects of early events. Additionally, transgenic models provide the ability to manipulate gene expression of selected genes in order to clarify their role. This session will examine novel comparative models and their utility in revealing key aspects of aging process and developmental events that impact aging. Speakers and the topic that they will address include: Cathy Wolkow, who will discuss aging models including *c-elegans*. Yonathan Zohar will consider a range of fish models, including transgenic fish and those that have varied lifespan. Don Ingram will discuss aging processes in a canine model as a surrogate for neurodegenerative disease. Finally, Mary Ann Ottinger will consider the non-human primate model with cognitive and endocrine aging. Discussion will focus on the attributes of each of these models and what each brings to understanding the process of neural aging.

40. Life and Death Decisions in the Oligodendrocyte Lineage: Novel Receptors and Immune Signaling

Chair: Pamela Knapp

Presenters: James Connor, Guillermina Almazan, Robert Skoff, Pamela Knapp

Oligodendrocytes are targeted in numerous disease and injury situations. It is critical to understand the signals involved in regulating dysfunction and/or death in cells of the oligodendrocyte lineage in order to develop protective strategies, and to retain myelin or promote remyelination. Disease processes causing oligodendrocyte abnormalities and myelin loss are complex, although inflammation is frequently a key component. However, even when an inflammatory event is precipitating, there is a cascade effect involving multiple downstream factors that target oligodendrocytes in both a primary and secondary

manner. Thus, combinatorial strategies may be required to protect oligodendrocytes and myelin, and specific strategies will likely be required for different disease/injury processes. This highly translational session brings together a group of investigators studying issues related to oligodendrocyte development, survival, and death across a range of de/dysmyelinating conditions. Each will present work related to a distinct pathological process. Dr. Almazan has found that oligodendroglial precursors are susceptible to developmental and ongoing toxicity mediated through dopamine exposure and generation of reactive species. Dr. Connor will present work showing that inappropriate cross-signaling between the immune system and CNS cells, involving Sema4A and Tim2, may drive oligodendrocyte cell death in EAE. Dr. Skoff will discuss unexpected findings of microglial activation in mice expressing extra copies of the proteolipid protein gene. Dr. Knapp will discuss findings that oligodendrocytes and glial progenitors are both targeted by HIV exposure, perhaps leading to the fulminant and quickly progressing neuropathology noted in pediatric HIV patients.

Panel • Tuesday 4:30–6:30 PM • Peak 6/7/8

41. NMDA Receptor from Biophysics to Disease

Chair: Stefano Vicini

Presenters: Stephen F. Traynelis, Jon W. Johnson, Stefano Vicini, Lynn A. Raymond

NMDA receptors are fundamental in many aspects of brain function and have been convincingly implicated in many neurological and psychiatric disorders. This panel will present recent findings on biophysical properties of distinct NMDA receptor subtypes and their presence in different brain areas relevant to diseases. First Dr. Stephen Traynelis will demonstrate with a chimeric strategy and single channel recordings that the NR2 amino terminal domain (ATD) influences key functional properties of NMDA receptors that are relevant for defining the NMDA component of the synaptic current. These data suggest that the ATD is a key determinant of functional properties of different NR2 subunits. Second, Dr. Jon Johnson will discuss the mechanisms responsible for variation in channel-specific properties among NMDA receptors containing different NR2 subunits, including channel block by Mg²⁺ and single-channel conductance. His data will show that channel properties differ among NMDA receptor subtypes due mainly to a difference in an M3 residue. Third, Dr. Stefano Vicini will compare and contrast properties of synaptic and extrasynaptic NMDA receptors using patch-clamp recordings in distinct neurons of two key centers of the basal ganglia (striatum and substantia nigra) from mice with specific NMDA receptor subunit deletions. Finally, Dr. Lynn Raymond will describe the impact on striatal NMDA receptor function and trafficking to synaptic and extrasynaptic sites of polyglutamine-expanded huntingtin in a Huntington disease mouse model.

42. Translational Challenges for Developing Cognition Drugs in Schizophrenia

Chair: Michael Egan

Presenters: David Michelson, Mark Geyer, John Sweeney, Michael Egan

Cognitive impairment, common in schizophrenia, has recently been recognized by the FDA as an indication for drug development. Basic research on the mechanisms of cognition has implicated many potential targets, but it is unclear which will translate into effective medications. Given these uncertainties, and the high cost of failure, translational tools to increase success rates are critical. David Michelson will review challenges facing industry, and the reasons drugs fail. These include poor predictive validity of some preclinical models, lack of evidence of target engagement in humans, and off target toxicity. Mark Geyer will describe an attractive approach to preclinical validation of cognition targets using animal models for specific cognitive domains. These studies show pharmacologically distinct effects of drugs targeting different mechanisms on specific cognitive domains, which can be seen across several non primate species. John Sweeney will review data using translational cognitive tasks combined with functional neuroimaging to monitor risperidone effects in treatment-naïve first episode patients with schizophrenia. These data demonstrate both deleterious and beneficial drug effects on distinct cognitive domains, similar to results obtained in nonhuman primate studies. This approach potentially offers an early read out on efficacy and indicates which domains are likely to improve in patients. Finally Michael Egan will present both preclinical cognition data, biomarker data in healthy volunteers, and results from Phase 2 studies in patients with schizophrenia using compounds targeting several mechanisms. He will discuss the implications of these results on efforts to increase the probability of success for cognition targets in schizophrenia.

43. A Newly Discovered Collection of GABA Neurons in the Brainstem Tegmentum that Projects Strongly to Midbrain Dopamine Cells and Influences Aversive Behavior

Chair: Susan Sesack

Presenters: Daniel S. Zahm, Susan Sesack, Michel Barrot, Thomas Jhou

Within the last 5–10 years, a newly defined brainstem region has been revealed as a major source of GABA input to midbrain dopamine cells. This region is variously regarded as the caudal tail of the ventral tegmental area (tVTA)

or as a distinct part of the brainstem reticular formation recently named the rostromedial tegmental nucleus (RMTg). This region receives afferents from multiple sensorimotor and limbic structures, in particular the lateral habenula, and projects primarily to monoaminergic and cholinergic brainstem areas, including the nigra-VTA complex. Neurons in the tVTA/RMTg show Fos/deltaFosB and/or physiological activation in response to psychostimulants and aversive events and also show inhibitory responses to rewarding stimuli. Lesions of this area interfere with passive but not active fear behaviors. In addition to revealing the functional significance of the tVTA/RMTg, these findings have important implications for understanding how this region regulates dopamine cell responses to rewards, aversive stimuli, and addictive substances. Scott Zahm will provide a comprehensive description of the afferent and efferent relationships of the tVTA/RMTg. Susan Sesack will describe the synaptic organization of the tVTA/RMTg and its efferent projections to dopamine neurons in the VTA. Michel Barrot will present anatomical and functional evidence for the influence of the tVTA/RMTg on the dopamine system and its molecular alteration by psychostimulant drugs. Thomas Jhou will provide evidence that tVTA/RMTg neurons encode negative reward prediction errors and are required to express several types of passive aversive behaviors.

Panel • Wednesday 7:30-9:30 AM • Peak 11/12

44. NMDA Receptor Trafficking in Synaptic Plasticity and Synaptogenesis

Chair: R. Suzanne Zukin

Presenters: R. Suzanne Zukin, June Liu, Graham Collingridge

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-dependent long-term potentiation (LTP) and long-term depression (LTD). An emerging concept is that activity-dependent, bidirectional regulation of NMDAR trafficking provides a dynamic and potentially powerful mechanism for regulation of synaptic efficacy and remodeling. Zukin will present an overview of recent advances in our understanding of NMDA receptor trafficking and synaptic targeting and the role of these processes in synaptic plasticity and synaptogenesis. She will also present recent findings that protein kinase C mediated phosphorylation of the SNARE protein SNAP-25 regulates insertion of NMDA receptors at the postsynaptic membrane. Liu will discuss recent exciting findings that a single fear-inducing stimulus induces transcription of the AMPA receptor subunit

GluR2 and a switch in the AMPAR phenotype from GluR2-lacking, Ca²⁺-permeable, to GluR2-containing Ca²⁺-impermeable receptors at synapses of cerebellar stellate cells. Malenka will discuss recent exciting evidence that cocaine generates silent synapses in the hippocampal CA1, that the generation of silent synapses requires expression of CaMKII and CREB and insertion of NR2B-containing NMDA receptors at synapses of the hippocampal CA1. Collingridge will discuss a unique role for GSK-3 β in metabotropic glutamate receptor (mGluR)-dependent LTD. These findings are of interest given that GSK-3 β is implicated in major neurological disorders including Alzheimer's disease, schizophrenia and bipolar disorders.

Panel • Wednesday 7:30-9:30 AM • Peak 14

45. Classical and Non-Classical Neuropeptides in Brain: From Opioids to Peptide Endocannabinoids

Chair: Lloyd Fricker

Presenters: Lloyd Fricker, Lakshmi Devi, Iris Lindberg

Neuropeptides represent a large and important group of cell-cell signaling molecules that function in a number of physiological roles. Traditionally, in order for a peptide to be considered as an authentic neuropeptide it had to undergo regulated secretion. However, a large number of brain peptides are not in the regulated secretory pathway, but are derived from cytosolic, mitochondrial, or nuclear proteins. Recently, some of these peptides have been found to have biological activities, leading to the idea that these peptides represent non-classical neuropeptides synthesized by a stimulus-dependent process, and then constitutively secreted. This is analogous to non-classical neurotransmitters such as NO and anandamide which are secreted after stimulus-induced synthesis, in contrast to the classical neurotransmitters synthesized in advance and secreted only upon stimulation. This session will provide evidence supporting the emerging idea of non-classical neuropeptides, as well as detail the latest research on classical neuropeptides. First, Lloyd Fricker will provide an overview of brain peptides that have been detected using peptidomics techniques, including both the classical secretory pathway and cytosolic (i.e. non-classical) peptides. Lakshmi Devi will focus on the peptide endocannabinoids, a group of brain peptides recently found to bind to and activate the cannabinoid receptor. Finally, Iris Lindberg will describe the discovery of novel classical neuropeptides.

46. Understanding the Neurobiology of Suicide: Translational Approaches

Chair: Stephen H. Koslow

Presenters: Victoria Arango, Gregory Ordway, Gustavo Turecki, John Keilp

Suicide is a tragic endpoint to many lives and is this country's 11th leading cause of death. Every day, approximately 90 Americans take their own life, and 2,300 make attempts. This panel focuses on the neurobiology of suicide. Arango will provide details on the clinical aspects of suicide as well as her own recent postmortem brain examination and in vivo studies which associate suicide with reduced serotonergic neurotransmission. She will discuss serotonergic findings using receptor autoradiography, immunocytochemistry, in situ hybridization and morphometry in the prefrontal cortex and brainstem of well-characterized suicides and controls. Ordway will review the bidirectional communication between noradrenergic neurons and glia. Data derived from laser microdissection of individual brain cell types from psychiatrically characterized humans, providing evidence of disrupted communication between noradrenergic neurons and astrocytes, contributing to the pathobiology of depressive illness associated with suicide. Turecki will focus on impulsive-aggressive behaviors and high anxiety traits as important mediators between early childhood adversity and suicide risk. Recent data suggesting that glucocorticoid promoter methylation may, at least in part, help explain why certain individuals abused during childhood are at an increased risk of depression and suicide. Keilp will report on the role of cognitive dysfunction in suicide risk as a component of illness severity not captured in standard rating scales and as a contributing factor to increased violence of attempts. This panel will discuss the interaction between and among these systems as a way to elucidate the underlying brain mechanisms.

47. Exercise and Brain Health

Chair: Justin Rhodes

Presenters: Justin Rhodes, Kirk Erickson, Monika Fleshner, Joanna Gill-Mohapel

Over the past several decades there have been numerous human cross-sectional studies and randomized clinical trials, along with meta-analyses, that have established the relationship between physical fitness and computer-based measures of cognition. Recent animal and human studies have begun to piece together the changes that take place in the brain from aerobic exercise that contribute to cognitive gain. For example, the volume of the hippocampus increases in

response to chronic exercise in humans. In mice and rats, exercise increases vascular density, concentration of growth factors, trophic factors, neurotransmitters, synapses, dendrites, long term potentiation, and total number of dentate gyrus granule neurons. This panel will review recent human and animal discoveries suggesting that exercise builds a healthy brain. Justin Rhodes will introduce the topic, and report results of recent experiments testing the role of adult hippocampal neurogenesis in pro-cognitive effects of exercise using mice as the model organism. Kirk Erickson will report on results of recent human randomized clinical trials comparing brain composition, as measured by magnetic resonance imaging, between older adults in a stretch and tone group versus a group that performed swift walking 3 days a week for 6 months. Monika Fleshner will discuss interactions between exercise and the stress axis and impacts on cognitive behaviors using rats as the model organism. Finally Joanna Gill-Mohapel will review mechanisms by which exercise can promote recovery from cognitive disabling disorders such as fetal alcohol syndrome, fragile-X syndrome, Alzheimers disease, and schizophrenia in rodent animal models.

Panel • Wednesday 4:30-6:30 PM • Peak 5

48. Integrating the Pleomorphic Roles of Hypocretin/Orexin

Chair: Barry Levin

Presenters: Louis de Lecea, Gary Ashton-Jones, Masashi Yanagisawa, Catherine Kotz

Hypocretin/orexin (Hcrt/Orx) is a hypothalamic neuropeptide implicated in several behaviors and metabolic processes. This panel will address the varied Hcrt/Orx roles in arousal, sleep/wake processes, reward, addiction and energy homeostasis, with the goal of presenting a comprehensive and integrated overview of its multiple actions. Luis DeLecea will discuss data on optogenetic deconstruction of the arousal circuitry and brain reward resulting from manipulating Hcrt/Orx neurons using channel rhodopsin. He will also address the functional interactions of Hcrt/Orx with other hypothalamic neuropeptides (e.g. melanin concentrating hormone) and the monoamines. Gary Aston-Jones, who found that the Hcrt/Orx system is involved in conditioned place preference for morphine, cocaine and food, will present self-administration studies showing that the Ox1, but not Ox2 receptor is critical for reinstatement of cocaine-seeking elicited by cues or contexts, whereas blocking this receptor does not affect self-administration of cocaine. Such findings suggest that the Hcrt/Orx system is importantly involved in conditioned reinforcement for stimuli associated with drugs and food. Masashi Yanagisawa will discuss the Hcrt/Orx pathway as a possible link between sleep/wake regulation and energy homeostasis with regard to its role in fasting-induced wakefulness, food-entrained

circadian rhythms and net-negative regulation of long-term energy homeostasis. Finally, Catherine Kotz will discuss physical activity related energy expenditure associated with hypothalamic and extrahypothalamic Hcrt/Orx activity in obesity prone and resistant animals. She will present data suggesting that variation in Hcrt/Orx receptor profiles in several brain areas may be important to differences in energy expenditure between obesity prone and resistant animals.

Panel • Wednesday 4:30-6:30 PM • Peak 17

49. Neuroprotection Revisited: Bridging the Chasm Between Pre-Clinical and Clinical Trials in TBI

Chair: Edward Hall

Presenters: Edward Hall, Stephen Scheff, Don Stein, Alan Faden

Traumatic brain injury (TBI) represents a major unmet medical need that in many cases results in either death or devastating life changes for the survivor and his/her family. The hope that a treatment might be feasible comes from the fact that much of the neural damage that underlies the lasting neurological deficits is due to a secondary injury process that is triggered by the primary mechanical trauma. Over the past 30 years, our knowledge of the molecular mechanisms of the secondary injury process has greatly increased leading to the discovery of several neuroprotective pharmacological agents that have been tested for safety and efficacy in phase I, II and/or III clinical trials. Disappointingly, none of these, including multiple glutamate receptor (NMDA) antagonists, free radical scavengers/antioxidants, magnesium or calcium channel blockers despite being shown in animal models to be effective neuroprotectants has been able to show significant improvement in neurological recovery after TBI in humans. The organizer E.D. Hall will briefly review the results of the major trials to date and deficiencies associated with them. He will then discuss recent studies that have more completely defined the inter-relationship between the critical secondary injury mechanisms oxidative stress/damage, mitochondrial functional collapse and calcium-activated calpain and caspase activation. S.W. Scheff will next present the rationale, phase II clinical trial results and phase III trial design associated with the ongoing development of the mitochondrial protectant cyclosporine A in severe TBI (CASTBI). D. G. Stein will then present the promising phase II TBI trial results and soon to be initiated phase III trial design focused on the multi-mechanistic neuroprotective hormone progesterone (ProTECT III). Finally, A.I. Faden will present his work on novel secondary injury targets and the rationale for the discovery and development of multi-mechanistic neuroprotective agents for TBI.

50. Post-GWAS in Psychiatry: Extending the Phenotype

Chair: Katherine Burdick

Presenters: Katherine Burdick, Steven Potkin, John Kelsoe, Anil Malhotra

Results from large-scale, genome-wide association studies (GWAS) in psychiatric genetics have been somewhat disappointing, with few if any, susceptibility loci that have been unambiguously identified. This is, at least in part, due to complex genetic architecture of many of the major mental illnesses including schizophrenia and bipolar disorder. A number of issues are raised when considering the best approach to utilizing existing GWAS data including: 1) the frequently referenced endophenotype approach; 2) improving power by using quantitative traits related to brain function as opposed to case-control analyses; 3) secondary analyses of subtypes within GWAS cohorts; and 4) clinical utility of pharmacogenetic predictors in retrospectively assessed samples. First, Dr. Katherine Burdick will present new data using neurocognitive performance as an endophenotype as initially described by Gottesman and colleagues. Specifically, we conducted a GWAS of neurocognitive function in healthy controls and subsequently tested the top five hits for association to disease in 280 probands with schizophrenia to test whether neurocognitive performance can be used as an endophenotype to identify susceptibility loci with smaller effect sizes than those typically detected in GWAS studies of diagnosis. Next, Dr. Steven Potkin will discuss methodological approaches to using quantitative traits as an alternative to case-control analyses, resulting in increased statistical power. Third, Dr. John Kelsoe will describe initial results from the GWAS study of bipolar disorder conducted by the GAIN and BiGS consortia and will describe evidence for an underlying genetic architecture with different sets of genes influencing different forms of illness such as irritable mania or rapid cycling. Finally, Dr. Anil Malhotra will conclude by presenting a pharmacogenetics approach to GWAS data collected naturalistically. Data will be presented using history of clozapine treatment as a proxy measure for poor treatment response in schizophrenia.

51. Modes of Mind: Intrinsic Coherent Networks (ICN) in Brain Function and Structure

Chair: Peter Fox

Presenters: Peter Fox, Stephen Smith, Simon Eickoff, David Glahn

Brain imaging studies are driving a fundamental paradigm shift in neuroscience. Persistent coherent systems—a.k.a. “intrinsic coherent networks” (ICNs) or “resting-state networks” (RSNs)—can be demonstrated with remarkable

reliability using both functional imaging methods (fMRI and PET) and, more recently, using structural imaging. ICNs for the most part (but not always) respect well-known, large-scale neural-system divisions (e.g., vision, audition, somataesthesia, motor). Originally extracted from resting-state data (hence “resting-state networks”), it is now established that ICNs can be extracted from functional data obtained during any state. This observation is motivating interpretation of all states—tasks, rest, anesthesia, sleep, etc.—as variable “weightings” of fundamental, underlying “functional modes.” Similar ICNs are observed in rodents and non-human primates, suggesting that these are evolutionarily ancient. ICNs can be extracted from structural images using both DTI tractography and inter-regional co-variances in cortical thickness. ICNs are influenced by disease states, are modified by treatment and are heritable, making them valuable endophenotypes. This session is a comprehensive, crest-of-the-wave survey of this scientific paradigm shift. The session is organized and introduced by Peter Fox and Steven Smith describes ICN’s derived from resting-state and task states using independent components analysis. Dr. Fox describes ICNs derived from coordinate-based meta-analysis (using the BrainMap database) and their correspondence to resting-state networks. Dr. Simon Eickhoff describes ICNs derived from DTI tractography and their correspondence to functionally-derived ICNs. Dr. Glahn presents the use of ICN’s in psychiatric disorders and as imaging endophenotypes for gene discovery.

Panel • Wednesday 4:30-6:30 PM • Peak 15/16

52. Novel Approaches to the Treatment and the Etiology of Alzheimers Disease

Chair: Steve Richardson

Presenters: Xin-Min Li, Weihong Song, Peter Yu, Charles Etienne Benoit

Although the complete role of β -amyloid ($A\beta$) in Alzheimers Disease (AD) remains unknown, the density of deposits of insoluble $A\beta$ in certain areas of the brain roughly correlates with the severity of the patient’s symptoms. Consequently, interventions that prevent or slow the formation of $A\beta$ deposits should prevent or slow the development, or the progression, of dementia in AD patients. Xin-Min Li will discuss the ability of the atypical neuroleptic, quetiapine, to reduce the formation of $A\beta$ plaques and to attenuate the development of impaired memory and abnormal emotional behaviour in a double transgenic mouse model of AD. Weihong Song will show that valproic acid, a drug widely used in the management of epilepsy and of bipolar disorder, reduces $A\beta$ production by inhibiting glycogen synthase kinase mediated γ -secretase activity, and reduces $A\beta$ formation and memory impairment in mouse models of AD. Peter Yu will demonstrate that formaldehyde and methylglyoxal formed by semicarbazide-sensitive amine oxidase (SSAO), an enzyme found on cerebral

blood vessels, increases the formation of A β oligomers, fibrils and β sheets, and reduces the clearance of A β by inhibiting the vascular smooth muscle A β transporter LRP-1. SSAO inhibitors should reduce the buildup of A β in the brain. SSAO may also be involved in the strong link between type 2 diabetes/metabolic syndrome and AD. Rémi Quirion will present evidence that transthyretin and quinone reductase-2 are not only involved in memory maintenance but also have neuroprotective actions that may be relevant to the treatment of AD.

Panel • Wednesday 4:30–6:30 PM • Peak 6/7/8

53. The Surprising Role of the Amygdala in Uncertainty and Attention

Chair: Geoffrey Schoenbaum

Presenters: Paul Whalen, Dan Salzman, Geoffrey Schoenbaum, David Bucci

Recently a number reports of neural activity in the amygdala have emerged that emphasize the role of surprise or uncertainty in the associative process. These data could be interpreted to contradict the monolithic view that amygdala is an acquirer of associative representations. This panel will consider some of these data and their significance to the current understanding of amygdala function. The panel will be led off by Paul Whalen, who will present data from human imaging studies indicating activation patterns that are sensitive to surprise and uncertainty. Subsequently, Dan Salzman and Geoffrey Schoenbaum will present evidence from recording work in primate and rat amygdala. These data show that amygdala neurons signal both associative representations, as has been demonstrated previously, as well as surprise or uncertainty. David Bucci will offer cfos data dissociating a role for subregions within amygdala in associative processing as it relates to surprise and uncertainty. As a whole, these data suggest that some functions ascribed to amygdala reflect a role in promoting vigilance and attention in order to facilitate learning in other brain regions.

Panel • Thursday 7:30–9:30 AM • Peak 5

54. Taking It All In: Functional Properties of Distinct Inputs to VTA Dopamine Neurons

Chair: Carl Lupica

Presenters: Paul Shepard, Carl Lupica, Hitoshi Morikawa, Cameron Good

The ventral tegmental area (VTA) is a core component of a network of brain regions involved in processing environmental information regarding reward presence and salience. Recent anatomical data suggest that the VTA receives information from a large number of brain structures. However, despite extensive knowledge of the physiological properties of VTA dopamine (DA) neurons,

and their importance in mediating reward, relatively little is understood of the influence of distinct afferents to these neurons. The members of this panel will discuss recent data from their laboratories examining the comparative influence of distinct inputs to VTA DA neurons studied both in vivo and in vitro. Paul Shepard (University of Maryland) will discuss the role of inputs to VTA DA neurons from the lateral habenula nucleus that may be involved in encoding the unexpected loss of a rewarding stimulus. Carl Lupica will provide evidence for a novel pathway to VTA DA neurons arising in the hippocampal CA3 sub-region, and passing through the lateral septum, that strongly modulates DA neuron activity, and may provide contextual information to the reward circuit. Hitoshi Morikawa (University of Texas, Austin) will present data demonstrating differential synaptic plasticity of glutamatergic neurotransmission mediated by distinct ionotropic glutamate receptors in VTA DA neurons. Finally, Cameron Good (NIDA-IRP) will provide evidence for distinct control of VTA DA neuron activity by cortical and subcortical glutamate afferents arising in the pedunculo-pontine nucleus (PPN), and the differential expression of synaptic plasticity in these pathways following exposure to abused drugs.

Panel • Thursday 7:30-9:30 AM • Peak 17

55. Reelin' and Rockin': Role of the Extracellular Matrix Protein from Development to Cognition

Chair: Pascale Chavis

Presenters: André Goffinet, Gabriella D'Arcangelo, Pascale Chavis, Edwin Weeber

The extracellular matrix (ECM) is a meshwork of proteins present in the extracellular space which role extends far beyond structural scaffolding. ECM proteins are important contributors to embryonic development and finely tune synaptic transmission and plasticity as well as experience-dependent plasticity in the postnatal and adult brain. ECM proteins are involved in physiological processes such as synaptic plasticity and in pathological conditions underlying psychiatric disorders. The secreted ECM glycoprotein reelin perfectly illustrates this duality. Reelin is crucial for the correct cytoarchitecture of laminated structures where it controls the migration and positioning of neurons crucial and modulates long-term synaptic plasticity but it has also been implicated in the etiology of diseases such as schizophrenia, depression and bipolar disorders. This panel will discuss recent advances in the understanding of reelin functions from development to cognition. First, using a novel mouse knock-out,

Andre Goffinet will show that in vivo, p73 controls the premature death of the reelin synthesizing Cajal-Retzius cells. Gabriella D'Arcangelo will discuss the role reelin in the formation of synaptic structures in cortical and hippocampal neurons. Pascale Chavis will show how reelin modulates synaptic plasticity and how it controls the maturation of the glutamate synapses. Finally, Edwin Weeber will provide evidences of a direct link between reelin signaling and cognitive ability in mammals.

Panel • Thursday 7:30-9:30 AM • Peak 11/12

56. Behavioral Correlates of Neurological Dysfunction and Recovery: Assessments for Translational Research

Chair: Kimberly Topp

Presenters: Gail Widener, Diane Allen, David Brown,Carolynn Patten

Neuropathology, plasticity, and recovery each affect brain function and ultimately result in behavioral manifestations, including disordered motor control. The relationship between the brain and behavior, however, is complex and multi-factorial, posing a challenge to basic and clinical scientists when relating behaviors and their neural correlates. For translational research to elucidate the mechanisms of neuropathology and neural recovery in humans it is necessary to choose and conduct appropriate assessments. The panelists share expertise in neurorehabilitation research, and will discuss their perspectives on assessment of human motor behavior following neuropathology. Kimberly Topp will introduce the panel and provide the context. Gail Widener will present the International Classification of Functioning as a framework for assessing levels of motor behavior including bodily function, activity and participation in persons with multiple sclerosis. Diane Allen will present a theory for choosing the dimensions of movement to assess in persons with neurologic dysfunction and assessing the gap between patient preferred and current movement abilities using item response theory measurement methods. David Brown will show how basic principles that have been developed with animal research can guide the development of sophisticated, quantitative measures of nervous system function during locomotor movement in persons post-stroke. Finally, Carolynn Patten will discuss concurrent assessments of impaired motor behavior and relevant neurophysiological mechanisms in persons with upper extremity dysfunction post-stroke.

57. Hypoxia—The Good, Bad and the Ugly: Clinical Relevance and Rationale for Using “Therapeutic Angiogenesis” as a Treatment Paradigm

Chair: Christian Kreipke

Presenters: Sami Harik, Christian Kreipke, Paula Dore-Duffy, Joseph LaManna

Following diffuse brain injury there is a rapid and pronounced vascular response that results in a general state of vasoconstriction and diminished perfusion to the brain that produces systemic or focal hypoxia with loss of CNS metabolic homeostasis. In order to restore CNS homeostasis the cellular constituents of the blood brain barrier (BBB) and the neurovascular unit make fine tuned regulatory adjustments in an attempt to maintain the balance between oxygen and glucose availability and tissue metabolic demand. This involves structural changes that underlie physiological or adaptive angiogenesis. Inadequate adaptation to injury may lead to defective vascular remodeling and to the development of some CNS diseases. Recent evidence suggests that promotion of endogenous/adaptive angiogenesis or may be a novel therapeutic paradigm. “Therapeutic angiogenesis” can be induced by exposure to chronic mild hypoxia, ketogenic diet, sensory or motor training and following exercise. In this panel we will discuss the use of exercise, normobaric (hypobaric) hypoxia and ketogenic diet in vascular remodeling. Dr. Sami Harik will present a brief overview of the effects of hypoxia on brain function and how controlled use of hypoxia can be therapeutic. Dr. Christian Kreipke will discuss the effect of exercise in management of traumatic brain injury (TBI). Dr. Paula Dore-Duffy will discuss the use of normobaric hypoxia in vascular remodeling seen in experimental autoimmune encephalomyelitis (EAE). Dr. Joseph LaManna will discuss the use of ketogenic diet in restoration of vascular adaptive responses in aged animals.

58. Web Collaborations in Neuroscience

Chair: Hakon Heimer

Presenters: June Kinoshita, Tim Clark, Matt McQueen

The World Wide Web has already been exploited in various ways to enhance research. This panel will present some successful examples from Web 1.0, as well as some of the Web 2.0 (and beyond) examples that are already being rolled out, especially collaborations between funders of research (NIH, foundations)

and the scientific community. Beyond presenting ideas, we want YOUR ideas for new collaborations, and will ask you to brainstorm with us to come up with new ideas for using the web to benefit science. June Kinoshita will discuss the current state of the art for web science communities—the Alzheimer and Schizophrenia Research Forums—as well a new resource called Semantic Web Applications in Neuromedicine (SWAN), which allows researchers to annotate, organize, and share information about hypotheses in research. Tim Clark will introduce the Science Collaboration Framework (SCF), a software toolkit to establish web-based virtual organizations for researchers in biomedicine. It enables researchers to publish and discuss on-line content such as articles, news, and perspectives, and to provide shared context using established scientific ontologies, automated text mining, and RDF data on the semantic web. Matt McQueen and colleagues have developed successful collaborations between researchers and nonprofit groups to systematically catalog and meta-analyze genetic association data. For each of the presently covered diseases (Alzheimer's, schizophrenia, Parkinson's, multiple sclerosis), these databases represent the most exhaustive and up-to-date accounts on genetic studies. As such, they vastly facilitate the design and execution of a broad spectrum of genetic and molecular follow-up projects.

Panel • Thursday 7:30-9:30 AM • Peak 6/7/8

59. Recent Advances in Neuromodulation of Neural Plasticity

Chair: Alfredo Kirkwood

Presenters: Nelson Spruston, Ricardo Araneda, Scott Thompson, Alfredo Kirkwood

The cholinergic and catecholaminergic systems play a crucial role in learning and memory by subordinating neural plasticity to the individuals behavioral state. Most of our understanding of the action of the neuromodulators on plasticity derives from their effects on membrane excitability and neurotransmitter release. For example, it is well recognized that by controlling neural activity, neuromodulators can facilitate or restrict the recruitment of activity dependent forms of plasticity such as LTP and LTD. The four presentations in this panel will review recent developments underscoring more direct mechanisms of action of these neuromodulators in plasticity. Nelson Spruston (Northwestern) will show evidence for a long-lasting bi-directional control of bursting firing by muscarinic acetylcholine and metabotropic glutamate receptors. Ricardo Araneda (U Maryland) will discuss a cholinergic/noradrenergic mechanism to increase perceptive saliency and memory encoding in the olfactory bulb. Scott Thompson (U Maryland) will discuss a serotonergic enhancement of glutamate responses of specific hippocampal pathways and its relevance for the

therapeutic actions of antidepressants. Alfredo Kirkwood (Johns Hopkins) will discuss how cholinergic and adrenergic receptors control polarity of synaptic plasticity and how agonists can be used to selectively potentiate or depress target synapses in vivo.

Panel • Thursday 4:30–6:30 PM • Peak 5

60. Seize The Day: Novel Therapies For Epilepsy

Chair: Janice Naegele

Presenters: Susan Masino, Nathaniel Hartman, Janice Naegele, Frances Jensen

Epilepsy is a common neurological disorder with diverse causes and symptoms. The speakers will discuss basic mechanisms of the epilepsies and several novel epilepsy therapies. The first speaker is Susan Masino, who will discuss the ketogenic diet and other drug treatments to increase adenosine. Adenosine is an endogenous anti-convulsant and the primary regulator of adenosine is adenosine kinase, expressed by astrocytes. Astroglialosis is a common response of the brain following seizures and upregulation of endogenous adenosine kinase from the reactive astrocytes may lower seizure thresholds. The second speaker is Nathaniel Hartman, who will discuss strategies for generating neuronal progenitors derived from human and mouse embryonic stem (ES) cells. He will present evidence for migration and integration of these cells in experimental models of epilepsy and neurodegenerative disorders. The third speaker is Jan Naegele, who will describe gene and stem cell therapies designed to increase inhibitory transmission in temporal lobe epilepsy. Her discussion will include electrophysiological and electroencephalographic studies of intrahippocampal grafts of fetal neural stem cells or ES-derived GABAergic progenitors in mice with chronic seizures. The last speaker is Frances Jensen, who will discuss neurological deficits after early life seizures, and interventional therapies aimed at cellular and molecular signaling cascades involved in epileptogenesis. She will discuss studies in human infants and the rat neonatal seizure models suggesting a role for glutamate and GABA receptor trafficking and activation of downstream activity-dependent signaling pathways to result in a dysplastic neuronal network.

Workshop • Thursday 4:30–6:30 PM • Peak 17

61. Who is the “Hemichannel” and What Does It Do?

Chair: David Spray

Presenters: Michael Bennett, Eliana Scemes, Roger Thompson, Gerhard Dahl

Gap junctions in mammalian cells are formed by the connexin family of proteins, where apposed hexamers contributed by adjacent cells form pathways

for intercellular diffusion of ions and signaling molecules. It has been proposed that the half gap junction channels contributed by one cell may form functional channels in the nonjunctional membrane in individual cells and that these connexin hemichannels may play important roles under physiological or pathological conditions by virtue of their high permeability and unitary conductance. This position will be defended by Mike Bennett and Rolf Dermietzel based on physiological and immunological datasets obtained in neurons, astrocytes and model systems. It has been proposed that vertebrate homologues of invertebrate gap junction proteins (pannexins) also form highly permeable non-junctional channels comparable to connexin hemichannels, and there is some agreement that they do not form gap junctions in mammals. A (relatively) extreme view is that only pannexins form the large channels, while others argue that both pannexins and connexins are capable of this function. The viewpoint that only pannexins perform the non-junctional functions previously assigned to connexins (as well as others) will be put forward by Roger Thompson, Gerhard Dahl and Eliana Scemes, based primarily on studies on neurons and glia. Finally, it is possible that other channels may fulfill this role or be part of a macromolecular superchannel complex, and Dave Spray will lead a discussion with audience participation in considering whether anion channels such as VRAC or VDAC could also be substrates for the phenomena attributed to connexin and pannexin “hemichannels.”

Panel • Thursday 4:30–6:30 PM • Peak 11/12

62. The Genetics of Pain from Rodent and Human Studies

Chair: William Lariviere

Presenters: Jeffrey Mogil, William Lariviere, William Maixner

Pain sensation is highly variable in the clinic and laboratory in animals and in people. To understand this variability, genetic studies have begun to identify molecular targets, including molecules newly implicated in pain processing altogether. This panel will discuss recent advances in identifying the molecular mechanisms of variability in pain in humans and lab animals. Jeffrey Mogil will give an overview of the field, and discuss current findings in mouse pain genetics. William Lariviere will discuss the use of mouse genetic reference populations to determine the molecular mechanisms of mechanosensation and inflammatory pain by combining genome-wide linkage mapping data and microarray data. William Maixner will discuss the use of association studies of complex persistent pain conditions and current approaches to assess genetic pathways of vulnerability in humans. This panel will give participants a broad overview of recent advances and current methods used to study the genetics

of pain, their strengths and limitations. Discussion is expected regarding the promises of the utility of information obtained and progress made toward these promises.

Panel • Thursday 4:30–6:30 PM • Peak 14

63. Cannabinoid Receptor Signaling and Modulation of Monoaminergic Circuits

Chair: Elizabeth Van Bockstaele

Presenters: Ken Mackie, Mary Abood, Eleni Tzavara, Ana Carvalho

The past decade has seen a tremendous growth in knowledge related to cannabinoid receptor signaling in brain. In addition, the impact and consequences of cannabinoid modulation of monoaminergic circuits is steadily emerging. Elisabeth Van Bockstaele will introduce the panel participants. The first presenter, Dr. Ken Mackie will provide an overview of the endocannabinoid system by drawing on experimental evidence obtained from a combination of electrophysiological, imaging, biochemical and immunological approaches. The second presenter, Mary Abood will elaborate on cellular mechanisms of cannabinoid receptor signaling and discuss a putative role of cannabinoid receptors in neurodegeneration. Eleni Tzavara will discuss interactions between cannabinoids, dopamine and glutamate in the basal ganglia. She will also discuss how cannabinoid receptor antagonism might constitute an integrated pharmacotherapeutic approach that impacts the affective, cognitive, appetitive and motivational neuronal networks involved in mood disorders. Finally, Ana Carvalho and Elisabeth Van Bockstaele will present anatomical, biochemical and behavioral evidence for cannabinoid modulation of noradrenergic circuits and discuss how increased indices of noradrenergic activity following repeated cannabinoid use may contribute to the etiology of depression and anxiety following chronic drug use.

Panel • Thursday 4:30–6:30 PM • Peak 15/16

64. Identification of Functional Variation across the Genome: Insights from Preclinical and Clinical Studies

Chair: Anil Malhotra

Presenters: Wolfgang Sadee, David Goldman, Harriet de Wit, Anil Malhotra

Genome-wide association studies (GWAS) are being utilized to detect genes for neuropsychiatric phenotypes. Although there have been positive GWAS results, the majority of variants that influence these phenotypes remain undetected. Identification and assessment of functional variants within the genome

may provide increased power, as these variants directly modify gene product action. Wolfgang Sadee will present allelic expression imbalance studies focused on the detection of regulatory variants modifying gene expression. This work has resulted in comprehensive characterization of regulatory variants within the DRD2 gene, and now includes multiple genes implicated in CNS function. David Goldman will discuss efforts to characterize functional variants, from in vitro studies assessing calcium mobilization to expression assays of polymorphisms in the serotonin system. Harriet de Wit will present a translational approach to amphetamine response in which mice are characterized for drug response, examined for expression differences, and assessed for associated quantitative trait loci. Results have implicated genes including casein kinase 1 epsilon (Csnk1e) in both mice and healthy human subjects. More recent work with more highly recombinant mouse populations provides more precise mapping. Anil Malhotra will report on efforts to utilize clinical phenotypes including neurocognitive function and brain imaging to detect functional variants. He will discuss work with ZNF804A, a gene implicated by GWAS in schizophrenia, indicating that the risk allele influences neurocognition, brain volume and psychotic symptomatology. Taken together, this panel will provide a comprehensive overview of complementary strategies to identify functional variation within the genome.

Panel • Thursday 4:30–6:30 PM • Peak 6/7/8

65. Functional Relevance of Hippocampal-Prefrontal Synchrony

Chair: Joshua Gordon

Presenters: Yukiori Goto, Hidehiko Takahashi, Patricio O'Donnell,

Avishek Adhikari

Synchrony between the hippocampus and medial prefrontal cortex (mPFC) has been proposed to underlie various cognitive functions, and disruptions in this synchrony may play a role in neuropsychiatric disease. Here we describe efforts to study the mechanisms underlying such synchrony and to explore its relevance to behavior. Data from both animal and human studies will be presented in an effort to highlight translational relevance. After a brief introduction, Y. Goto will characterize the respective roles of the dorsal hippocampus, the mPFC, and their interaction using local infusions of inactivating agents and dopaminergic blockers in rodents. His data suggest that the dynamics of dopamine activity at its receptors regulates the interactions between these structures. Next, H. Takahashi will present human studies of D1 and D2 receptors in these areas, correlating binding potentials with neurocognitive performance. These studies lend further support to the notion that dopaminergic activity plays an important role in orchestrating hippocampal-mPFC interactions that support

cognition. Returning to rodent studies, P. O'Donnell will present data assessing changes in synchrony between the mPFC, hippocampus and nucleus accumbens during spatial exploration and lever-pressing for reward, suggesting that during the latter condition this synchrony is suppressed. Finally, A. Adhikari will demonstrate synchrony between the ventral hippocampus and the mPFC during anxiety-like states, coincident with the emergence of anxiety task-related activity in mPFC neurons. Together these presentations will provide further evidence in support of the hypothesis that hippocampal-prefrontal synchrony plays an important role in a variety of behaviors that require both brain regions.

Panel • Thursday 8:30-10:00 PM • Peak 5

66. Gap Junctions and Plasticity in the CNS

Chair: Michael Bennett

Presenters: Martin Theis, Alberto Pereda, Rolf Dermietzel, John O'Brien

After a brief historical introduction by Michael Bennett and Martin Theis will address the role of connexins in adult neurogenesis, a fundamental form of plasticity. Transgenic animals provide the primary investigatory tool. Pereda will address the parallel mechanisms of modulation of excitatory electrical and chemical transmission at a mixed synapse. Signaling systems found at chemical synapses, including dopaminergic inputs, NMDA receptors, and CaMKII, act to enhance or depress both components in parallel. O'Brien will report on phosphorylation pathways by which the same transmitter, dopamine, increases or decreases coupling at separate retinal sites by activation of diverging signaling pathways. Dermietzel will describe binding sites for CaMKII on the NR2B subunit of NMDA receptors and on the neuronal connexin, Cx36. These sites are remarkably similar in the two channel proteins, which suggests that the same kinase can effect both chemical and electrical transmission. Although once thought of as rigid and inflexible, it has become clear that electrical synapses can be regulated to a similar extent as chemical synapses and by similar molecular pathways.

67. Poring over Ion Channel Pores: Gating and Modulation of Central and Novel Gating Pores of Ion Channels

Chair: Todd Scheuer

Presenters: Todd Scheuer, Baron Chanda, Michael Sanguinetti

Ion channels are key regulators of neuronal activity and the targets for many drugs for modulating that activity. Archetypical voltage-gated ion channels have a peripheral voltage-sensing domain formed by transmembrane segments S1–S4 that responds to voltage, which, in turn, opens a separate central ion conducting pore formed by transmembrane segments S5 and S6. But what is THE ion channel pore? In recent years, new knowledge of channel structure, genes encoding novel ion channel-related structures and functional studies driven by this information have shown that the S4 voltage sensor resides in a separate gating pore and demonstrated voltage-gated ion movement through this pore through the voltage sensor itself. The presentations of this panel will examine both this novel gating pore as well as the classical central pore. After an introduction, Scheuer will describe studies of the detailed movements of the S4 voltage sensor as it drives activation in response to voltage as well as disruptions of these interactions that form gating pores through the sensor itself and lead to specific human diseases. Larsson will describe proton-conducting ion channels that lack a classical pore and where the gating pore serves as the normal ion conduction pathway. Finally, Sanguinetti will discuss new information concerning the mechanism by which ions and pharmacological compounds modulate and block conductance through the classical central pore of Herg potassium channels.

68. The Immune System and CNS Function in Health and Disease

Chair: Klas Blomgren

Presenters: Lena Brundin, Steven Levison, Marcela Pekna, Alan Faden

Despite the brain's status as an immune privileged site, an extensive bi-directional communication takes place between the nervous and the immune system in both health and disease. Immune cells and molecules such as cytokines, chemokines, and growth factors modulate brain function through multiple signaling pathways throughout the lifespan. Immunological, physiological and psychological stressors engage cytokines and other immune molecules as mediators of

interactions with neuroendocrine, neuropeptide, and neurotransmitter systems. For example, brain cytokine levels increase following stress exposure. The innate immune system, including the complement system, serves to regulate neurogenesis both under normal and pathological conditions. Chemokines, like CCL2, may regulate and direct migrating neural precursor cells (NPCs), and injury-induced IL-6 may alter the fate of differentiating NPCs. Microglia are the major antigen-presenting cells and phagocytes of the brain and may as such be critical in eliciting different responses to injury, including regenerative and degenerative mechanisms. First, Lena Brundin will reveal that suicide attempters and healthy control human subjects have different cytokine profiles in their cerebrospinal fluids. Steven W. Levison will discuss the effects of neuroinflammation on neural stem cell responses to brain injury. Marcela Pekna will discuss different roles of the complement system in healthy and diseased brains. Finally, Alan I. Faden will present data showing that either early or delayed inhibition of microglia activation significantly improves outcome after brain and spinal cord injury.

Panel • Thursday 8:30-10:00 PM • Peak 14

69. The Aging Brain on Super Foods and Supplements: Hope or Hype

Chair: Donald Ingram

Presenters: Barbara Shukitt-Hale, Paula Bickford, Richard Hartman, Michael Forster

Nutrition is evolving as one of the major factors modulating brain aging and a range of neurodegenerative diseases. Epidemiological evidence supports the view that diets rich in fruits and vegetables are associated with reduced risk of neurodegenerative diseases, particularly Alzheimer's disease. Experimental evidence emerging from studies of various animal models confirm the potential of foods containing high levels of polyphenols providing antioxidant protection for attenuating brain aging assessed at molecular, cellular, anatomical, and functional levels. Supported by epidemiological evidence, the view that dietary supplements of antioxidants also provide potential neuroprotection has begun to wane in the face of contrary evidence indicating high levels of antioxidant intake may actually increase risks of age-related disease including heart disease and cancer. Bombarded by advertising, the public faces the quandary of hope or hype regarding what foods and supplements can offer a safe and effective dietary avenue to healthy aging. Based on a wide range of careful preclinical research in various animal models, Don Ingram will moderate a panel to review progress in assessing the potential health benefits and risks of a wide range of so-called "super foods" and dietary supplements. Barbara Hale will review data

examining the effects of diets enriched in blueberries and other berryfruits on behavior and brain inflammation in aged rodents. Paula Bickford will present findings examining dietary supplementation with the algae, spirulina, and mixtures of other food-derived antioxidants, in rodent models of brain aging and neurotrauma, including stroke and effects on stem niches. Rich Hartman will discuss effects of pomegranate and grape juice on memory and pathogenesis in mouse models of Alzheimer's disease. Mike Forster will discuss the effects on brain function of short- and long-term co-supplementation with vitamins C and E as well as the mitochondrial antioxidant coenzyme Q10. Jim Joseph will serve as a Discussant.

Panel • Thursday 8:30-10:00 PM • Peak 15/16

70. Time to Hit the Gym? Improvements in Diabetic Neuropathy via Exercise and Lifestyle Intervention

Chair: Doug Wright

Presenters: Gordon Smith, J. Robinson Singleton, Patricia Kluding, Doug Wright

Distal symmetrical polyneuropathy (DSP) is a debilitating complication of diabetes, affecting up to 50% of diabetic patients. Patients with DSP display slowed nerve conduction, loss of vibration and thermal sensitivity, and gait/balance disturbances. In addition, certain neuropathic patients develop chronic pain. Identification of pharmacological treatments that improve diabetic DSP has been unsuccessful, leaving clinicians few treatment options outside of pain control and/or recommendations for better glycemic control. Improvements in lifestyle and exercise programs are recommended for patients with diabetes, but little is known about how these interventions impact peripheral nerve dysfunction. This panel will provide new evidence that lifestyle and exercise intervention can provide significant benefits for peripheral nerve function in both humans and animal models. Gordon Smith will provide an overview of DSP and discuss how diet and exercise counseling for patients with impaired glucose tolerance results in cutaneous reinnervation and improved pain. Rob Singleton will describe clinical symptoms that may play an important role in the progression of diabetic neuropathy and provide evidence that exercise improves small fiber function in diabetic subjects without neuropathy. Patricia Kluding will present data about how a supervised exercise intervention improves certain aspects of nerve dysfunction in diabetic subjects with neuropathy, including measures of proprioception. Doug Wright will conclude with a discussion of how exercise intervention in diabetic rodents can improve painful neuropathy, and provide evidence that these improvements may be related to exercise-induced increases in neurotrophin expression.

71. Do In Vitro Models Shed Light on Neural Disease?

Chair: Rosemary Schuh

Presenters: Rosemary Schuh, Samir Jafri, Jean Harry, Hey-Kyoung Lee

The use of in vitro models allows precise dosing of selected cells or tissues with specific measurement of the relevant responses. However, how meaningful are these methods for predicting the in vivo progression and characteristics of neural disease? The purpose of this session is to examine several in vitro approaches that have been widely used to gain insight into age-related processes and the accompanying functional changes. The hippocampus is greatly affected in Alzheimer's disease and in neurodegenerative conditions associated with cognitive decline. As such, hippocampal slice culture can provide extremely valuable data. Rosemary Schuh will consider the conditions, interpretation of data, pitfalls, and validity of using this system to model a degenerative disease. Similarly, the hallmark of Parkinson's disease is deterioration of dopaminergic systems in the substantia nigra. Samir Jafri will discuss the in vitro approaches to testing interventions and their potential efficacy in cell and tissue culture systems of models of Parkinson's disease. A key element of many neurodegenerative diseases is the neuroinflammation process that accompanies the disease progression. Jean Harry will address the characteristics and cellular involvement of neuroinflammation including the use of in vitro approaches to discern the sequence of events. Finally, the use of transgenic models provides a venue for examining cellular mechanisms underlying neurodegenerative disease. Hey-Kyoung Lee will speak to the insights from using these models to develop effective therapeutics for Alzheimer's disease.

72. The More We Learn, the Less We Know about Axonal Plasticity and Regeneration in the Nervous System

Chair: Mark Tuszynski

Presenters: W. Marie Campana, George M. Smith, Mark Tuszynski

Understanding of basic mechanisms underlying neural plasticity after nervous system injury has clearly advanced remarkably in the last 30 years. For example, in the PNS axons can regenerate, resulting in extensive functional recovery after nerve compression injury: mechanisms that underlie PNS regeneration include formation of a permissive extracellular matrix in lesion sites, secretion of trophic molecules, provision of structural guidance for regenerating axons,

and an absence or the sequestration of inhibitory molecules. While CNS axons do not normally regenerate, they nonetheless exhibit striking forms of reorganization following injury that can contribute to adaptive functional improvement, including axonal sprouting and circuit reorganization. This session will present recent advances in the study of adaptive neural plasticity to injury, while highlighting how recent discoveries in fact point to substantial gaps in our knowledge that must be studied anew to lead to the development of potential therapies for neural injury. Marie Campana will discuss positive signaling mechanisms in peripheral nerve injury, suggesting the existence of greater diversity in activation of trophic signaling than previously appreciated. George Smith will discuss the challenge of axonal guidance after CNS injury, and use of trophic signaling to address this need. Mark Tuszynski will highlight sets of challenges that remain to be addressed in reconstructing adult CNS circuitry, including corticospinal axonal regeneration and the need to remyelinate reconstructed CNS circuitry.

Panel • Friday 7:30–9:30 AM • Peak 17

73. Cell Migration and Its Control in the Nervous System

Chair: James Fawcett

Presenters: Harold Cremer, James Fawcett, Joel Levine, Francis Szele

Cell migration events are critical to neuronal development, and are also involved in the function of the normal and adult nervous system. Migration can involve the whole cell, or just the motile tips of the axon and dendrites. In order to migrate and progress through the CNS environment, cells must have the appropriate cell surface receptors linked to intracellular signalling pathways, the various mechanisms that control the cytoskeleton must be working correctly, and then the migration has to be guided so that the axon or cell goes to the right place. The panel will discuss migration events amongst the stem cells of the subventricular zone, the rostral migratory stream, Schwann cells and axon growth cones. James Fawcett will discuss Schwann cell migration. There are several mechanisms that inhibit Schwann cell migration into the CNS, but if Schwann cells are to be useful for spinal cord repair or remyelination they have to be altered to make them able to mix with astrocytes. Harold Cremer will present his recent work on the birth of neuronal precursors in the subventricular zone and their migration down the rostral migratory stream to form olfactory bulb neurons. By electroporating genes or siRNAs into these cells *in vivo* he has made new findings about the control of the differentiation and migration of the cells. Francis Szele will present his work on subventricular zone stem cell migration, using two-photon microscopy in slices to identify the way in which the cells migrate, which cells are migratory, and factors that influence their migration.

Joel Levine will speak about the Role of Atypical Protein Kinase C and the Par complex in Axon Growth. Atypical PKC and the par complex is a regulator of several different forms of cell polarity and motility. Joel will present recent observations showing that this multiprotein complex participates in the cellular responses to extracellular cues that can inhibit axon extension.

Panel • Friday 7:30–9:30 AM • Peak 11/12

74. Taking STEPs to Improve Cognition

Chair: Paul Lombroso

Presenters: Susan Goebel-Goody, Paul Lombroso, Gloster Aaron, Michael Browning

Tyrosine phosphorylation regulates many aspects of neuronal development, as well as synaptic function in mature cells. Tyrosine phosphorylation is involved in the modification of synaptic activity, including long-term potentiation or depression. The STRiatial-Enriched protein tyrosine Phosphatase (STEP) family of phosphatases has been implicated in this process through the regulation of several key substrates. STEP dephosphorylates a regulatory tyrosine in the activation loop of ERK1/2, p38 and Fyn and thereby inactivates them. In addition, STEP promotes NMDAR and AMPAR internalization (NR1/NR2B and GluR1/GluR2). The current model of STEP function is that it opposes the development of synaptic strengthening. A prediction of this model is that decreasing STEP levels may promote synaptic plasticity, while increasing STEP levels may lead to cognitive deficits. The purpose of this panel is to bring together investigators who have been studying this interesting family of phosphatases. Recent findings indicate that STEP is involved in the pathophysiology of several neuropsychiatric disorders. Susan Goebel-Goody will discuss the role of STEP in Fragile X Syndrome (FXS) and efforts to reverse FXS symptoms by reducing STEP levels in a FXS mouse model. Paul Lombroso will review the role of STEP in Alzheimer's disease, and the efforts to reverse cognitive deficits by reducing STEP levels in transgenic Alzheimer models. Gloster Aaron will then present his work on the role of STEP in seizure disorders. Michael Browning will present the evidence for STEP in mediating the depressive effects of ethanol.

75. Astrocyte Intermediate Filament (Nanofilament) System and Its Role in Adult Neurogenesis, Regeneration, and CNS Pathologies

Chair: Milos Pekny

Presenters: Milos Pekny, Michael Brenner, Yang (Ted) Teng, Albee Messing

Astrocyte intermediate filaments (also known as nanofilaments) are 10 nm thin filaments composed of GFAP, vimentin, nestin and synemin (the latter two are present in reactive astrocytes). Intermediate filaments and intermediate filament proteins emerge as important regulators of cell signaling and have been suggested to regulate cellular processes such as migration and differentiation, both in health and disease. Genetic ablation of GFAP and vimentin in mice negatively affects the ability to cope with the acute stress of neurotrauma or ischemic stroke, but allows better regeneration later on and creates environment more permissive to transplanted neural grafts and neural stem cells. Mutations in GFAP lead to Alexander disease, a devastating leukodystrophy. Milos Pekny will introduce the topic and show recent data on the role of GFAP and vimentin in the adult neurogenic niche. Michael Brenner will focus on transcriptional regulation of GFAP in response to neurotrauma. Ted Teng will present experimental evidence showing that attenuation of reactive gliosis by genetic ablation of GFAP and vimentin combined with neural stem administration improves the outcome after spinal cord injury. Albee Messing will show results from animal models of Alexander disease which give new insights into the molecular pathogenesis of this disease and will outline pharmacological approaches aiming at decreasing the GFAP levels in astrocytes.

76. New Vistas in Understanding and Treating Alcohol Abuse

Chair: Bart Hoebel

Presenters: Charles O'Brien, Sarah Leibowitz, Friedbert Weiss, Philippe DeWitte

O'Brien will describe mechanisms of reinforcement produced by alcohol. Rodent studies show a predominance of opioidergic mechanisms, while primates including humans have more variable pathways. A variant in the gene for the mu opioid receptor has been found to be a marker for an endophenotype

of alcoholism marked by high stimulation from alcohol. This has important implications as the first psychiatric treatment based on pharmacogenomics. Leibowitz will describe new findings relating orexigenic peptide systems to the consumption of ethanol, which is both a food and a drug. Evidence focuses on enkephalin, galanin, orexin and melanin-concentrating hormone in the relationship between high-fat diet intake and ethanol intake. Studies in genetically-engineered mice that over-express or have a deletion of the galanin gene further support a role for this peptide in the control of ethanol intake and abuse. Weiss will discuss the lateral hypothalamic orexin/hypocretin (Orx/Hcrt) system that plays a role in feeding and arousal. His data suggests that in rats with a history of cocaine or ethanol self-administration, the Orx/Hcrt system acquires control over motivated behavior, and participates in compulsive-like conditioned drug-seeking, as opposed to behavior motivated by natural reward essential for well-being and healthy hedonic pursuits. De Witte used microdialysis in the accumbens to discover that glutamate is released by voluntary alcohol intake immediately after a binge-drinking episode. During chronic alcoholization in a vapor chamber, this release of glutamate is delayed, occurring 6-8 hours later, suggesting that it is due to alcohol withdrawal. These talks represent four approaches to understanding alcoholism.

Panel • Friday 7:30-9:30 AM • Peak 6/7/8

77. DISC1 and the Gang: How DISC1 Acts in Concert with other Mental Illness Candidate Proteins

Chair: Carsten Korth

Presenters: Atsushi Kamiya, Qi Wang, Carsten Korth, Josef Kittler

The identification of candidate genes in mental illnesses has been a major advance in the last decade providing a handle on deciphering the neurobiology of these diseases. The DISC1 gene has been genetically linked and associated to a variety of mental diseases like schizophrenia, bipolar disorder and recurrent depression. So far, it is the best investigated candidate gene for mental disease with several transgenic animal models displaying behavioral, anatomical and physiological abnormalities supporting the notion of DISC1 being a key player in maintaining mental health. As a protein, DISC1 is seen as a multi-interacting protein localizing to mitochondria, nucleus, centrosome and synapses. A key question is now whether DISC1 interacts with other candidate proteins for mental diseases in order to identify common pathways converging to behavioral phenotypes. In this panel we report and discuss recent progress on DISC1 interactions conceived to be critical for its function. Atsushi Kamiya is introducing

in utero gene manipulation of the CNS for investigating gene interactions such as DISC1-neuregulin1 or DISC1-NDEL1. Qi Wang will present the role of DISC1 at the synapse, focussed on DISC1 interactions with Traf-2- and Nck-interacting kinase (TNIK) suggesting that deficits of the TNIK-DISC1 signalosome contribute to altered synaptic transmission. Carsten Korth will focus on protein biochemistry of DISC1 showing how different DISC1 multimerization modulates NDEL1 interaction and indirect interactions with dysbindin1. Josef Kittler will present how DISC1 interactions modulate motor protein dependent trafficking of organelles.

Panel • Friday 4:30-6:30 PM • Peak 5

78. Structure and Function of the Cerebellar Cortex and Nuclei

Chair: Detlef Heck

Presenters: Dieter Jaeger, Ray Turner, Chris De Zeeuw, Robert Sachdev

The cerebellum plays a crucial role in motor control and motor learning. How it performs these tasks on a neuronal level is largely unknown. Anatomically the cerebellum is unique because of the highly crystalline network architecture of the cerebellar cortex. To arrive at a neuronal understanding of cerebellar function it is essential to understand neuronal interactions within the cerebellar cortex and between the cortex and its target structures, the cerebellar nuclei (CN), which contain the output neurons of the cerebellum. In recent years several groups have used novel approaches to investigate neuronal interactions within the cerebellar cortical and nuclear networks and between the cortex and nuclei. These experiments provided important new insights into the neuronal mechanisms of cerebellar function. This panel will discuss novel insights into neuronal interactions within the cerebellar cortex and nuclei, between the cortex and CN and between the cerebral and cerebellar cortices. Dieter Jaeger will present dynamic clamp and modeling studies on how Purkinje cell inputs may be integrated by cerebellar nuclear neurons. Ray Turner will discuss the ionic basis for differential coding mechanisms across deep cerebellar nuclei. Chris De Zeeuw will present results from whole-cell recordings of DCN neurons in vivo which indicate that Purkinje cell information mediated by the climbing fiber pathway can be distinguished from that relayed by the mossy fiber—parallel fiber pathway. Robert Sachdev will discuss results from in vivo recordings showing widespread synchronized oscillations between cerebral and cerebellar cortex.

79. Signaling Interaction and Transcriptional Regulation during Hypothalamic Pituitary Adrenal Axis Adaptation to Stress

Chair: Greti Aguilera

Presenters: Stoney Simons, Greti Aguilera, Stafford Lightman, Arshad Khan

Abnormal regulation of corticotrophin releasing hormone (CRH) expression and glucocorticoid production leads to maladaptive stress responses resulting in systemic and psychiatric disorders. This panel will address the molecular mechanisms underlying the regulation of HPA axis activity and the effects of glucocorticoids in the brain. Stoney Simons will start by discussing factors regulating the transcriptional activity of glucocorticoid receptors. Events downstream of receptor binding such as alteration of the level of selected transcription factors can modify the potency of steroids inducing exogenous and endogenous genes. Greti Aguilera will follow by discussing the requirement of nuclear translocation of the CREB co-activator, transducer of regulated CREB activity (TORC), for activation of CRH transcription, and how interaction of different signaling pathways initiated by stress will result in activation and termination of CRH transcription. Stafford Lightman will present experimental evidence for rapid genomic signaling by glucocorticoids. He will discuss single cell and whole body studies indicating how the pattern of glucocorticoid secretion impacts on pulsatility of GR:DNA binding and gene transcription. Finally, Arshad Khan will provide evidence that activation of CRH transcription by glycemic challenge depends on ascending catecholaminergic projections to the PVN, leading to activation of the Erk/MAP kinase pathway which is critical for transcriptional activation of the CRH neuron. Discussion of these topics will provide a better understanding on the mechanisms of regulation of the HPA axis, and will open novel perspectives for the development of diagnostic and therapeutic tools for neuroendocrine disorders.

80. Mitochondria in Synaptic Plasticity

Chair: Elizabeth Jonas

Presenters: George Spirou, Jennifer Morgan, J. Marie Hardwick, Elizabeth Jonas

Synaptic plasticity is thought to underlie such important processes as learning and memory as well as adaptation to the sensory environment and may also play an important role in nerve regeneration after injury. Although the mechanisms of synaptic plasticity may differ among model systems, there may be

underlying phenomena that occur commonly in all forms of synaptic plasticity. Recently, mitochondrial morphologic changes, movement and metabolism in neurons have been investigated by a number of groups. In this session we will further explore the idea that long term changes in mitochondria may underlie processes that lead to synaptic strengthening. George Spirou will discuss how heterogeneous release probability and Ca^{2+} -handling in synapses of the Calyx of Held in the mammalian auditory system contribute to maintaining appropriate responses to a changing acoustic environment. He will show detailed images of mitochondria positioned adjacent to the active zones at these synapses and suggest how they may contribute to modulation of Ca^{2+} levels at the active zone. Jennifer Morgan will discuss her exciting new model of synaptic plasticity that accompanies re-innervation of motor neurons by descending reticulospinal (RS) neurons after spinal lesion in the lamprey. Mitochondrial morphological changes may contribute to this unusual form of synaptic plasticity. Marie Hardwick will discuss how the anti-apoptotic Bcl-2 family protein Bcl-xL regulates mitochondrial fission, fusion and biomass in mammalian neurons. Finally Liz Jonas will discuss how the long term morphological and bioenergetic changes induced by BCL-xL expression may play an important role in synaptic plasticity in the mammalian hippocampus.

Panel • Friday 4:30-6:30 PM • Peak 14

81. NMDAR Hypofunction Induced Deficits in Psychiatric Illness—Its Not All About Changes in Long Term Plasticity!

Chair: Robert Greene

Presenters: Margarita Behrens, Janet Finlay, Terrence Sejnowski, Craig Powell

Hypofunction of glutamate N-methyl-D-aspartate receptors (NMDAR) has been implicated in the pathophysiology of psychiatric illnesses, including schizophrenia and autism. In pathological conditions, NMDAR dysfunction may be associated with alternations in neuronal structure and function quite different from those typically associated with long-term plasticity (LTP). For example, one of the most consistent findings in schizophrenia is a dysfunction of inhibitory neural systems. Current evidence suggests this dysfunction occurs in fast-spiking parvalbumin-positive (PV) inhibitory interneurons. Margarita Behrens has used a pharmacologic model of schizophrenia, involving exposure to NMDAR antagonists, to link diminished activity of NMDAR in PV-interneurons to alterations in PV-interneuron phenotype and function. Janet Finlay will discuss data from studies in which localized deletion of a functionally requisite exon for the NR1 subunit of the NMDAR in the prefrontal cortex (PFC) and/or CA3 subregion of the hippocampus differentially impairs sustained attention

and working memory, respectively. Terrence Sejnowski has found that in PFC projection cells, information processing may rely on transient “up and down” states of depolarized, increased excitability and hyperpolarized, decreased excitability, respectively. NMDAR activation has a vital role in the stabilization of these states resulting from both the kinetics and permeability peculiar to this ligand-gated channel. Its absence can disrupt the timing of these up and down states, interfering with PFC dependent cognition. Craig Powell will be speaking on behavioral and electrophysiological consequences of NMDAR hypofunction caused by deletion of the synaptic cell adhesion molecule neuroligin 1, a gene recently implicated in human autism. Areas for general discussion will include whether deficits associated with NMDAR-induced hypofunction occurring by non-LTP associated mechanisms are brain region specific, disease specific, and amenable to recovery by pharmacologic intervention.

Panel • Friday 4:30-6:30 PM • Peak 15/16

82. DA-Mediated Reward Processing: Interactions with Opioids and Sex Differences

Chair: Tiffany Love

Presenters: Charles O'Brien, Tiffany Love, Jill Becker

Dopaminergic mechanisms have long been implicated in responses to reward and the effects of natural and drug reinforcers. A number of areas related to these processes remain unresolved, however. For example, both dopaminergic and opioid systems appear involved in the effects of most drugs of abuse, with therapeutic options targeting either system depending on the substance under study. Furthermore, sex differences in both these mechanisms are readily apparent that have been, at best, insufficiently studied and may have important clinical implications. Charles O'Brien will present new data in animal models and humans examining dopamine—opioid interactions in the rewarding effects of alcohol. Tiffany Love will focus on dopamine—opioid systems as integral parts of a special example of reward processing, the elicitation of placebo responses in human clinical studies. Newly observed sex differences in these processes will be presented. She will also discuss the effects of common genetic variants on dopaminergic and opioid function. New data on the effect of variants in the oxytocin gene on striatal dopamine function will be presented. These include sex by gene interactions and relationships with attachment styles. Jill Becker will discuss sex differences in the function of the ascending dopamine system and drug abuse. New data on the mechanisms mediating sex differences in the effect of estrogen on dopamine function will be presented. These also extend to developmental aspects, with sex differences in adolescent vs. adult drug taking behavior.

83. Neural Substrates of Social Cognition: New Frontiers for Nonhuman Primate Studies

Chair: Ludise Malkova

Presenters: Ludise Malkova, Christopher Machado, Michael Platt

A crucial component of primate behavior is social cognition, which involves processing of social signals and applying that information toward making decisions and achieving goals, such as attracting a mate or getting food in a social environment. Our understanding of the neural substrates underlying social behavior in nonhuman primates has been largely based on lesion studies and electrophysiological recordings. These studies pointed to the amygdala and orbital frontal cortex as key structures of the neural circuitry involved in mediating social interactions, but other components yet remain to be determined. The panel will discuss recent advances in this field using novel techniques and new behavioral tasks to shed light on the underlying neural circuitry. Ludise Malkova will present behavioral data showing how activation of the brain's defense system by reversible disinhibition of the deep layers of superior colliculus (using intracerebral drug infusions) affects dyadic interactions in monkeys and how the resulting behavioral changes are affected by manipulations within the amygdala. Chris Machado will review his results based on video eye-tracking, psychophysiological measures, and microPET data comparing conditions, in which monkeys watch videos depicting species-specific social interactions versus nonsocial animate stimuli. He will discuss the neural structures specifically involved in the perception and evaluation of socially-relevant visual information. Michael Platt will discuss his research on adaptive behavior, which requires selecting actions that maximize gains and minimize costs. He will describe his work on the neural circuitry mediating learning and decision making in human and nonhuman primates using neuroeconomic and neuroethological approaches.

Poster Abstracts

P1. Self-Administration of Heroin and Incubation of Heroin-Seeking in Adolescent vs. Adult Male Rats

James Doherty, Kyle Frantz*

Heroin abuse is prevalent among human adolescents. Yet few laboratory experiments explore adolescent sensitivity to heroin using animal models, such as intravenous drug self-administration and reinstatement of drug-seeking after abstinence. In this study, adolescent (postnatal day 35 start) and adult (postnatal day 86 at start) male Sprague-Dawley rats spontaneously acquired lever-pressing maintained by heroin. In Experiment 1, 13 days of self-administration on fixed ratio 1 (FR1) schedule of reinforcement (0.05, then 0.025 mg/kg/infusion; 3 hr-sessions) were followed by a reinstatement test after 1 or 12 days of abstinence. Adolescents took more heroin and exhibited higher rates of non-reinforced responding, compared to adults. In reinstatement, adolescent-onset groups exhibited less heroin-seeking than older adults, and levels of reinstatement increased between 1 and 12 days of abstinence for both age groups (incubation). In Experiment 2, 9 days of acquisition (0.05 mg/kg/infusion; 3 days each on FR1, 2, and 5) were followed by 9 days of testing on a progressive ratio (PR) schedule (0.0125, 0.05, or 0.1 mg/kg/infusion; max 9-hr sessions), and a reinstatement test after 12 days of abstinence. No age differences in self-administration or reinstatement were observed. Body weight and fecal boli were quantified, and heroin affected these somatic signs less in adolescents than adults. Overall, this study suggests that younger rats may be less sensitive than adults to some acute and long-term effects of heroin. Thus, further investigation of adolescent rats may reveal neuroprotective factors that could be mimicked for relapse prevention in humans.

P2. Dysregulation of Genes that Control Dopaminergic Activity in the Clock Mutant Mice, a Model of Mania

Sade M. Spencer, Rachel N. Arey, Edgardo F. Falcon, M. Marvin, Matthew Goldberg, Colleen A. McClung*

The cause of bipolar disorder is unknown, but one hypothesis concerning the etiology of the disease is a disruption in circadian function. Our lab utilizes mice mutated at the Clock gene with a behavioral profile similar to humans in the manic state. Previously we demonstrated that dopamine (DA) cells in the ventral tegmental area (VTA) of these mice show increased firing and bursting.

Additionally, levels of tyrosine hydroxylase protein (TH) and the active form phospho-TH (Ser 31) are elevated in the VTA of Clock mice. Conversely, levels of cholecystokinin mRNA are reduced. This suggests that the disruption of Clock in the VTA may mediate changes in DA transmission resulting in the manic-like behaviors. Therefore, we wanted to determine if the Clock mutation leads to changes in the molecular rhythms of DA-related genes in the VTA. We find changes in the rhythms of multiple key genes involved in dopaminergic activity. Interestingly, TH mRNA levels are elevated at most time-points in Clock mutants compared to WTs. This suggests that CLOCK is involved in reducing levels of TH at particular times of day. Using chromatin immunoprecipitation assays, we find that CLOCK binds to the TH promoter, thus the regulation of TH by CLOCK is direct. Ongoing studies will determine whether levels of dopamine are altered in the nucleus accumbens of Clock mutants compared to WT mice consistent with the changes in TH expression. These studies will help determine the importance and regulation of rhythmic DA signaling in the development of manic-like behaviors.

P3. Neurocognitive Improvement among Alcohol-Dependent Individuals Treated with a Combination of Flumazenil and Gabapentin

Joseph P. Schacht, Patrick K. Randall, Raymond F. Anton*

Neurocognitive deficits are pronounced among alcohol-dependent individuals, but the extent to which pharmacotherapy affects these deficits is unclear. This study analyzed data from sixty alcohol-dependent participants randomized to receive either active flumazenil and gabapentin or two placebos (Anton et al., 2009) to determine whether these medications improved neurocognitive performance. Participants completed the Trail Making Test (TMT), Stroop Color and Word Test, and Conners' Continuous Performance Test (CPT) at baseline and again on days 3 and 7 of treatment. Individuals with greater pre-treatment alcohol withdrawal demonstrated poorer baseline performance on all measures. Mixed modeling with dichotomous predictors for treatment, alcohol withdrawal, and drinking during the first week of treatment, and baseline performance for each neurocognitive variable covaried, revealed main effects of withdrawal and treatment on TMT Part B and the Stroop interference effect on days 3 and 7, such that, regardless of treatment, individuals with high baseline withdrawal performed worse at both points, and, regardless of baseline withdrawal, individuals who received active medication performed better. There was also an interaction between treatment and drinking during treatment for all three measures, such that, as compared to placebo and to individuals who received active medication but did not drink, individuals who received active medication and continued to drink performed worse. These data suggest that alcohol withdrawal impairs neurocognitive performance both acutely and up to 7 days

after beginning pharmacotherapy, that flumazenil and gabapentin resolve some of these deficits, and that continued drinking while taking these medications is particularly deleterious to cognition.

P4. Synthetic Triterpenoids Induce a Cytoprotective Pathway in Astrocytes and Attenuate Immunological Activation in Microglia

*David J. Graber, William Hickey, Brent T. Harris**

Oxidative stress and overactive immunological events are involved in the pathology of several neurodegenerative diseases including amyotrophic lateral sclerosis (ALS). Although the role of glia in neurodegeneration is not fully understood, these cells remain a potential target for treatment. Triterpenoids belong to the group of saponin compounds and are naturally produced in some plants. They have a structure similar to cholesterol and steroids, and are bioactive in mammals. Synthetic triterpenoids generated as derivatives of oleanolic acid have enhanced action on several cellular pathways including attenuating the synthesis of harmful oxidative/nitrosative products and stimulating the production of cytoprotective enzymes. We examined the effects of four synthetic triterpenoids as derivatives of 2-Cyano-3,12 dioxooleana-1,9 diene-28-imidazolide (CDDO) on microglia and astrocytes using cell lines and primary cell cultures. Pre-treatment of cells for one day with CDDO compounds attenuated endotoxin-stimulated nitric oxide production in microglia and increased an enzyme (NADPH:quinone oxidoreductase) that is a known product of antioxidant response element induction in astrocytes. The observed effects in both microglia and astrocytes occurred with nanomolar concentrations. We propose that the dual properties of synthetic triterpenoids in glia provide a novel approach for neuroprotection and that these compounds should be tested in animal models of neurodegenerative diseases including the mutant human superoxide dismutase-1 transgenic model of ALS for their ability to delay onset and prolong survival.

P5. Role of Dopamine Receptors, but not $\alpha 2$ Adrenoceptors, in Yohimbine-Induced Reinstatement of High-Fat Food Seeking

Brittany Navarre, Sunila Nair, Tristan Adams-Deutsch, Charles Pickens, Yavin Shaham*

In humans, relapse to maladaptive eating habits during dieting is often provoked by stress. We adapted a reinstatement model, commonly used to study drug relapse, to study the role of stress in relapse to food seeking. We found that the prototypical alpha-2 adrenoceptor antagonist yohimbine, which induces stress-like states in humans and laboratory animals, reinstates food seeking. Here, we

first attempted to verify whether yohimbine's effect on reinstatement is mediated by alpha-2 adrenoceptors. We then studied the role of dopamine receptors in this reinstatement. We trained food restricted rats (~16 g/day) to lever press for 45 mg high-fat (35%) pellets for 9-10 training days (3 h/day, every other day). After 10-14 days of extinction of lever responding, we tested the rats for food reinstatement induced by yohimbine (2 mg/kg, i.p.) injections. We found that the effect of yohimbine on reinstatement was neither blocked by the alpha-2 adrenoceptor agonist clonidine (0.04, 0.08 mg/kg, i.p.) nor mimicked by the selective alpha-2 adrenoceptor antagonist RS79948 (0.5, 1.0, 1.5 mg/kg, i.p.). In contrast, yohimbine-induced reinstatement was dose-dependently attenuated by the D1-family receptor antagonist SCH23390 (5, 10 µg/kg, s.c.). These doses of SCH23390 had no effect on high rates of food-reinforced lever responding during training. Further, dorsal (but not ventral) medial prefrontal cortex injections of SCH23390 (0.5 or 1 µg/side) attenuated yohimbine-induced reinstatement. Surprisingly, our data indicate a critical role of dopamine receptors (localized at least in part to the dorsal prefrontal cortex), but not alpha-2 adrenoceptors, in yohimbine-induced reinstatement of food seeking.

P6. Fluoxetine (Prozac) Potentiates Methylphenidate (Ritalin)-Induced Gene Regulation in Addiction-Related Brain Regions

Vincent Van Waes, Joel Beverley, Michela Marinelli, Heinz Steiner*

Use of the psychostimulant methylphenidate (Ritalin), both in the treatment of attention-deficit hyperactivity disorder, and as a "cognitive enhancer" in the healthy, has increased considerably over the past decade. Methylphenidate differs from the psychostimulant cocaine in that it does not enhance extracellular serotonin levels. Recent studies indicate that serotonin contributes to cell-signaling effects of cocaine. Therefore, the inability of methylphenidate to affect the serotonin neurotransmission may explain why this drug mimics some but not all of the molecular effects of cocaine. We investigated whether exposure to methylphenidate combined with the prototypical selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac) would produce more "cocaine-like" molecular changes in brain regions related to addiction. Gene induction (zif 268 and c-fos) in the forebrain was mapped by in situ hybridization histochemistry after a concomitant treatment with methylphenidate (2-5 mg/kg, i.p.) and fluoxetine (5 mg/kg). Fluoxetine by itself did not produce significant changes in gene regulation. In contrast, when given together with methylphenidate, fluoxetine robustly potentiated methylphenidate-induced c-fos and zif 268 expression throughout the striatum and, to a lesser degree, in the nucleus accumbens. These molecular effects were associated with a selective potentiation of motor stereotypies. Together, these findings suggest that SSRI antidepressants may increase the drug addiction liability of methylphenidate. This is

of concern as methylphenidate is often prescribed together with fluoxetine, and methylphenidate+SSRI exposure may also occur due to “cognitive enhancer” use by patients on SSRIs.

P7. Cerebrovascular Reactivity after Intracisternal Blood Injection in Insulin Resistant Rats

Adam Institoris, David W. Busija*

Insulin resistance (IR) impairs cerebrovascular function to some but not all stimuli in Zucker obese (ZO) rats. However cerebral artery responses after experimental subarachnoid hemorrhage (SAH) has not been described in IR. We investigated the dilator responses of the basilar artery and its side branch in a SAH model of intracisternal hemolysate injection in ZO (n=15) and lean (ZL) rats (n=15). Hemolyzed blood (300 μ l) or saline was infused (10 μ l/min) into the cisterna magna of spontaneously breathing, isoflurane (2%) anesthetized, 11-13 week-old ZO and ZL rats. Twenty-four hours later, the diameter changes of the basilar artery and its side branch to acetylcholine (10-6M), cromakalim (10-7M, 10-6M) and sodium nitroprusside (10-7M) were recorded with intravital videomicroscopy over an open cranial window preparation. Saline injected ZO animals showed reduced dilation to acetylcholine (basilar=7 \pm 4% vs. 21 \pm 5%; branch=20 \pm 5% vs. 37 \pm 8%) compared to respective ZL rats. Blood injection blunted the response to acetylcholine in both the ZO (basilar=4 \pm 3%; branch=11 \pm 3%) and ZL rats (basilar=7 \pm 2%; branch=16 \pm 4%). Cromakalim (10-6M)-induced dilation was significantly reduced both in the blood injected ZO animals compared to the saline control (basilar=11 \pm 3% vs. 27 \pm 5%; branch=23 \pm 7% vs. 43 \pm 11%), and in the blood injected ZL rats vs. its saline control (basilar=24 \pm 4% vs. 29 \pm 3%; branch=39 \pm 3% vs. 58 \pm 9%). No difference in SNP reactivity was observed. In summary, cerebrovascular reactivity to both endothelium- and smooth muscle-dependent stimuli is severely compromised by extravascular blood in IR animals. Supported by NIH grants HL065380 and HL 077731.

P8. MRI and Histological Analysis of Beta-Amyloid Plaques in Both Human Alzheimer’s Disease and APP/PS1 Transgenic Mice

Mark D. Meadowcroft, James R. Connor, Michael B. Smith, Qing X. Yang*

Imaging of beta amyloid (A β) plaques in human Alzheimer’s disease (AD) and the APP/PS1 mouse model has been of great interest for AD research. However, the histo-pathological basis of the image contrast and relaxation mechanism associated with A β plaques has not been well-understood. With the aid of the previously developed histological coil, T2*-weighted images and R2*

parametric maps were directly compared to histology stains acquired from the same set of Alzheimer's and APP/PS1 tissue slices. The electronic microscopy and histology images revealed significant differences in plaque morphology and associated iron concentration between AD and transgenic APP/PS1 mice tissue samples. For AD tissues, T2* contrast of A β -plaques was directly associated with the gradation of iron concentration. Plaques with significantly less iron load in the APP/PS1 animal tissues are equally conspicuous as the human plaques in the MR images. These data suggested a duality in the relaxation mechanism where both high focal iron concentration and highly compact fibrillar beta-amyloid masses cause rapid proton transverse magnetization decay. For human tissues, the former mechanism is likely the dominant source of R2* relaxation; for APP/PS1 animals, the latter is likely the major cause of increased transverse proton relaxation rate in A β -plaques. The data presented are essential for understanding the histo-pathological underpinning of MRI measurement associated with A β plaques in humans and animals.

P9. Receptor Kinetic Computational Model Distinguishes mEPSC Contributions of NR2A and NR2B Subunit-Containing NMDA Receptors during Status Epilepticus

*David E. Naylor**

Previously we showed that surface accumulation of NR2B subunit-containing NMDA receptors contributes to an increase in phasic and tonic NMDA currents during status epilepticus (SE). During SE, NMDA-mEPSC amplitudes increase from -16.4 ± 0.6 pA to -20.2 ± 2.7 pA and 63% decay times increase from 21.0 ± 12.8 ms to 24.4 ± 8.3 ms ($p < .01$). Mean-variance analysis of NMDA-mEPSCs estimates that the number of NMDA receptors increases from 8 ± 1 receptor per synapse in controls to 11 ± 2 per synapse with SE ($p < .001$). With blockade of NR2B subunit-containing receptors by ifenprodil (3 micromolar), SE NMDA-mEPSC amplitudes and decay times decrease to control values indicating that the increase in postsynaptic content of NR2B subunits with SE accounts for both the amplitude and decay time changes. Further characterization of the kinetic properties that distinguish NR2B and NR2A subunit-containing receptor contributions during SE was obtained through computational models of NMDA-mEPSCs that include parameters for 6-state NMDA receptors and synaptic cleft concentration of glutamate. While NR2B subunit-containing receptors show lower glutamate binding affinity, their decreased unbinding rates compared to NR2A subunits can explain the SE-induced NMDA-mEPSC kinetic changes. The peak glutamate concentration in excitatory synapses after SE is estimated at 1.8 mM with an exponential decay time constant of 128 microseconds.

P10. Dopamine Transporter Coding Variant Ala559Val Associated with Attention Deficit Hyperactivity Disorder Impairs AMPH-Induced DAT Internalization and DAT-Mediated DA Efflux

Erica Bowton, Heinrich Matthies, Dhananjay Sakrikar, Randy Blakely*

The human dopamine (DA) transporter (hDAT) is the site of action for psychostimulants such as amphetamine (AMPH), which is also used therapeutically for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Evidence indicates a genetic link between DAT and ADHD, and recent work by our laboratory has identified a nonsynonymous single nucleotide polymorphism in DAT which converts Ala559 to Val (A559V) in two male siblings with ADHD. Importantly, treatment with AMPH leads to increased intracellular accumulation of DAT, as well as an increase in PKC activity. AMPH-induced PKC activation leads to a subsequent increase in N-terminal phosphorylation of DAT and has also been shown to regulate DAT-mediated DA efflux. While the molecular mechanism by which AMPH induces trafficking is not clear, data suggests that intracellular AMPH accumulation is required, possibly due to the ability of AMPH to increase intracellular Ca²⁺ levels and stimulate Ca²⁺-dependent kinases such as PKC. Here, we show that AMPH has a differential impact on DAT trafficking in cells transfected either with hDAT A559V or hDAT. Our data demonstrates that while AMPH induces DAT trafficking away from the plasma membrane in hDAT cells, it has no effect in hDAT A559V cells. Additionally, AMPH fails to elicit DAT-mediated DA efflux in hDAT A559V cells. However, both AMPH-induced internalization as well as AMPH-induced DA efflux are restored by preventing phosphorylation of the A559V DAT N-terminal serines or by inhibiting PKC β activity, suggesting that phosphorylation of A559V DAT N-terminal serines by PKC β may support anomalous activity of hDAT A559V. Notably, when AMPH is delivered intracellularly, hDAT A559V internalization is restored. These data are consistent with the hypothesis that A559V in its phosphorylated state does not allow for the transport of AMPH through DAT, thereby preventing AMPH from eliciting its intracellular effects that may subsequently result in DAT internalization and/or DA efflux.

P11. The Western Diet Alters Blood-Brain Barrier and Microglial Activation in Middle-Aged Rats

Lotta Granholm, Linnea Freeman*

The “Western Diet” (WD) is a dietary habit chosen by many people in developed countries, and it has been spreading throughout developing countries in recent years. WD is characterized by increased caloric intake, predominantly red meat, high-fat dairy products, high-sugar drinks and desserts. The intake of a “Western diet” (WD) has adverse effects on blood lipids, most notably

on triglyceride and cholesterol levels, representing a strong cardiovascular risk factor. Western diets give rise to memory loss and accelerated aging processes both in humans and animal models but the mechanisms are currently not understood. We have demonstrated that WD gives rise to elevated triglycerides, memory loss, and microglial activation in the hippocampus. Our recent data suggest that aged subjects are more sensitive to this diet, based on previous literature showing an exaggerated response to peripheral and central inflammation with aging. We found that WD-induced alterations of hippocampal morphology were reversed by a selective IL-1 inhibitor, IL-1Ra (Kineret), supporting the notion that WD induced damage to hippocampal morphology via IL-1 transfer from serum via activated endothelial cells to the brain parenchyma. Our data therefore suggest that blocking IL-1 receptors, either peripherally, on central endothelial cells, or on microglial cells in the hippocampus, may prevent memory loss and morphological degeneration caused by long-term exposure to high levels of triglycerides and cholesterol in the diet.

P12. BDNF Signaling to the Jak/STAT Pathway via the P75 Neurotrophin Receptor

Amy Brooks-Kayal, Rebecca Benham, Yogendra Raol, Marco Gonzalez, Shelley Russek*

Temporal lobe epilepsy (TLE) is the most common form of epilepsy and is frequently medically intractable. Evidence indicates that abnormalities in inhibitory neurotransmission are important in TLE. Our laboratories have identified long-term decreases in GABA(A) Receptor alpha1 subunit gene (*Gabra1*) expression in hippocampal dentate gyrus following status epilepticus (SE) that are associated with later development of epilepsy (Brooks-Kayal et al., *Nature Med* 1998; Raol et al., *J Neurosci*, 2006). We recently established that this transcriptional repression of *Gabra1* after SE is mediated by inducible cAMP early repressor (ICER) and phosphorylated CREB, and that ICER transcription is driven by the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling cascade via the actions of brain derived neurotrophic factor (BDNF) (Lund et al., *Science Signaling* 2008). We now have further preliminary data suggesting that spontaneous seizures themselves activate the JAK/STAT pathway, and that BDNF signals to JAK/STAT through the p75 neurotrophin receptor (NTR). In cultured rat hippocampal neurons siRNAs specific for the p75NTR as well as novel, small molecule p75NTR ligands that inhibit neurotrophin-mediated p75NTR signaling reduce BDNF induced STAT3 phosphorylation. Further, activation of the JAK/STAT pathway after SE can be attenuated by pre-treatment with these small molecule p75NTR ligands. Results of these studies suggest that BDNF induced activation of the JAK/STAT pathway is mediated in part by p75NTR and identifies this receptor system as a potential new therapeutic target for the prevention or treatment of epilepsy.

P13. Axonal Microdomains of PI3K Activity Drive the Formation of Axonal F-Actin Patches that Serve as Precursors to the Formation of Filopodia

Gianluca Gallo, Andrea Ketschek*

Axonal filopodia are precursors to the formation of pre-synaptic structures and axon collateral branches. However, the mechanisms underlying the initiation of axonal filopodia are poorly understood. We have shown that axonal filopodia are formed from precursor cytoskeletal structures that we termed axonal F-actin patches (Loudon et al., 2007 *J. Neurobiol.* 66:847). As revealed by live imaging of axonal actin dynamics, F-actin patches are spontaneously formed along axons, grow in size and then dissipate. Filopodia form from patches, although only a fraction of patches give rise to filopodia before fully dissipating. Live imaging of actin dynamics and phosphoinositide 3 kinase (PI3K) activity in axons, using EGFP-Akt-PH, revealed that microdomains of PI3K activity form in spatio-temporal synchrony with F-actin patches. Pharmacological inhibition of PI3K and Akt kinase blocked formation of axonal F-actin patches and filopodia. Conversely, a cell permeable PI3K activating peptide increased the rate of formation of F-actin patches and the numbers of axonal filopodia. Nerve Growth Factor (NGF) induces the formation of axonal filopodia, which we now show is specifically due to increases in the rate of formation of F-actin patches. The effects of NGF on F-actin patches are in turn dependent on PI3K-Akt activity. Collectively, the data elucidate the earliest steps in the formation of axonal filopodia by demonstrating (1) the existence of localized axonal microdomains of PI3K that drive the formation of axonal F-actin patches, and (2) that NGF regulates the numbers of axonal filopodia by increasing the rate of formation of axonal F-actin patches.

P14. Synaptotagmin 1 Overexpression Increases Cell Process Complexity in Developing Embryonic Chicken Forebrain Neurons In Vitro

Karen F. Greif, Bailey Baumann, Gianluca Gallo*

Synaptotagmins are a family of 16 vesicle membrane proteins that are broadly expressed in neurons and play roles in coordinating membrane fusion. Synaptotagmin1 (Syt1), which contains two calcium binding C2 domains, is believed to respond to changes in Ca²⁺ concentration leading to vesicle fusion and release of neurotransmitter at the synapse. Although the role of Syt1 at the synapse has been well studied, less is known about its potential role in the regulation of axonal morphology. Many neuron types express Syt1 days before synaptogenesis begins, and in vitro Syt1 is targeted to growth cones and axons. Localized changes in calcium ions regulate axon outgrowth at growth cones, as well as the

formation of axonal filopodia and branches. We hypothesize that Syt1 contributes to axonal morphology by providing new membrane at sites of filopodia and branch development. This hypothesis predicts that over-expression and down-regulation of Syt1 should increase and decrease the numbers of axonal filopodia, respectively. We over-expressed Syt1-YFP in E8 chicken forebrain neurons in vitro using adenoviral-mediated gene delivery. Control cells were transfected with an adenovirus-GFP construct. Syt1 over-expressing Banker Stage II neurons exhibited increased numbers of minor processes that were also more branched than controls. Stage III neurons, those in which a clearly defined axon is present, showed a significant increase in the number of primary axon branches ($p < 0.05$) and a robust increase in axonal filopodia ($p < 0.0001$) and lamellipodia ($p < 0.0005$). These results suggest that levels of Syt1 may promote the branching of axons by increasing filopodial protrusion in response to calcium signals. Supported by grants from the NIH, the State of Pennsylvania and Bryn Mawr College.

P15. Neuronal Pentraxin 1 Regulates the Neuronal Activity-Dependent Intrinsic Program of Apoptosis by Facilitating Bax Translocation to Mitochondria

Ramon Trullas, Marta Enguita, Kevin Clayton, Maria Alba Abad, Joana Figueiro*

Neuronal activity regulates a complex program of gene expression that determines the fate of the neuron. The signaling pathways set in motion when neuronal activity increases are important for neuronal survival, differentiation, synaptogenesis and memory and have been the subject of intense research. However, less is known on the cell-signaling pathways and the gene expression program that are specifically switched on when neuronal activity decreases. Reduction of neuronal activity in cultured cerebellar granule neurons after lowering the extracellular concentration of potassium triggers the intrinsic program of apoptotic cell death. This program of apoptosis requires macromolecular synthesis-dependent BAX translocation from cytoplasm to mitochondria, cytochrome c release and caspase activation. However, the mechanisms by which neuronal activity regulates this apoptotic program remain unclear. We have previously reported that apoptosis caused by low neuronal activity depends on the new synthesis of Neuronal Pentraxin 1 (NP1), a glycoprotein that is predominantly expressed in the nervous system. We have now investigated the role of NP1 within the sequence of biochemical events leading to apoptosis. Here we report that lentiviral mediated transgene overexpression of NP1 induces apoptosis in cerebellar granule neurons from wild type but not in neurons from Bax deficient mice. Moreover, overexpression of NP1 potentiates apoptosis, cytochrome c release and cleavage of caspase 3, but does not modify induction of Bim expression evoked by low potassium. We also found that

NP1 facilitates the translocation of Bax to mitochondria and that reduction of neuronal activity causes a marked increase in NP1 protein levels in mitochondria. Altogether, these results place the induction of NP1 expression upstream of Bax activation in the sequence of events of the intrinsic pathway of neuronal apoptosis, and indicate that NP1 induced by low potassium is pro-apoptotic by facilitating the translocation of Bax to mitochondria.

P16. Differential Expression of Myostatin in the Brain of Genetically-Modified Mice

*Stephen Murata, Suzanne Porszasz-Reisz, Andrea Abraham, Sonsoles de Lacalle**

Inhibition of Myostatin (Mst), a secreted protein that negatively regulates skeletal muscle mass, is a promising therapy for muscular atrophy. For example, intraperitoneal administration of an Mst antibody slows the progression of motor neuron loss in the ventral horn of a rodent model of Amyotrophic Lateral Sclerosis. We have also observed behavioral differences between wild-type mice (WT) and mice in which the Mst gene has been modified to either abolish (KO) or overexpress (TG) Mst protein. Particularly, TG animals are significantly more active than the WT or KO mice, are faster learners during the treadmill training stage, and also show higher exercise tolerance. To clarify a possible neural component in these effects, we investigated the differential expression of Mst in the brain of these mice. Western blot analysis identified the 52 kDa unprocessed protein in TG mouse brain. RT-PCR revealed the mRNA transgene in the brain of the TG. Expression of the Mst receptor ActRIIB in TG was almost double that in WT, and KO had none. Application of a Pathway Finder Array identified significant upregulation in a number of signal transduction cascades in the brain of the TG mice, such as the Jak-Stat pathway, as well as a substantial downregulation of signaling in the KO mice, affecting the Wnt pathway among others. Among the genes represented in these arrays, the expression of several was significantly altered compared to WT. These results raise the possibility that Mst is involved in other functions than just myogenesis.

P17. Molecular Determinants of Antidepressant Selectivity at the Human Serotonin and Norepinephrine Transporters

Anders Kristensen, Jacob Andersen, Linda Zachariassen, Kristian Strømgaard*

The serotonin transporter (SERT) and the norepinephrine transporter (NET) are key regulators of serotonergic and noradrenergic neurotransmission, respectively, by facilitating Na⁺/Cl⁻ dependent neuronal re-uptake of released transmitter. SERT and NET are the molecular targets for a wide range of drugs used in the treatment of depressive, anxiety and behavioral disorders. In

particular, the majority of currently used anti-depressants are competitive inhibitors of SERT and/or NET. The SERT vs. NET selectivity ratio of these drugs is thought to be an important parameter for their clinical profile. However, the molecular basis for SERT vs. NET drug selectivity is poorly understood; including localization of drug binding sites and the identity of the amino acid residues that confer selectivity. A major obstacle has so far been lack of structural information for SERT and NET. The recent arrival of structural information on a bacterial transporter related to SERT and NET has opened new opportunities for breaking down this barrier. Combining mutational analysis of the human SERT and NET with determination of structure-activity relationship of selective SERT and NET inhibitors have allowed us to identify transporter residues and ligand moieties that are responsible for conferring selectivity of the SERT-selective antidepressants citalopram (Lexapro) and fluoxetine (Prozac) and their close analogs talopram and nisoxetine, respectively, which both are selective NET inhibitor. The experimental data sets are used to guide molecular modeling and ligand docking of the SERT and NET antidepressant binding pockets; providing novel insight into the molecular basis for selective SERT and NET inhibition.

P18. Sub-Second Measures of Glutamate Dynamics in Non-Human Primates: A Step Towards Clinical Application

Francois Pomerleau, Michelle L. Stephens, Jorge E. Quintero, Peter Huettl, Greg A. Gerhardt*

Minimally invasive ceramic based microelectrode arrays (MEAs) have proven very reliable for measuring neurotransmitters in various brain areas (frontal cortex, hippocampus, dorso-ventral striatum) of the rodent brain. Furthermore the configuration of the 4 Pt recording sites and their close proximity allow us to routinely use a technique for reliable measures of resting levels of glutamate on a sub-second basis. We have recently developed MEA designs for recordings in non-human primate (NHP). Our initial study was performed in anesthetized rhesus monkeys. We compared extracellular glutamate in the pre-motor and motor cortices of young, middle-aged, and aged animals. We observed that mean resting glutamate levels were five times higher in the aged group ($\sim 20 \mu\text{M}$) compared to the young group ($\sim 4 \mu\text{M}$). In addition, we measured reproducible phasic glutamate release and uptake that showed a significantly decreased rate of glutamate uptake (47%) in aged animals. We also recorded from the striatum in awake NHPs and observed a resting glutamate level of $\sim 5 \mu\text{M}$ with rapid transient changes of glutamate levels. These successful recordings in NHPs form a foundation for future uses of the MEA technology in neurosurgical application in humans.

P19. Exercise and Time-Dependent Benefits to Learning and Memory

Nicole Berchtold, Nicholas Castello, Carl Cotman*

While it is well established that exercise can improve cognitive performance, it is unclear how long these benefits endure after exercise has ended. Accordingly, the effects of voluntary exercise on cognitive function and brain-derived neurotrophic factor (BDNF) protein levels, a major player in the mechanisms governing the dynamics of memory formation and storage, were assessed immediately after a 3-week running period, or after a 1-week or 2-week delay following the exercise period. All exercised mice showed improved performance on the radial arm water maze relative to sedentary animals. Unexpectedly, fastest acquisition (fewest errors and shortest latency) occurred in animals trained following a 1-week delay, while best memory performance in the probe trial was observed in those trained immediately after the exercise period. Assessment of the time course of hippocampal BDNF availability following exercise revealed significant elevations of BDNF immediately after the exercise period (186% of sedentary levels) and at 1 and 2 weeks after exercise ended, with levels returning to baseline by 3-4 weeks. BDNF protein levels correlated strongly with cognitive performance on day 1 of acquisition and with memory performance on day 4, supporting the idea that BDNF availability contributes to the time-dependent cognitive benefits of exercise revealed in this study. Overall, this novel approach assessing the temporal endurance of cognitive and biochemical effects of exercise unveils new concepts in the exercise-learning field, and reveals that beneficial effects of exercise on brain plasticity continue to evolve even after exercise has ended.

P20. Role of V2a Interneurons in the Mouse Spinal Locomotor Network

Ronald Harris-Warrick, Guisheng Zhong, Stephen Crone, Kamal Sharma*

The organization of the network controlling vertebrate locomotion is not well understood. Transgenic methods for labeling and manipulating neurons help to map the locomotor network. The V2a interneurons (INs) express the Chx10 transcription factor, and are excitatory ipsilaterally projecting INs. We have studied their properties and activity in the neonatal spinal cord. About half of Chx10-CFP INs are rhythmically active during NMDA/5HT-evoked fictive locomotion, firing either in phase or out of phase with ipsilateral ventral root discharges. The electrophysiological properties of V2a INs are heterogeneous and form three major classes; there is electrical coupling between V2a interneurons within each class. When the V2a INs are eliminated (in Chx10-DTA mice which express diphtheria toxin in these neurons), the mice walk normally at low

speeds, but are uncoordinated at intermediate speeds and switch to synchronous left-right “galloping” at high speeds. Similar results are seen in the isolated spinal cord, with alternating left-right motor bursts at low speeds and synchronous left-right bursts at high speeds. The percentage of rhythmically active Chx10-CFP INs increases at higher speeds, and their spikes are more clustered into rhythmic bursts. These data suggest that V2a interneurons normally drive the commissural network to assure normal left-right alternation at high speeds, but are redundant at low speeds. Supported by NSF Collaborative Grant 0749467 to RH-W and KS.

P21. Methamphetamine-Induced Neurotoxicity in Dorsal Striatum Affects Phasic Dopamine Release, Striatonigral Neuron Function, and Striatum-Dependent Learning and Memory

Kristen A. Keefe, David P. Daberkow, Paul A. Garris, Jong-Hyun Son, Elissa Pastuzyn, Christopher D. Howard*

Exposure to methamphetamine (METH) induces a long-lasting, partial depletion of striatal dopamine in both rodent models and human abusers. Under such conditions, there is a relative sparing of gross behavioral function, especially motor function. However, several lines of evidence suggest that this partial dopamine loss negatively affects striatal function, perhaps by decreasing phasic dopamine transmission. We have used fast-scan cyclic voltammetry, in situ hybridization histochemistry, and behavioral pharmacology to assess the impact of METH-induced partial dopamine loss on striatal function. Our data indicate that such partial dopamine loss decreases phasic, but not tonic, dopamine release in dorsal striatum. Furthermore, this decrease is associated with impaired basal and behaviorally evoked gene expression (preprotachykinin and activity regulated, cytoskeletal-associated gene) in striatonigral, but not striatopallidal, neurons of the dorsal striatum. Finally, our results indicate that there are changes in the learning and memory functions of striatum. For example, although rats appear to perform normally on a motor response-reversal learning task on a T-maze, the pattern of errors made is different than that observed in control rats, and their performance is no longer dependent on the functional integrity of dorsal striatum. These findings suggest that although animals and individuals (METH abusers, early Parkinsons disease patients) with partial striatal dopamine loss may appear to be functioning relatively normally, the system as a whole does not fully compensate for the partial loss. We propose that impaired phasic dopamine transmission and consequent impairment of striatonigral / direct-pathway neuron function may contribute to such behavioral deficits.

P22. Synaptic Modulation by Glutamate and Dopamine is Altered in Striatal Medium Spiny Neurons Lacking the NR2A Subunit

John G. Partridge, Stefano Vicini*

N-methyl D-aspartate (NMDA) type receptors are integral components of glutamatergic neurotransmission. They have been suggested to be permissive in diseases of the basal ganglia including Huntington's disease. Four NR2 subunits contribute differential properties to synaptic receptors. We utilized a novel NR2A knock-out ($-/-$) mouse strain to determine the consequences of this genetic deletion in dorsal striatum. Mating NR2A $-/-$ with BAC-drd2-EGFP animals preserved genetic identification of striato-pallidal neurons. Voltage clamp recordings of medium spiny neurons (MSNs) were analyzed from acute brain slices. The lack of NR2A decreased the rate of decay of evoked NMDA-receptor excitatory postsynaptic currents (NMDA-EPSCs) in all MSNs. To determine modulatory roles of glutamate on NMDA-EPSCs, we stimulated metabotropic glutamate receptors (mGluRs) with tACPD (3-50 μ M). Activation of mGluRs dose dependently decreased the amplitude of NMDA-EPSCs differently in MSNs from drd2-EGFP and NR2A $-/-$ MSNs. The efficacy of tACPD was greater in the NR2A $-/-$ strain. We did not observe differences in tACPD modulation comparing striato-pallidal and striato-nigral neurons in either strain. The effects of tACPD were blocked by an mGluR2 antagonist, LY341495 (5 μ M), suggesting a presynaptic action. Further experiments were performed with dopamine receptor agonists. Application of D1 class agonists (SKF 38393, 10 μ M) decreased peak NMDA responses in all drd2-EGFP MSNs. However, in NR2A $-/-$ animals, we observed a potentiation of NMDA-EPSCs. These data suggest that the complement of NMDA-receptor complexes interact in distinct fashions between pre- and postsynaptic elements to regulate the modulatory actions of glutamate and dopamine at excitatory synapses onto MSNs.

P23. Advances in Microelectrode Arrays: A Novel Turnkey Probe for In Vivo Neurochemical Recordings

Peter Huettl, Jorge E. Quintero, Francois Pomerleau, Jason Burmeister, Greg A. Gerhardt*

The ability to directly record neurotransmitter resting levels, release and uptake on a second-by-second basis is an important analytical tool for neuroscientists. Improved methodologies in microelectrode technology are key in expanding their use. We have recently redesigned our advanced, uniquely fabricated, microelectrode arrays (MEA) to be easier to use for chronic recordings by

combining them with a guide cannula allowing for the MEA to be replaced as needed. Using this replaceable design, researchers can extend the duration of their chronic awake recording studies in the same animal for weeks and possibly months and re-use the MEAs. Combined with our multi-channel, dual recording site technology, our MEAs can be used repeatedly to selectively measure resting glutamate, choline, adenosine, glucose, lactate, acetylcholine and dopamine in the CNS of awake animals. These MEAs used with amperometric recordings have sub-second (600 msec) time resolution with high selectivity over major electroactive CNS interferents such as DOPAC and ascorbate. Average resting glutamate levels in striatum, hippocampus and prefrontal cortex of the rat (7, 8 and 13 μM respectively) are in the range of previously reported microdialysis measures (0.7, 0.9 and 0.8 μM respectively) based on typical microdialysis probe recoveries (10-20% *in vitro*). Also, MEA placement is much closer to the synaptic release source than microdialysis probes while causing less damage. Less dilution and loss of signal to diffusion occurs and thus the MEA signals should be larger than those observed with microdialysis studies. These MEAs will provide new avenues to understanding neurotransmission in the CNS.

P24. Role of Dopamine, Ca^{2+} and α -Synuclein in Vulnerability of SN Neurons in PD

Eugene V. Mosharov, Ellen Kanter, Krystal Wilson, Kester A. Phillips, David Sulzer*

A long-standing hypothesis of neuronal neurodegeneration in Parkinson's disease (PD) postulates that the buildup of cytosolic dopamine (DAcyt) with associated oxradical stress and its possible interaction with α -synuclein and other PD-related proteins underlie neurotoxicity. It is not clear, however, why subpopulations of DA neurons have differential susceptibility in. We recently adopted intracellular patch electrochemistry, the technique that allow direct measurements of cytosolic catecholamine concentration, for studying DAcyt in cultured mouse ventral midbrain neurons. Our results confirm the relationship between the levels of DAcyt and neurotoxicity and demonstrate that neuronal death depends on the dose (concentration* time) of elevated DAcyt. Substantia nigra (SN) neurons, the population that show increased susceptibility in PD, display significantly higher DAcyt than ventral tegmental area (VTA) neurons when treated with identical L-DOPA doses, which also correlated with higher susceptibility of SN neurons to L-DOPA-induced stress. The data indicate that "multiple hits," consisting of high cytoplasmic Ca^{2+} , elevated DAcyt and α -synuclein expression are required to evoke selective death of neurons from SN and show that interference with any of these three factors rescues the cells. Preliminary *in vivo* data show the loss of DA content and the reduction of TH and DAT densities in the striatum of α -synuclein overexpressing mice chronically

treated with L-DOPA for 2.5 month. This study is important for understanding the pathways that lead to differential susceptibility of neuronal populations to stress and for the development of treatments that might prevent the death of SN neurons in PD.

P25. Power Spectral Analyses of Sleep EEG in Abstinent MDMA Users Suggest Non-Restorative Sleep

Una D. McCann, Francis P. Sgambati, George A. Ricaurte*

3,4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug and a potent brain serotonin (5-HT) neurotoxin in animals, including non-human primates. Neuroimaging studies indicate that humans who use MDMA recreationally also develop serotonergic neurotoxicity. Although it has been challenging to identify functional consequences of MDMA-induced neurotoxicity, abstinent MDMA users have been found to have subtle cognitive changes as well as altered sleep architecture. We recently reported that cognitive deficits in MDMA users are mediated, in part, by sleep disturbance. The purpose of the present study was to employ power spectral analyses to better characterize the nature and timing of sleep differences in 41 abstinent MDMA users and 41 controls. After an adaptation sleep night, subjects in both groups underwent all-night sleep studies in a controlled inpatient research unit. Polysomnograms were scored using standard visual methods and by power spectral analysis. MDMA users had altered sleep architecture, with significantly less stage 2 and more stage 3/4 sleep. Power spectral analyses revealed highly significant differences between groups in all spectral bands in both NREM and REM sleep. The pattern of changes in MDMA users, including increased delta power during NREM sleep and increased theta power during REM sleep, suggests that sleep in MDMA users is not sufficiently restorative, and that MDMA use leads to lasting changes in sleep regulatory processes. Whether or not these changes are secondary to MDMA-induced 5-HT neurotoxicity remains to be determined, as does the relationships between and among neurotoxicity, sleep disturbance and cognitive dysfunction in abstinent human MDMA users.

P26. Determination of the Amnestic Concentration of Midazolam and Its Metabolites in Brain Tissue: Implications for In Vitro Studies

Robert Pearce

Introduction: Midazolam produces anxiolysis, hypnosis, and amnesia. To establish conditions appropriate for studies of midazolam's effects *in vitro* at

concentrations that correspond to behaviorally defined end points, we determined the brain and free aqueous concentrations of midazolam and its chief metabolite 1-OH-midazolam, and their diffusion and concentration profiles in brain slices. **Methods:** We measured memory impairment in mice using contextual fear conditioning, brain tissue concentrations and diffusion and partition coefficients using HPLC analysis, and physiological modulation of GABAA receptors using recombinant receptors expressed in HEK293 cells. **Results:** Midazolam impaired contextual fear conditioning with an ED₅₀ dose of approximately 1.25 mg/kg. This dose produced brain concentrations at the time of conditioning of 76±12 ng/g midazolam and 89±22 ng/g 1-OH-midazolam. Taking into account their brain:ACSF partition coefficients (35.7±1.7 and 15.9±0.9), this corresponds to an EC₅₀,amnesia aqueous concentration of 6.8 nM midazolam plus 16.4 nM 1-hydroxymidazolam. In physiological studies, both compounds enhanced currents approximately three-fold at saturating concentrations. However, the potency of 1-OHmidazolam was approximately 6-8 times that of midazolam, both for α1β2γ2L receptors (EC₅₀=29±2.3 nM vs. 176±30 nM) and α5β3γ2L receptors (EC₅₀ = 32±9.4 nM vs. 238±101 nM). **Conclusions:** Amnesia from an ED₅₀,amnesia dose of midazolam derives primarily from its highly potent active metabolite 1-OH-midazolam. This information provides an estimate of the free aqueous concentrations of midazolam plus 1-OH-midazolam that correspond to EC₅₀,amnesia, as well as the degree of GABAA receptor modulation that impairs hippocampus-dependent memory formation.

P27. Predictors of Buprenorphine-Naloxone Dosing in Opioid-Addicted Youth

George Woody, Amit Chakrabarti, Margaret L. Griffin, Geetha Subramaniam, Ramya Desai*

This study explores predictors of buprenorphine-naloxone dosing in a secondary analysis of data collected during a NIDA Clinical Trials Network study of opioid-dependent youth. Of 74 patients randomized to a 12-week dosing condition in that study 42 (56.7%) reported their main problem as heroin dependence; 27 (36.5%) identified prescription opioids (PO) as the problem, and 5 (6.7%) attributed their addiction to both. Of the 69 that identified heroin or PO as their main problem, most (75.4%) had either “some” (n=40, 58 %) or “extreme” (n=12, 17.4%) physical pain on enrollment. Maximum daily dose of buprenorphine-naloxone in the heroin and PO groups was similar; 14.7 and 16.1 mg, respectively. However, maximum dose received by patients reporting “extreme” pain at the baseline assessment (19.7 mg) was significantly higher in than patients with “some” pain (15.0 mg) and without pain (12.8 mg) (F(2,65)=8.10, p=0.001). When outcome was examined across the 12-week dosing period, there were no significant differences in opioid positive urine

tests in subjects with “some” or “extreme” as compared to those without pain. These data suggest that the presence of pain predicts buprenorphine-naloxone dose levels in opioid-addicted youth, that patients with pain have comparable treatment outcome to those without pain but require higher buprenorphine-naloxone doses, and that buprenorphine may have a role in managing chronic pain in opioid addicted youth.

P28. Effect of Repeated Nicotine and Cocaine on Changes in Synaptoneurosomal Neurofilaments and Receptors

Henry Sershen, Krisztina Kovacs, Abel Lajtha*

A major focus of research has been the study of neuroplasticity changes that occur from cellular adaptations that underlie process of drug addiction. For example, repeated drug administration is thought to produce a number of long-term neurobiological adaptations that produce persistent changes in neurotransmission as a result of significant redistributions of receptors and scaffolding proteins into synaptosomal membranes. Since results have suggested divergent changes in brain neurofilaments (NFs) after exposure to stimulant drugs in humans and in animal models, the present study further examined the changes in NFs after repeated nicotine and cocaine in brain total tissue homogenates and in a synaptoneurosomal (pre- and post-synaptic terminal) preparation, to see whether brain regional and terminal region specific changes to NF expression occurs and whether the changes contribute to persistent changes in synaptic structure, trafficking, and signaling. We looked at the dopamine D1, NMDA R1, and alpha7-nAChR since they have been shown to interact with NF subunits, and are affected by repeated drug administrations. The results suggest that there are differences depending on brain region and tissue preparation, yet that NFs may indeed be common targets for nicotine and cocaine. Differences from published data may reflect differences in species, age, drug dosing, antibodies, and tissue preparation. Since total tissue preparations include neuronal axons and synaptoneurosomes mostly pre- and post-synaptic sites, the observed changes in the two tissue preparations indicate different functional response to drug treatment, for example in axonal processes and terminal cytoskeletal links to receptors.

P29. Characterization of PREPL, a Brain-Enriched Serine Oligopeptidase Deleted in Patients with Hypotonia-Cystinuria Syndrome

John Creemers, Luc Regal, Kurt Boonen, Kevin Martens*

Proteolytic cleavage is an essential step most biological processes in the human body, including neuropeptide and peptide hormone metabolism, signal

transduction and intracellular transport. PREP is a proline-specific oligopeptidase selective for peptides (<30 amino acids) and is highly enriched in brain. Several lines of evidence suggest an important role of PREP in neuronal plasticity and that aberrant PREP activity is involved in the progression of neurodegenerative disorders. Recently we have discovered a novel but related enzyme, PREPL. It is deleted in patients with Hypotonia-Cystinuria Syndrome (HCS), an autosomal recessive disorder. HCS is characterized by cystinuria type I, generalized hypotonia at birth and failure to thrive, growth hormone hyposecretion and minor facial dysmorphic features. PREPL is highly expressed in brain and to a lesser extent in kidney, heart and skeletal muscle. Although it reacts with an activity-based probe derived from the serine protease inhibitor diisopropylfluorophosphate, no peptide-based substrates have yet been found. PREPL is mostly localized in the cytoplasm of the cell, although a small portion is secreted. This work is funded by the European Community's Seventh Framework Program under Grant Agreement No. 22307

P30. Network Structure and the Collapse of Consciousness during Anesthesia

*Anthony G. Hudetz**

Consciousness has been an elusive target of scientific inquiry. General anesthesia is a unique tool to reversibly manipulate the state of consciousness. Anesthetics are thought to suppress consciousness by reduce the brain's capacity to integrate information. Cortical network structure is a significant determinant of how anesthetic agents disrupt information integration in the brain. Neuronal architecture of the brain resembles a small-world pattern characterized by segregated clusters with high internal connectivity and sparse long-range connectivity. Due to the sparseness of long-range connections, this topology is relatively vulnerable to transmission failure when individual information channels are compromised. We hypothesize that as anesthetics suppress synaptic transmission in more and more circuits, more and more networks become isolated until, at some critical level, connectivity across the whole system is disrupted and unconsciousness ensues. An abrupt transition from consciousness to unconsciousness as seen clinically may be a direct consequence of global communication failure. Long-range fiber connections between the medial prefrontal and medial parietal (posterior cingulate and precuneus) cortex appear to be the principal sites of disconnection underlying diminished integrative capacity. The parietal region is a principal network hub and together with the medial prefrontal cortex, forms a major backbone of cortico-cortical connectivity. Computer simulations suggest that a suppression of communication along long-range fibers can lead to an abrupt collapse of cortico-cortical connectivity. Thus, unconsciousness during general anesthesia is viewed as a global disconnection syndrome of the brain as determined by its network structure.

P31. Identifying Molecular Neuroadaptations in Cocaine-Activated Rat Striatal Neuronal Ensembles Using Fluorescence Activated Cell Sorting (FACS)

Danielle Guez-Barber, Brandon K. Harvey, Christopher Cheadle, Marina R. Picciotto, Bruce T. Hope*

Context-specific sensitization is due to a learned association between drug and stimuli in the administration environment. We have shown that this learned association is encoded by a pattern of sparsely distributed neurons called a neuronal ensemble. Until now, scientists have studied molecular neuroadaptations in brain homogenates without differentiating between activated neuronal ensembles and surrounding non-activated neurons. This likely obscures the changes seen only in the activated cells. Therefore, we developed a novel method for purifying activated neurons from rat striatal neuronal ensembles and assessing their unique set of cocaine-induced molecular neuroadaptations. We used *c-fos-lacZ* transgenic rats to identify cocaine-activated neuronal ensembles in striatum. Electrophysiological activation of these neurons induces β -galactosidase protein that can be labeled with a fluorescent antibody against β -galactosidase. We then separated these fluorescently labeled activated neurons from the majority of non-activated neurons using Fluorescence Activated Cell Sorting (FACS). Microarray analysis of mRNA obtained from β -galactosidase-positive and -negative neurons after acute cocaine showed that β -galactosidase-positive neurons had much higher expression levels of the immediate early genes *arc*, *junB*, *fos*, and *egr1*, as well as prodynorphin and dopamine 1 receptor. We are currently assessing differential mRNA expression in β -galactosidase-positive and -negative neurons in nucleus accumbens and caudate-putamen following context-specific sensitization. We use microarray and quantitative PCR to characterize changes in mRNA levels for various genes including glutamate receptor subunits, signaling molecules, and calcium channel subunits. For the first time, we can examine unique molecular neuroadaptations in selectively activated neuronal ensembles that mediate a learned association.

P32. Defining a Sensitive Period for Iron in the Development of Hippocampal CA1 Dendritic Structure and Spatial Memory Behavior

Stephanie Fretham, Erik Carlson, Jane Wobken, Anna Petryk, Michael Georgieff*

Perinatal iron deficiency (ID) results in concurrent and persistent alterations in hippocampal mediated behavior and structure. Rodent dietary models show that timing and duration of ID affect the long-term phenotypes, suggesting a sensitive period for iron. A recently developed, mouse model of hippocampal ID generated with an inducible, non-functional, dominant negative transferrin receptor (dnTfR) has made it possible to more precisely identify sensitive periods. Expression of the dnTfR using a CaMKIIa-tetracycline responsive activator impairs iron uptake in hippocampal neurons. Dietary doxycycline inhibits dnTfR expression, resulting in iron repletion. Hippocampal behavior and structure was assessed at postnatal day (P) 70 using Morris water maze (MWM) and transgenic thy-1 YFP expression in 1) Iron deficient dnTfR and iron sufficient wild-type (WT) littermates never given doxycycline 2) Iron sufficient dnTfR and WT mice treated with doxycycline at P21 and 3) Iron sufficient dnTfR and WT mice treated at P42. Iron deficient dnTfR mice demonstrated deficits compared to WT on MWM including less time in the target quadrant during probe trials (21% vs. 55%, $p < 0.001$) accompanied by disrupted dendritic structure. In contrast, iron sufficient dnTfR mice treated at P21, performed similarly to WT in time spent in target quadrant (41% vs. 43%, $p = 0.72$) as well as normalized structure. Despite iron repletion, dnTfR mice treated at P42 spent less time in target quadrant than controls (43% vs. 30%, $p < 0.001$) and also exhibited disrupted dendritic structure. These results demonstrate that iron is required between P21 and P42 for hippocampal dendritogenesis and spatial memory behavior.

P33. Glutamate Evoked Calcium Signal in Individual Spines in D1-Dopamine Receptor Containing Medium Spiny Neurons in the Nucleus Accumbens after Chronic Cocaine Treatment

*Alice Dobi, Paul F. Kramer, Veronica A. Alvarez**

Biochemical and electrophysiological investigations suggest that during withdrawal from cocaine treatment, the number of synaptic AMPA receptors in the nucleus accumbens is increased by the addition of new GluR1 homomeric AMPA receptors (Churchill et al., 1999; Conrad et al., 2008; Mameli et al., 2009). These GluR2-lacking AMPA receptors form channels with larger conductance than those containing GluR2 subunits and they are blocked by

spermine, causing rectifying I-V curve when spermine is present inside the cell (Mameli et al., 2009). Furthermore, recent studies showed that in vivo inhibition of these channels by a polyamine toxin substantially reduces cue-induced cocaine seeking after withdrawal implying that these new receptors mediate the incubation of cocaine craving after prolonged withdrawal from cocaine self-administration (Conrad et al., 2008). One other relevant characteristic of GluR2-lacking AMPA receptors is that they display a significant calcium conductance and thus they could contribute to the synaptically evoked calcium signals in spines and dendrites of medium spiny neurons (MSNs) of the accumbens. In this study, we combined electrophysiology with 2-photon imaging and glutamate uncaging to investigate the glutamate evoked electrical and calcium signals in individual spines of MSNs from saline and cocaine treated animals. The study investigates changes AMPA and NMDA receptor number and composition at the single spine level following early (1-2 days) and extended (45 days) withdraw from repeated cocaine treatment (15mg/kg/day, 10 day i.p.) and also asks how these changes contribute to the calcium signal in the individual spines of MSNs. Section on Neuronal Structure (SNS), Laboratory for Integrative Neuroscience, NIAAA, NIH, Bethesda, MD, USA

P34. Genetic Variation in GRIK4 is Associated with Serotonin Transporter Binding Potential in the Cingulate Cortex

Gonzalo Laje, Dara M. Cannon, Wayne C. Drevets, Francis J. McMahon*

Previous studies noted an association between GRIK4 variation and citalopram response. Because chronic SSRI administration selectively inhibits the serotonin transporter (5-HTT), it is conceivable that genetic variation within GRIK4 also influences pre-treatment 5-HTT function or serotonergic transmission. We used 70 markers to cover common GRIK4 variation. 5-HTT binding potential (BPND) was assessed in healthy controls (n=22) and in unmedicated bipolar (n=16) or major depressive disorder (n=17) patients undergoing a major depressive episode. Fifty-five DNA samples from subjects who underwent PET scanning with [¹¹C]DASB were tested for genetic association with covariates to control for, ethnicity, age, and diagnosis in eight regions of interest. Six SNPs were declared of interest. Markers rs879602 (p=0.001, FDR:0.07) and rs1954787 (p=0.004, FDR:0.15) were associated with 5-HTT BPND in the subgenual anterior cingulate cortex. Associations were also noted for rs474867 (p=0.006, FDR:0.1), rs591252 (p=0.003, FDR:0.1), and rs602104 (p=0.003, FDR:0.12) in the pregenual anterior cingulate cortex, and for rs2850806 (p=0.0005, FDR:0.03) in the posterior cingulate cortex. We conclude that genetic variation in GRIK4 may affect antidepressant treatment response by modulating 5-HTT binding in the cingulate cortex.

P35. Replication of Association of the NTRK2 Gene with Lithium Response in Bipolar Disorder in a Prospective Sample

Susan Leckband, Anna Demodena, Rebecca McKinney, Tatyana Shekhtman, John Kelsoe*

Lithium is the oldest mood stabilizer medication and the gold standard for treatment of bipolar disorder. Lithium responders comprise a clinically distinct subset of bipolar disorder patients many of whom have an excellent response to the drug. The identification of genes that predict response would be invaluable in guiding clinicians in treatment selection. 144 lithium responders and 102 non-responders were identified by retrospective review of research interviews and medical records. A SNP (rs1387923) 3' of the gene for the trkb neurotrophin receptor (NTRK2) was associated to response ($p=0.005$). This association was observed only in patients who had predominantly euphoric rather than dysphoric mania. Though retrospective assessment of response is easier, a prospective trial is more definitive. We now report initial results from a prospective trial of lithium response. 77 subjects were entered into a clinical trial the goal of which was to stabilize the patients on lithium monotherapy over 3 months and then follow them for 2 years. In this initial analysis, total time in the study was examined using Cox proportional hazard survival analysis. After incorporating several clinical co-variables, the same SNP in NTRK2 also showed association in the prospective sample ($X^2=14.1, p=0.028$). The same allele was associated with response as in the retrospective sample. These data provide further support for the role of NTRK2 in lithium response.

P36. Linking Food and Mood: Insulin Regulation of the Norepinephrine Transporter (NET) via Akt

Sabrina Robertson, Heinrich Matthies, Anthony Owens, Vidiya Sathanathan, Aurelio Galli*

Noradrenergic signaling in the central nervous system plays an essential role in circuits involving attention, mood, appetite, memory, anxiety, and stress as well as providing pivotal support for autonomic function in the peripheral nervous system. The high affinity norepinephrine (NE) transporter (NET) is the primary mechanism by which noradrenergic synaptic transmission is terminated. Data indicates that NET function is regulated by insulin, a hormone critical for the regulation of metabolism. Given the high co-morbidity of metabolic disorders such as diabetes and obesity with mental disorders such as depression and schizophrenia we sought to determine how insulin signaling regulates NET function and thus noradrenergic homeostasis. Here, we show that acute

in vitro, insulin treatment significantly decreases NET surface expression and function in mouse hippocampal slices, superior cervical ganglion neuron (SCGN) boutons (sites of synaptic NE release), and in heterologous cells. In vivo manipulation of insulin/Akt signaling, with streptozotocin (STZ), a drug that induces a hypoinsulinemic Type 1-like diabetic state in mice, also results in aberrant NET function and NE homeostasis. Moreover, we demonstrate that Akt, a component of the insulin signaling pathway is required for this insulin-induced regulation of NET, and importantly, Akt inhibition or stimulation, independent of insulin, is capable of determining NET surface availability. These data suggest that aberrant states of Akt signaling such as in diabetes and obesity have the potential to alter NET function and noradrenergic tone in the brain. Furthermore, these data provide one potential molecular mechanism by which Akt, one of the attractive candidate genes for mood disorders such as schizophrenia and depression, can impact brain monoamine homeostasis.

P37. Lithium Treatment Selectively Restores Dopamine Cell Size, Excitability and Mood-Related Behavior in the Clock Mouse

Laurent F. Coque, Jun-Li Cao, Shibani Mukherjee, Don C. Cooper, Colleen A. McClung*

Manic and depressive episodes of bipolar disorder patients can be prevented by lithium treatment. However the mechanisms of actions of lithium are not well understood. Our previous studies have found that mice with a mutation in the Clock gene behave very similarly to manic patients. Furthermore, lithium treatment of the Clock mouse results in behavior normalization. In vivo recordings from the Clock mutant mice showed that they have an increase in dopaminergic cell firing and bursting in the ventral tegmental area which correlates with their manic-like behavior. We find a similar increase in dopaminergic firing in a slice preparation suggesting that influence from distal regions such as the suprachiasmatic nucleus are not the cause of this increased firing. Interestingly, chronic lithium treatment restores the firing rates to near wild type levels in the Clock mutants without significantly influencing the firing rate in wild type mice. Moreover, dopamine cells stained with tyrosine hydroxylase have a smaller soma volume in Clock mutants than in wildtype littermates. The soma volume of the Clock mutant is also brought back to wildtype levels when the mice are treated with chronic lithium and this change again is specific to the Clock mutants and the cells are unaffected in wild type mice. Since smaller soma size is correlated with increased firing rates, this change in cell size may underlie the increased excitability. In turn, the increase in size by lithium and decrease in firing rate could be important for its therapeutic action in manic patients.

P38. Neural Activity in Central Nucleus Drives Increased CS and US Processing in Response to Decrements, but Not Increments, in Reward Value

Donna J. Calu, Matthew R. Roesch, Richard Haney, Domenic Cerri, Geoffrey Schoenbaum*

Variations in processing of conditioned and unconditioned stimuli are theorized to influence associative learning. Evidence for such processes comes from unblocking tasks, in which excitatory learning is induced by changing the value of an expected reward. Such learning in response to downshifts in reward value cannot be explained by classical reinforcement learning theories and instead requires attention mechanisms such as those proposed by Pearce and Hall. The central nucleus of the amygdala (CN) is critical for learning in these situations; however, lesion studies cannot determine whether CN signals variations in processing of the CS directly or whether it might act by encoding changes in processing of the US, nor do these studies address whether CN is only involved in responding to decrements in reward or whether it may play a more general role. To address these questions, we recorded from CN in rats performing a choice task in which we manipulated the value of an expected reward. Consistent with lesion studies, activity in CN neurons increased in anticipation of cues immediately after shifts in reward value. This signaling was correlated with increased activity in a separate population of neurons that increased firing at the time of the reward shift on the preceding trial. Increased activity was evident in response to downshifts but not upshifts in reward value. These data suggest that CN is selectively involved in incrementing attention in response to unexpected decreases in reward value, and that this reflects increased processing of both the CS and the US.

P39. New Insights to Trafficking of the Neurokinin 3 Receptor to the Nucleus of Hypothalamic Neurons

Dane D. Jensen, Francis W. Flynn*

The Neurokinin 3 receptor (NK3R) is a G-protein coupled receptor (GPCR) that is expressed on vasopressin magnocellular neurons in the paraventricular nucleus of the hypothalamus. The NK3R is activated and internalized in response to hyperosmotic challenges and the activation of NK3R results in the release of vasopressin from these magnocellular neurons. The NK3R is activated and internalized to the cytoplasm of hypothalamic vasopressin neurons in response to hyperosmolarity. Subsequently, the NK3R is transported to the nucleus of hypothalamic neurons and this transport may involve the binding

of importins to a nuclear localization sequence. Co-immunoprecipitation experiments showed that the NK3R associates with the nuclear import receptor, importin β -1 following hyperosmotic challenge. This association with importin β -1 is an important step the movement of the NK3R from the cytoplasm into the nucleus. Western blot and transmission electron microscopy (TEM) analysis of isolated nuclei demonstrated that the NK3R was present only in the nuclei of challenged rats and not control rats. TEM also demonstrated that the NK3R is present in the nucleoplasm and not on the nuclear membrane. These data suggest that the NK3R has two important roles in neuronal signaling in response to a hyperosmotic challenge; the first is to facilitate the release of vasopressin, and the second is an unknown nuclear role. The NK3R is part of a small but growing family of GPCR that are transported to the nucleus where they can alter cell signaling or gene expression via direct or indirect mechanisms.

P40. Locus Coeruleus Stimulation and Norepinephrine Application Produce Opposite Effects on Accumbens-Projecting Neurons in the Ventral Subiculum

Witold Lipski, Anthony Grace*

The ventral subiculum (vSub) and the noradrenergic neurons of the locus coeruleus (LC) are known to be primary components within the stress response circuit of the brain. The vSub, which receives a dense projection from the LC, also plays an important role in modulating midbrain dopamine neuron population activity in the VTA via its output to the nucleus accumbens (NAc). Thus, it has been suggested that stress-induced changes in vSub activity may provide a functional link between stress and dopaminergic pathophysiology of schizophrenia and drug abuse. Nonetheless, the effects of noxious stimuli and LC activation on vSub neuron electrophysiological activity have not been studied. We examined the response of vSub neurons to these stimuli using in vivo extracellular recordings of single neurons in the vSub of urethane anesthetized rats. In order to examine the response of single vSub neurons to norepinephrine (NE), we also applied the transmitter using microiontophoresis during extracellular recording. We found that single vSub neurons are either activated (50%) or inhibited (15%) by both LC stimulation and footshock, a noxious stimulus known to activate the LC, in anesthetized rats. Importantly, we found that responses to footshock and LC stimulation are correlated at the level of single neurons. This finding suggests that stress signaling in the vSub may be mediated in part through these noradrenergic inputs. Systemic application of the beta noradrenergic receptor antagonist propranolol partially blocked the response to LC stimulation. In contrast, we found that norepinephrine dose-dependently inhibited the firing of all accumbens-projecting vSub neurons tested (10–40 nA, 20%–83% inhibition; N = 10). Preliminary results suggest that this effect is

independent of alpha-2 adrenoreceptors. The fact that iontophoretic application of norepinephrine in the vSub does not reproduce the excitatory effect of LC stimulation suggests that LC stimulation may act on other afferent elements to the vSub. These experiments demonstrate that the NE signal of LC projections to vSub is likely to be critical in mediating the response to stress, and provides a potential mechanism for the interaction between stress and dopaminergic system dysregulation as occurs in schizophrenia and drug abuse.

P41. A Reduction of miR-17 Family Expression in Cultured Neuroblasts as a Hallmark of Their Transition through Differentiation

Natalie Beveridge, Paul Tooney, Adam Carroll, Nham Tran, Murray Cairns*

Gene and microRNA expression was examined during retinoic acid induced differentiation of neuroblasts in vitro using micro array analysis. While this revealed a number of changes, the miR-17 family was conspicuous among the down-regulated miRNA. The implications of this are considerable, as target gene prediction suggests the miR-17 family is involved in the regulation of the mitogen-activated protein kinase (MAPK) signaling pathway, long term potentiation and axon guidance. Significantly, many of the target responses predicted by differentially expressed miRNA were supported by the observed changes in gene expression. As expected, markers of neuronal differentiation such as anti-apoptotic protein B-cell lymphoma 2 (BCL2), myocyte enhancer factor-2D (MEF2D) and zipper protein kinase (MAP3K12) were each up-regulated in response to differentiation. The expression of these genes was also reduced in response to miR-17 and miR-20a transfection, and more specifically they were each shown to contain functional miRNA recognition elements for members of the miR-17 family by reporter gene assay. This study suggests that the miR-17 family has a role in maintaining an undifferentiated state in neuronal progenitor cells and is attenuated during differentiation to allow the activation of pathways involved in neural development.

P42. An Inducible, Reversible Strategy to Regulate Klf-9 Expression in the Developing Dentate Gyrus and during Adult Hippocampal Neurogenesis

Kimberly Scobie, Amar Sahay, Rene Hen*

The dentate gyrus (DG) is modified throughout life by integration of new adult-born neurons. Similarities in neuronal maturation during DG development and adult hippocampal neurogenesis suggest that intrinsic regulatory mechanisms controlling these temporally distinct processes are conserved and reused. We

have recently identified a novel transcriptional regulator of dentate granule neuron maturation, Krüppel-like factor 9 (Klf-9). During development, dentate granule neurons lacking Klf-9 show delayed maturation. Adult Klf-9-null mice exhibit normal stem cell proliferation and cell fate specification in the DG but show impaired differentiation of adult-born neurons, decreased neurogenesis-dependent synaptic plasticity and decreased survival. Behavioral analysis of Klf-9-null mice revealed impairments in the dentate-gyrus dependent task of contextual fear discrimination learning. Klf-9-dependent neuronal maturation may therefore represent a regulatory mechanism underlying the temporally distinct processes during dentate gyrus development and adult hippocampal neurogenesis. To address this possibility, we have made a mouse line called Floxed-Stop-tetO-Klf-9 that allows us to reversibly over-express, suppress, or rescue expression of Klf-9 in specific regions of the mouse brain during dentate gyrus development or during adult hippocampal neurogenesis. This strategy allows us to determine the temporal and spatial requirement of Klf-9 in DG granule cell maturation and dentate gyrus dependent tasks such as discrimination learning.

P43. Adult Mouse Subventricular Zone Stem and Progenitor Cells are Sessile and Epidermal Growth Factor Receptor Negatively Regulates Neuroblast Migration

Yongsoo Kim, Isabelle Comte, Philip E. Hockberger, Francis G. Szele*

The adult subventricular zone (SVZ) contains stem and progenitor cells that generate neuroblasts throughout life. Although it is well accepted that SVZ neuroblasts are migratory, recent evidence suggests their progenitor cells may also exhibit motility. Since stem and progenitor cells are proliferative and multipotential, if they were also able to move it would have important implications for SVZ neurogenesis and its potential for repair. We studied whether SVZ stem and/or progenitor cells are motile in transgenic GFP+ slices with two photon time lapse microscopy and *post hoc* immunohistochemistry. We found that stem and progenitor cells; mGFAP-GFP+ cells, bright nestin-GFP+ cells and Mash1+ cells were stationary in the SVZ and rostral migratory stream (RMS). In our search for motile progenitor cells, we uncovered a population of motile β III-tubulin+ neuroblasts that expressed low levels of EGFr. This was intriguing since EGFr drives proliferation in the SVZ and affects migration in other systems. Thus we examined the potential role of EGFr in modulating SVZ migration. Interestingly, EGFr^{low} neuroblasts moved slower and in more tortuous patterns than EGFr⁻ neuroblasts. We next questioned whether EGFr stimulation affects SVZ cell migration by imaging Gad65-GFP+ neuroblasts in the presence of transforming growth factor alpha (TGF- α), an EGFr-selective agonist. Indeed, acute exposure to TGF- α decreased the percentage

of motile cells by approximately 40%. In summary, the present study directly shows that SVZ stem and progenitor cells are static, that EGFr is retained on some neuroblasts, and that EGFr stimulation negatively regulates migration.

P44. Alterations in Dopamine Neurotransmitter Dynamics in Brain-Derived Neurotrophic Factor Deficient Mice

T. A. Mathews, K. E. Bosse, F. Maina, M. M. France, J. J. P. Roberts*

In addition to acting as a nerve growth factor, brain-derived neurotrophic factor (BDNF) has been proposed to modulate synaptic neurotransmission. For example, acute administration of exogenous BDNF in adult rodents was shown to influence striatal dopamine release and modulate dopamine-related behaviors including locomotor stimulation. In the present study, we evaluated if low endogenous levels of BDNF alter dopamine system function using in vivo microdialysis and in vitro fast scan cyclic voltammetry in the dorsal striatum of heterozygote BDNF mice (BDNF+/-). Using zero net flux, apparent extracellular dopamine levels were found to be elevated in the BDNF+/- mice compared to wildtype controls (12 vs. 5 nM). In vitro voltammetry revealed extracellular dopamine levels were increased due to a decrease in dopamine reuptake rates in the BDNF+/- mice. Additionally, electrically-evoked dopamine release appeared to be decreased in BDNF+/- mice using this technique. Preliminary studies evaluating the phasic-to-tonic-evoked dopamine release suggests a greater ratio in the dorsal striatum of BDNF+/- compared to wildtype mice. Finally, dopamine efflux was evaluated in BDNF+/- mice after an acute administration of ethanol. Preliminary ethanol studies show that BDNF+/- mice have an attenuated dopamine response to a systemic injection of ethanol (2 g/kg). By utilizing both microdialysis and voltammetry, this study demonstrated that BDNF-deficient mice have a hyperdopaminergic striatal system. Future work will use these complimentary techniques to further identify the parameters that differentially regulate dopamine neurotransmission in wildtype compared to BDNF+/- mice.

P45. Regulation of CB1 Cannabinoid Receptor Expression in the Cortex during Postnatal Development

Heinz Steiner, Joel Beverley, Kuei Y. Tseng*

Evidence indicates that schizophrenia is a developmental brain disorder. It is therefore of interest to determine the developmental trajectory of neural systems that may confer predisposition for this neuropsychiatric condition. Among these, the endocannabinoid system is implicated, as recent epidemiological findings show a strong association between cannabis use during

adolescence and increased risk of schizophrenia. We investigated the expression of the CB1 cannabinoid receptor in the cortex in juvenile [postnatal day (P) 25], adolescent (P40) and adult (P70) rats, by in situ hybridization histochemistry. CB1 receptor expression was mapped in a total of 22 cortical areas on 4 rostrocaudal levels. Overall, the expression of CB1 receptors displayed a medial-lateral gradient, with maximal levels in the medial prefrontal cortex and lowest levels in somatosensory areas. Across development, CB1 receptor expression were highest in juveniles and then decreased towards adult levels. Interestingly, these changes followed a differential trajectory for limbic/associative vs. sensorimotor cortical areas. Thus, in limbic/associative areas, there was a progressive decrease from P25 to P40 to P70, independent of the rostrocaudal level. In contrast, in sensorimotor areas, especially on more caudal levels, a significant reduction in CB1 expression only occurred between P40 and P70. Together, these results indicate that CB1-mediated signaling is developmentally regulated. Moreover, our results suggest that cannabis use during adolescence may differentially alter the maturation of limbic/associative and sensorimotor cortical circuits, which may contribute to an increased risk for neuropsychiatric disorders such as schizophrenia.

P46. Neonatal Habenula Lesion as a Novel Animal Model of ADHD

Young-A Lee, Yukiori Goto*

The habenula is one of brain areas regulating the dopamine (DA) system, and therefore its deficit may underlie psychiatric disorders with DA malfunctions. We found that neonatal habenula lesion (NHL) in rats induced behavioral and brain alterations that are consistent with those observed in individuals with attention deficit/hyperactivity disorder (ADHD). NHL induced hyperlocomotion and impulsive behavior in juvenile rats, which however diminished when they reached to adulthood. A low dose of amphetamine improved these behaviors in juvenile, whereas adult rats with NHL exhibited augmented responses to amphetamine. These behavioral changes appear to be associated with decreased expression of DA D3 receptors in the prefrontal cortex and volume reduction of this brain structure, which were present in juvenile, but not adult, rats with NHL. Moreover, temporal inactivation of the habenula with tetrodotoxin, instead of NHL, was sufficient to induce hyperlocomotion, suggesting that habenula deficit by itself is not required for such behavioral and brain alterations, but transient interruption of habenula activity during early development triggers altered neurodevelopmental trajectory that is prominent during

childhood, but disappears at adulthood. Impairment on sustained attention was also observed in rats with NHL; however, this deficit was present not only in juvenile but also adult animals, suggesting that attention deficit is caused by a different mechanism from that inducing hyperlocomotion and impulsive behavior. These results suggest that habenula deficit in neurodevelopment, although its association to the pathophysiology of ADHD has not yet been unveiled to date, may be involved in this psychiatric disorder.

P47. Post-Depolarization Potentiation of GABA-A Receptors: A Novel Mechanism Regulating Tonic Inhibition in Hippocampal Neurons

Christopher Ransom, Yuanming Wu, George Richerson*

Ambient GABA in the brain activates GABAA receptors to produce tonic inhibition. Membrane potential influences both GABA transport and GABAA receptors and could regulate tonic inhibition. We investigated the voltage-dependence of tonic inhibition in cultured hippocampal neurons using patch clamp techniques. Tonic GABAA conductance increased with depolarization. The capacitance-specific tonic conductance was 15 and 30 pS/pF at -80 mV and -40 mV, respectively. Inhibition of vesicular or nonvesicular GABA release did not prevent voltage-dependent increases of tonic conductance. Currents evoked with exogenous GABA (1 mM) were outwardly-rectifying similar to tonic currents due to endogenous GABA. These results indicate that voltage-dependent increases of tonic conductance were due to GABAA receptor properties rather than elevated ambient GABA. Following transient depolarization to $+40$ mV, tonic currents measured at -60 mV were increased by 75-123%. This novel form of modulation of tonic inhibition, termed post-depolarization potentiation (PDP), recovered slowly with a time constant of 63 s and was inhibited by GABAA receptor antagonists applied during depolarization. PDP of currents evoked with exogenous GABA was concentration-dependent. Measurements of reversal potential showed PDP was due to increased conductance and not Cl⁻ shifts. We used waveforms that replicated epileptiform activity during voltage-clamp experiments. PDP was produced by this pathophysiological depolarization. These data show that depolarization produces prolonged potentiation of tonic currents due to intrinsic voltage-dependence of GABAA receptors. These properties are well suited to limit excitability during pathophysiological depolarization accompanied by rises in ambient GABA, such as occur during seizures and ischemia.

P48. High Purity Human Cell Populations from Human Embryonic Stem Cells: Their Utility in Screening and Therapeutic Development

Monica Siegenthaler, Gabriel Nistor, Aleksandra Poole, Craig Fredrickson, Chris Airriess, Hans Keirstead*

California Stem Cell, Inc., has developed methods to derive high purity cell populations from human embryonic stem cells (hESCs). These high purity cell populations are of great value to researchers for the purposes of drug development, screening, predictive toxicology and therapeutic development. We provide these cells free of charge, in a collaborative capacity, to academic institutions that are conducting innovative research. To date, we have derived motor neuron progenitor (MNP) cells, neuronal progenitor (NP) cells, cardiomyocyte progenitor (CP) cells, and hepatocyte progenitor (HP) cells and can successfully provide these hESC-derivates in 96-well and 384-well plate formats that are suitable for high throughput screening assays for drug development and predictive toxicology. These products are of great utility to researchers as they contain cell types that do not regenerate efficiently and have to date been difficult to obtain and culture from primary sources. California Stem Cell has collaborated with and provided various academic and industry institutions these high purity cell populations. MotorPlate™, hESC-derived MNPs, has been utilized for high throughput screening of compounds to protect against glutamate toxicity and in predictive toxicology. NeuroPlate™, hESC-derived NPs, has been utilized in high throughput screening to examine neurite outgrowth. CardioPlate™, hESC-derived CPs, has been used in predictive toxicology to determine chemotherapy drug- induced cardiotoxicity. HepatoPlate, hESC-derived HPs, will be useful in predictive toxicology of all newly developed drugs. The examples presented here highlight the value of high purity cell populations derived from hESCs and their utility in screening and therapeutic development.

P49. Aberrant Activation and Localization of Mammalian Target of Rapamycin (mTOR) Pathway Targets in Hippocampus following Prolonged Limbic Seizures

Anne Anderson, Amy Brewster, Joaquin Lugo*

Previous studies have shown aberrant mTOR signaling in epilepsy. We investigated the effects of pilocarpine-induced status epilepticus (SE) on mTOR signaling in hippocampus of juvenile rats. We used western blotting (WB) and immunohistochemistry (IHC) to evaluate levels and distribution of

phosphorylated ribosomal S6, a downstream effector and marker of mTOR activation. We used antibodies against two phospho-regulatory sites within S6 (Ser 240/244 and Ser 234/236) and also WB and IHC with antibodies against S6, AKT and phosphorylated AKT (Ser 473). Phosphorylation levels of AKT were used as a marker upstream in the pathway. A subset of animals was treated with the mTOR inhibitor, rapamycin. SE induced a significant and long-lasting increase in phospho-S6 in the hippocampus, beginning at 1 hr of SE ($p < 0.01$) and lasting up to 2 weeks ($p < 0.05$). The highest phospho-S6 staining following SE was in CA3, DG and stratum radiatum of hippocampus compared to controls that had highest labeling in stratum lacunosum moleculare. Pre-treatment with rapamycin prevented the SE-induced changes in the levels and subcellular distribution of phospho-S6. Phospho- and total- AKT levels decreased in hippocampus following SE ($p < 0.05$). Our findings reveal a significant activation of the mTOR signaling immediately following SE that lasts for at least 2 weeks in selective regions of the hippocampus, corroborating and expanding previous work in this area. The AKT pathway does not appear to contribute to these changes. Future studies will be aimed at determining the role of mTOR pathway activation and upstream regulators of mTOR following SE.

P50. Effect of the Cannabinoid CBII Receptor Partial Agonist Gw405833 on Neurological Damage Caused by Hypoxia Ischemia in Rats

Jack Rivers, John Ashton*

Two G-protein coupled cannabinoid receptors have been described in mammals. Cannabinoid receptor type 1 (CBI) is ubiquitously expressed in the central nervous system (CNS), whereas cannabinoid receptor type 2 (CBII) is expressed chiefly in systemic immune cells. Cannabinoids that activate both receptors have been long known to have therapeutic effects that include suppression of inflammation and pain, and regulation of nausea, emesis and appetite. More recently, cannabinoids have been shown to be neuroprotective in various animal models. However, the use of cannabinoids as therapeutic drugs has been limited by their psychoactive side-effects, caused by activation of CBI. Following the recent discovery of CBII receptor expression in the CNS, together with evidence to suggest that activation of the CBII receptor causes few or no psychoactive effects, we have investigated whether specific CBII activation is neuroprotective. We therefore tested whether a CBII selective partial agonist GW405833 is neuroprotective in a rat model of hypoxia-ischemia (HI). 26 day old rats ($n = 7-8$) were administered with 3mg/kg GW405833 or vehicle (i.p) either before or immediately following HI. Neurological damage was assessed at 3 days and 15 days following treatment. Rats administered GW405833 had a

reduction in the loss of hemisphere at 15 days post HI (vehicle 8.4% \pm 0.89% loss of volume, 3 mg/kg GW405833 4.1% \pm 0.64% loss of volume, $P=0.001$). Our results demonstrate that CBII activation is neuroprotective in the chronic phase of injury following HI and that CBII is a potential target for the treatment of cerebral ischemia.

P51. Altered Neuroligin Expression Is Involved in Social Deficits in a Mouse Model of the Fragile X Syndrome

Regina Dahlhaus, Alaa El-Husseini*

The fragile X syndrome (FXS) is the most common form of inherited mental retardation. Caused by a transcriptional silencing of the fragile x mental retardation protein (FMRP), a mRNA binding protein itself, misregulated translation is thought to be the leading cause of the fragile X syndrome. Interestingly, recent results indicated several Neuroligin interacting proteins to be affected by this misregulation, including Neurexin1 and PSD95, who have also been implicated in autism spectrum disorders. Using Co-immunoprecipitation assays and RT-PCR, FMRP is shown to interact with Neuroligin1 and 2 -mRNA, while no interaction with Neuroligin3-mRNA is observed. In line with FMRPs role in translation regulation, western blot as well as immunohistochemistry analysis reveal changes in protein expression levels suggesting impaired synaptic function. As increasing evidence indicates Neuroligin expression to be critical to synapse maturation and function, consequences of impaired Neuroligin1 expression in FXS are assessed by overexpressing HA-Neuroligin1 in *FMR1* $^{-/-}$ mice, a model for FXS. Behavioural assessments demonstrate that enhanced Neuroligin1 expression improves social behaviour in *FMR1* $^{-/-}$ mice, whereas no positive effect on learning and memory was seen. These results provide for the first time evidence for an involvement of a Neuroligin-Neurexin protein network in core symptoms of FXS

P52. On the Role of Clock in Cocaine Reward-Related Behaviors: Region-Specific Influence?

Edgardo Falcon, Shibani Mukherjee, Angela Ozburn, Colleen McClung*

Drug addiction is a devastating disease that affects millions of people worldwide. Increasing evidence suggests that disruptions in circadian rhythms are associated with psychiatric disorders, like mood disorders and drug addiction. Several of the genes that form the circadian clock have been found to have a role in behavioral responses to drugs of abuse. Thus, the expression of these genes in reward-related areas like the mesolimbic dopaminergic pathway between the Nucleus Accumbens (NAc) and Ventral Tegmental Area (VTA) might mediate drug reward-related behaviors. Previous studies from our lab showed that mice

that carry a mutation in the Clock gene exhibit an increase in preference for rewarding stimuli, like cocaine, sucrose and intracranial self-stimulation; along with an array of behavioral abnormalities that are very similar to human mania. Several of these behavioral responses were reversed when a functional CLOCK protein was expressed specifically in the VTA. Therefore, we set out to explore the role of the Clock gene in reward-related behaviors via localized knock-down of the gene in the NAc and VTA using RNA interference (RNAi). Male wild-type C57/BL6 mice were injected with AAV-Clock shRNA or AAV-scrambled shRNA in the NAc or VTA. Mice were then subjected to several behavioral tests including locomotor activity, cocaine sensitization, and conditioned place preference. We find that knock-down of Clock in these regions cause different behavioral responses, which are dependent upon the region where Clock expression is reduced. These studies suggest that Clock may have a role in modulating reward-related behaviors in a region-specific manner.

P53. Long-Lasting Effects of Alcohol on Glutamatergic Transmission in the Nucleus Accumbens

Vincent Marty, Igor Spigelman*

Alcoholism is a neuropsychiatric disorder characterized by uncontrolled heavy drinking and a chronic relapsing course. The alcohol withdrawal syndrome is a particularly severe manifestation of alcohol abuse, presenting with a variety of symptoms such as anxiety, agitation and seizures. Alcohol can induce synaptic plasticity in key brain circuits, such as the mesolimbic dopamine system, including nucleus accumbens (NAcc), which plays a critical role in the drug-induced neuroadaptations underlying addiction. Little is known about the long-lasting effects of alcohol on synaptic transmission in the NAcc. The goal of this study was to characterize the long-lasting effects of alcohol on excitatory synaptic transmission on medium spiny neurons in the NAcc core using whole cell patch-clamp recordings. We used a rat model of chronic intermittent ethanol (CIE) treatment (≥ 60 doses, 5-6 g/kg) followed by 40 days of withdrawal, which encompasses all of the major characteristics of human alcoholism, including anxiety and enhanced alcohol preference after withdrawal. Recordings of spontaneous excitatory postsynaptic currents (sEPSCs) were obtained from coronal brain slices of CIE or vehicle-treated (CIV) rats during pharmacological blockade of inhibitory currents by an investigator blinded to the rat treatment. The kinetics of sEPSCs in CIE rats ($n=7$) compared to CIV ($n=4$) were: area: 35.4 ± 4.9 fC vs 55.6 ± 6 fC ($p=0.04$, t-test); frequency, CIV: 0.5 ± 0.3 Hz vs CIE: 1.75 ± 0.6 Hz ($p=0.2$); amplitude, CIV: 5.3 ± 0.8 pA vs CIE: 9.3 ± 1.7 pA ($p=0.1$). These preliminary data suggest that CIE treatment induces long-lasting increases in excitatory transmission in the NAcc. Supported by NIH grant AA016100.

P54. Absence of NMDA Receptors in Dopamine Neurons Attenuates Dopamine Release but Not Pavlovian Conditioned Approach

Jones Parker, Larry Zweifel, Jeremy Clark, Paul Phillips, Richard Palmiter*

During reinforcement learning, the development of phasic dopamine transmission to reward-predicting stimuli is believed to contribute to learning. Accumulating evidence suggests that these phasic events require signaling by N-methyl-D-aspartate-type glutamate receptors (NMDARs). Furthermore, NMDAR signaling in the ventral tegmental area is thought to be critical for learning. To investigate the specific contribution of NMDARs in dopamine neurons to phasic dopamine release during learning, we adapted a method to monitor dopamine release across multiple days by fast-scan cyclic voltammetry (FSCV) in control mice and mice lacking NMDAR signaling exclusively in DA neurons (KO mice). Despite having significantly attenuated phasic dopamine release in the nucleus accumbens following reward delivery, KO mice developed phasic dopamine release to the predictive stimulus and acquired a simple appetitive Pavlovian association at the same rate as their littermate controls. Contrary to some previous reports in rats, we observed that phasic dopamine release to the primary reward persisted and remained larger than conditioned-stimulus-evoked release throughout training. By adapting FSCV for long-term use in mice and characterizing phasic dopamine release during a simple learning paradigm, we have established a framework for utilizing genetic tools to mechanistically dissect the cellular processes underlying learning.

P55. Sleep Dysfunction and the Effects of Extended-Release Zolpidem during Cannabis Withdrawal

Ryan Vandrey, Una McCann, Michael Smith, Alan Budney*

A significant withdrawal syndrome can occur when heavy cannabis users try to quit and there is currently a need to identify medications that can aid the treatment of cannabis use disorders. Sleep difficulty is a commonly reported withdrawal symptom, but objective assessments of sleep during withdrawal are lacking. The present study characterized the effects of cannabis withdrawal on sleep architecture during 3-day periods in which participants received extended-release zolpidem or placebo at bedtime. Baseline assessments were also conducted during 2-day periods in which they smoked cannabis ad libitum. Twenty daily cannabis users completed the within-subject crossover study. Sleep EEG recordings were collected each night. Repeated measures ANOVA's were conducted to detect differences in sleep architecture across study conditions. Compared with when participants were allowed to use cannabis, abrupt abstinence in the absence of active medication resulted in decreased sleep

efficiency, reduced time spent in Stage 1 and Stage 2 sleep, and an increase in REM sleep. Administration of extended-release zolpidem during abstinence attenuated the reduction in sleep efficiency and alterations in Stage 2 and REM sleep. These data provide objective evidence that sleep function can be disrupted in heavy cannabis users when they abruptly quit. The magnitude of sleep disturbance observed was clinically significant. This study also indicates that the sleep disruption associated with cannabis withdrawal can be attenuated by approved hypnotic medications, suggesting that such medications might be useful as adjunct pharmacotherapies in the treatment of cannabis use disorders. This research was supported by NIDA Grants DA025794 and DA12471.

P56. Novel NMDA Receptor Antagonists Identified Using a Cell-Based Screening Assay for Allosteric Modulators of NR2D-Containing NMDA Receptors

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NMDA receptors are ligand-gated ion channels that mediate a slow, Ca²⁺-permeable component of excitatory synaptic transmission in the central nervous system. They are tetrameric complexes comprised of glycine-binding NR1 subunits and glutamate-binding NR2 subunits, of which there are four different subtypes (NR2A, NR2B, NR2C and NR2D). Here, we describe the development of a fluorescence-based assay that measures NMDA receptor-mediated changes in intracellular calcium in a cell line stably expressing NR2D with NR1 under the control of a tetracycline-inducible promoter. The assay was designed to selectively identify non-competitive and un-competitive modulators by using supramaximal concentrations of glutamate and glycine. We initially screened a focused library of 520 compounds and the Lopac library of 1280 pharmacologically active compounds, including 20 known non-competitive and un-competitive NMDA receptor antagonists and 20 competitive antagonists. The screen identified all 20 non-competitive and un-competitive inhibitors, but only identified one of the competitive antagonists. This result validates the screening assay and demonstrates the ability of the assay to selectively identify modulators of NMDA receptor function. Hits from the screens were further validated using a secondary screen that used two-electrode voltage-clamp recordings on recombinant NMDA receptors expressed in *Xenopus* oocytes. This approach was successful in identifying numerous potent novel NMDA receptor antagonists, including the TRPV1 receptor antagonist capsazepine (IC₅₀ ~10 μM) and the histamine H3 receptor antagonists clobenpropit (IC₅₀ ~1 μM) and iodophenpropit (IC₅₀ ~1 μM). The unexpected activity of these ligands at NMDA receptors prompted further electrophysiological characterization of their mechanism of inhibition and their potencies at all NMDA receptor subtypes.

P57. Phasic Striatal Dopamine Release to Cues and Rewards with Escalating Costs

Matthew J. Wanat, Camelia M. Kuhnen, Paul E. M. Phillips*

Electrophysiological studies demonstrate that dopamine neuron firing can encode reward value while pharmacological manipulations highlight that dopamine in the striatum is critical for overcoming costs in goal-directed behaviors. However, it is unknown how striatal dopamine release to reward-predictive cues and reward delivery is affected by escalating costs. In other words, does working harder change one's value of rewards and associated cues? To examine this question, we utilized fast-scan cyclic voltammetry to identify phasic dopamine release in the nucleus accumbens of rats trained to lever press for food pellets under escalating costs (progressive ratio) or static costs (fixed ratio). We found no difference in dopamine release to reward-predictive cues whether the costs were static or escalating. Furthermore, there was no relationship between cue-evoked dopamine release and when a rat ceased responding in the operant task. Interestingly, dopamine release to reward delivery increased with escalating costs; however, this result was due to the temporal uncertainty of the reward delivery, and not to the amount of effort expended. Therefore, our results suggest that working harder does not alter how dopamine signals the value of rewards and associated cues.

P58. Structural Basis for Subunit-Specific Activation of NMDA Receptors

Kasper B. Hansen, Pieter Burger, Katie M. Vance, James P. Snyder, Rasmus P. Clausen, Stephen F. Traynelis*

NMDA receptors are ligand-gated ion channels assembled from two NR1 and two NR2 subunits, and are activated upon simultaneous binding of glycine and glutamate to the NR1 and NR2 subunits, respectively. We have developed a series of N-hydroxypyrazole-5-glycine (NHP5G) compounds that are partial agonists for the glutamate binding site of the NR2 subunit. We will use this structurally related series of partial agonists that weakly activate the channel to study the steps associated with channel opening and determine how these changes are specific for the NR2 subunit. One of the NHP5G agonists, propyl-substituted NHP5G, shows strong subunit selectivity in that it activates NR1/NR2D (37%), but does not appear to activate NR1/NR2A (~0%). Ethyl-NHP5G activates both NR1/NR2D (70%) and NR1/NR2A (5%). We have performed electrophysiological recordings from outside-out membrane patches from HEK293 cells that contain a single active NMDA receptor channel activated by saturating concentrations of agonist. Performing these single-channel

recordings for NR1/NR2D using partial agonists and the full agonist glutamate enable us to determine which states in the process of channel activation can be modulated in an agonist-specific manner. These data show that glutamate, ethyl-, and propyl-NHSPG have strikingly different mean open times for NR1/NR2D (0.75 ms, 0.32 ms, and 0.18 ms, respectively). We have also performed molecular dynamics (MD) simulations of the agonist binding domains of NR1/NR2A and NR1/NR2D with bound glutamate or propyl-NHP5G to predict how the agonists interact differentially with NMDA receptor subtypes. The synthesis of these single-channel recordings and MD simulations will be used to identify structural elements that can be modified using mutagenesis to test working hypotheses on the structural basis for subunit-specific activation of NMDA receptors.

P59. Corticotropin Releasing Factor (CRF) Increases Accumbal Dopamine Release in Naïve, but Not Stressor Exposed Mice

Julia Lemos, Charles Chavkin, Paul Phillips*

Stress responses are adaptive and critical to an organism's survival. However, repeated stressor exposure can lead to maladaptive responses to external stimuli. CRF is a stress neuropeptide that modulates neuronal excitability in limbic brain regions. Particularly, it has been demonstrated that CRF modulates the release of monoamines in the forebrain. While CRF modulation of noradrenergic and serotonergic circuits have been well characterized, the precise way in which CRF modulates the dopaminergic system remains unclear. Dopamine release in the nucleus accumbens (NAcc) is critical for mediating goal-directed behavior. Furthermore, CRF infusions directly into the NAcc increases lever pressing for sucrose reward. Therefore, we hypothesized that CRF increases dopamine release by acting directly at dopamine terminals within the accumbens. Using fast scan cyclic voltammetry (FSCV) in coronal slices containing the NAcc, stimulated (single pulse) dopamine release was measured in the accumbens core. CRF (10, 100 or 1000 nM) was bath applied to the slice and changes in dopamine release were observed. CRF (100, 1000 nM) significantly increased dopamine release compared to vehicle control (One way ANOVA, $p < 0.01$). This effect was not present in CRF R1 $-/-$ mice. Moreover, in mice exposed to repeated swim stress, CRF had no effect on accumbal dopamine release. This data indicates that in a normal state, acute CRF increases accumbal dopamine release at the site of the terminals in a CRF R1 dependent fashion. However, following repeated swim stress, this CRF effect is abolished suggesting one potential mechanism for stress-induced maladaptive changes in behavioral responses.

P60. Alcohol Use during Adolescence Alters Future Reinforcement Learning: Behavioral Evidence for the Aberrant Learning Theory of Addiction

Nicholas A Nasrallah, Annie Collins, Andrew Hart, Jeremy Clark, Ilene Bernstein*

Adolescent alcohol use is a major public health concern and is strongly correlated with the development of addictive disorders. An emerging view regarding drug addiction is that it arises from a pathological enhancement of learning and memory for rewards and reward-associated cues. Drugs of abuse have been shown to modify brain circuitry that mediate behaviors related to natural rewards (e.g. food and sex), and such changes are thought to be causal factors leading to addiction. This theory of “aberrant learning” is supported by anatomical, electrophysiological, and biochemical evidence for drug effects on neural mechanisms of learning. Direct behavioral evidence demonstrating reinforcement learning corrupted by prior drug experience has been less forthcoming. To test this central behavioral hypothesis of aberrant learning theory, the present study assessed the long-term influence of alcohol consumption during adolescence on instrumental learning. An alcohol jello-shot protocol was used to provide Sprague Dawley rats with unlimited access to alcohol for twenty days (PND30-50). Animals began training in a drug-free state during adulthood two months following cessation of alcohol access. A fixed-ratio instrumental task assessed the effects of prior alcohol use on reinforcement learning. Analysis of learned responses generated hyperbolic learning curves and revealed that alcohol-exposed animals had accelerated learning rates, acquiring response-reward associations faster than controls. This research supports behavioral predictions of the aberrant learning theory of addiction and provides a model for investigating the relationship between drug use and addiction.

P61. A Single Episode of Early Life Seizures Results in Long-Lasting Changes to the Expression Mechanisms of Long Term Depression

Paul Bernard, Anna Castano, Tim Benke*

Previous research in our lab has indicated that following a single episode of early life seizures (sELS), induced using kainic acid on post-natal day (PND) 7, rats display increased LTD (long term depression), as well as cognitive deficits at PND 60+. These changes occur in the absence of pronounced hippocampal injury (cell loss and synaptic reorganization) and are consistent with molecular alterations at the sub-cellular or synaptic level. We speculate that increased LTD expression (in conjunction with decreased LTP) may be responsible for the observed learning abnormalities. LTD can be mediated by two distinct

mechanisms, NMDA receptor (NR) dependent and metabotropic glutamate receptor (mGluR) dependent. The NR dependent and mGluR dependent forms are differentiated by the effectiveness of different chemical and electrical LTD inducing stimulation paradigms. In order to further explore this issue we utilized different induction paradigms in conjunction with pharmacological agents to determine whether changes in NR dependent LTD or mGluR dependent LTD (or both) are responsible for the observed changes in LTD following sELS. We further hypothesize that the expression levels of sub-synaptic machinery and scaffolds associated with LTD will reflect their role as potential mediators of the changes following sELS. These issues will be characterized using semi-quantitative western blot expression assays of crucial intracellular signaling proteins and subunits associated with LTD. Using these methods potential for therapeutic intervention may also be identified.

P62. Acquisition and Extinction of Fear Memory in a NR2C Knockout Mice

Shashank Dravid, Brandon Hillman*

Fear conditioning and fear extinction are learning processes mediated by interactions between the hippocampus, amygdala and medial prefrontal cortex. The N-methyl-D-aspartate (NMDA) receptors are tetramers composed of two NR1 and two NR2 subunits, mediate excitatory glutamatergic neurotransmission in the CNS and play an important role in fear learning and fear extinction. The identity of the NR2 subunit (NR2A-D) influences the electrophysiologic and pharmacologic properties of the receptor. The purpose of this study was to determine the role that the NR2C subunit plays in fear learning and extinction. We used a Pavlovian model of fear learning where a conditioned stimulus (tone) was paired with an aversive unconditioned stimulus (foot-shock) to obtain conditioned fear in NR2C wild-type and knock-out mice. The degree of fear was assessed by measuring the freezing behavior during exposure to the conditioned stimulus (CS). Our results indicate that the NR2C subunit may be important in acquisition of fear memory.

P63. Stress-Enhanced Fear Learning Increases Voluntary Alcohol Consumption and Preference

Edward Meyer, Virginia Long, Michael Acasio, Michael Fanselow, Igor Spigelman*

Post-traumatic stress disorder (PTSD) may develop after trauma. PTSD patients exhibit high rates of alcohol abuse. Molecular mechanisms of co-morbidity are unknown. A rodent model of stress-enhanced fear learning (SEFL) mimics several human PTSD features, including resistance to exposure therapy and amnesic treatment. We set out to determine whether SEFL rats exhibit higher levels of voluntary ethanol (EtOH) consumption than conditioned controls.

Freezing, used to assess fear learning, in SEFL rats was significantly ($p=0.018$) higher ($M=78.21$) than control rats ($M=28.28$). The 2-bottle-choice intermittent access EtOH (20%) drinking paradigm (2BC) generates escalated voluntary EtOH intake which remains high after 40 d withdrawal and reinstatement; SEFL rats ($n=6$) increased their EtOH consumption from 0.4 ± 0.1 (1st EtOH presentation) to 6.1 ± 1.1 g/kg/24h (31st EtOH presentation), conditioned controls ($n=8$) did not escalate their drinking as quickly or to the same extent as the SEFL rats (1.3 ± 0.6 to 3.9 ± 0.6 g/kg/24h). To determine if SEFL rats are simply learning the 2BC paradigm better than controls or if stress causes rats to drink more we trained rats in 2BC prior to withdrawal, SEFL conditioning and reinstatement ($n=8$). Unfortunately this group began drinking at high levels without significant escalation in EtOH consumption (4.7 ± 1.3 to 5.9 ± 0.9 g/kg/24h) during training or increases in drinking after SEFL and EtOH reinstatement. These data demonstrate that a single stress episode sufficient to produce SEFL, produces long-term increases in voluntary alcohol consumption in rats previously naïve to alcohol.

P64. Attenuation of Morphine-Induced Astrocyte Activation and Tolerance Development by Ultra-Low Dose Naltrexone

Catherine Cahill, Thersa Mattioli, Brian Milne*

Ultra-low doses of naltrexone (ULD-N) inhibit the development of spinal morphine antinociceptive tolerance. Chronic morphine administration induces spinal astrogliosis in tolerant animals. Activated astrocytes are characterized by increased production of glial fibrillary acidic protein (GFAP) and increase in cell size. Spinal cord sections from rats administered chronic morphine showed significant increase in GFAP immuno-labelling compared to saline controls ($p<0.001$). GFAP labelling was attenuated in rats co-administered ULD-N ($p<0.001$ compared to morphine alone) and did not differ from controls. 3-D images of astrocytes from animals administered chronic morphine had significantly larger volumes compared to saline controls ($p<0.001$). Co-injection of ULD-N attenuated this increase in volume ($p<0.001$), but the mean volume differed from saline treated controls ($p<0.05$). Thus, there is a positive correlation between prevention of tolerance and inhibiting activation of spinal astrocytes by treatment with ULD-N. Further research is required to determine if the ULD effect on modulation of astrocyte function is direct or indirect.

P65. Lucid Dreaming and Prefrontal Task Performance

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Brian Pittman

Study Objectives. Activity in the prefrontal cortex may distinguish the meta-awareness experienced during lucid dreams from its absence in normal dreams. The objective of this study was to test the hypothesis that the ability to have lucid dreams is related to function of the prefrontal cortex. **Design.** Prospective study of prefrontal cognitive task performance and dream lucidity. **Setting.** Ambulatory study in a public high school. **Participants.** 28 healthy high school students. **Interventions.** Participants performed computer based versions of the Wisconsin Card Sort Task and the Iowa Gambling Task. Participants were instructed in a technique for lucid dream induction and practiced the technique for one week while keeping records of their sleep quality, dreams, and lucidity. **Measurements and Results.** Participants who exhibited a greater degree of lucidity performed significantly better on a task that engages the ventromedial prefrontal cortex (the Iowa Gambling Task). Degree of lucidity achieved did not distinguish performance on a task that engages the dorsolateral prefrontal cortex (the Wisconsin Card Sort Task), nor did it associate with differences in reported sleep quality or baseline participant characteristics. **Conclusions.** The association between performance on the Iowa Gambling Task and lucidity is consistent with the higher activity of the ventromedial prefrontal cortex during rapid-eye movement sleep, and suggests a connection between lucid dreaming and other ventromedial function, like emotion regulation.

P66. Opioid Self-Administration in Inflammatory and Neuropathic Chronic Pain Conditions

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Carolyn A. Fairbanks

Opioid tolerance and self-administration has previously been shown to be modulated by the glutamatergic system. We have shown that morphine tolerance and fentanyl self-administration is modulated using a low-affinity NMDA receptor antagonist, agmatine. We have developed a specific anti-agmatine antibody that when administered centrally (i.t. or i.c.v.) may immunoneutralize the endogenous levels of agmatine present in the CNS. Using the anti-agmatine antibody we show that the anti-agmatine IgG increases susceptibility to acute opioid tolerance and decreases chronic opioid tolerance and self-administration. These seemingly paradoxical results may be explained by compensatory changes that occur the agmatinergetic system following chronic morphine exposure. Mice administered the anti-agmatine antibody ICV show a decreased induction of morphineevoked analgesic tolerance and a decreased rate of fentanyl self-administration. These results appear to be opioid specific; when given the

anti-agmatine antibody ICV under the conditions of food maintained responding, a non-opioid reinforcing paradigm, there was no change in response rates. To address the possibility of potential agmatinergetic compensatory changes, we examined the expression of arginine decarboxylase and agmatinase, the synthetic and degradative enzymes responsible for the synthesis and metabolism of agmatine following chronic delivery of anti-agmatine IgG given centrally.

P67. Analysis of Epileptic Seizures via Nonlinear Computational Tools

Matin Daneshyari

Epileptic seizures affect patient life dramatically, therefore finding a systematic method to analyze is being discussed in this study. Two sets of individuals have been adopted. One set as hospitalized epileptic patients, and another set healthy individuals. For epileptic patients, two sets of data are used: one set for the period of epileptic seizures, and the other one their normal brain activity. From each individual, time series of electroencephalograph (EEG) signals have been largely recorded and associated with their seizure period and/or normal brain activity. The nonlinear properties of the electroencephalograph signals are then investigated by comparing these sets of EEG with each other. Adopting measures of nonlinear and chaos theory on these time series and their associated phase space diagram, the chaotic behavior of these sets are quantitatively computed. Lyapunov exponent, correlation dimension, Hurst exponent, fractal dimension and Kolmogorov entropy are the exemplar and the most useful tools to analyze the nonlinearity behavior of time series which are widely adopted in this study. The statistical results of these analyses will be demonstrated for different sets of brain activity. Analyzing brain behavior using these tools altogether clearly demonstrates the differences between the normal healthy group of individuals, the normal brain activity, and the epileptic seizures. The statistical results along with phase space diagram noticeably verify that brain under epileptic seizures possess limited trajectory in the state space than in healthy normal state, consequently behaves less chaotically compared to normal condition.

P68. Effects of Nigella Sativa on the Neuronal Alterations of the Striatum and Parkinsonism Induced by Haloperidol

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The neuroanatomical status of Haloperidol (HP) induced Parkinsonism remains unclear, but several lines of evidence suggested that persistent neuronal alterations in the basal ganglia cause motor impairment produced by HP

provoked oxidative stress. The goal to design this study was to evaluate the possible protective effects of *Nigella sativa* (NS) oil on HP induced neuropathological alterations and related motor impairment in the rodent striatum (Str). To achieve these objectives HP treated animals treated with NS oil. The motor coordination was monitored in HP treated groups and the animals treated with NS alone and placebo. In the HP treated group with high motor impairment shown significant never cell depletion, shrunken cytoplasm, nuclear membrane breakdown and chromatin disorganization. Scaring was also prominent feature due to perfusion of astrogliosis in the dorso and ventro—lateral regions of the caudate putamen and in the core of the nucleus accumbens. Moderate levels of halo and pyknotic neurons were also observed in the HP rodents. The morphological HP induced changes observed in the neurons were almost absent in the HP plus NS group of animals. However slight astrogliosis was observed with no obvious indication of cell loss in the NS plus HP treated Str. We conclude the NS therapy has preventive effects on HP induced neuronal degeneration in the Str. We believe that the further preclinical research into the utility of NS may indicate its usefulness as a potential cure from irreversible Parkinsonism during neuroleptic treatment.

P69. Ipsilateral Orbitofrontal Lesions Alter Signaling of Reward Prediction Errors by Dopamine Neurons In Rat Ventral Tegmental Area

Yuji K. Takahashi, Matthew R. Roesch, Jason C. Trageser, Geoffrey Schoenbaum*

The orbitofrontal cortex (OFC) is implicated in signaling information about expected outcomes. This signal is used to guide behavior, but the same signal may be important for learning when outcomes change by contributing to the calculation of reward prediction errors. To test this hypothesis, we recorded activity from putative dopamine neurons in ventral tegmental are (VTA) in rats with ipsilateral sham or OFC lesions. The neurons were recorded in a simple choice task in which different odor cues indicated that a sucrose reward was available in one of two nearby fluid wells. During recording, we independently manipulated timing or size of reward in one or the other well to induce discrepancies between expected and actual rewards. In this setting, many dopamine neurons in sham rats exhibited a phasic increase in firing to reward. This activity was greater for an unexpected reward and declined with learning. After learning, these same neurons also suppressed firing if the reward was omitted and developed a phasic response to the cue. These features are consistent with signaling of positive and negative prediction errors. By contrast, dopamine neurons in OFC-lesioned rats exhibited phasic firing to the rewards; however this activity was only poorly modulated by whether or not that reward was expected. Thus

relatively few of these neurons showed significant changes in the reward-evoked firing with learning, and none suppressed firing on reward omission after learning. The development of cue-evoked firing was also relatively minimal. These changes are consistent with the proposal that OFC contributes to learning when outcomes change by supporting error signaling in downstream brain areas such as VTA.

P70. Sequential Ion Pair Formation during Activation of a Sodium Channel Voltage Sensor

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S4 transmembrane segments of voltage-gated ion channels move outward upon depolarization initiating a conformational change that opens the pore. Formation of ion pairs between gating charge-carrying arginine residues in S4 and negatively charged amino acid residues in neighboring transmembrane segments is an essential feature of the *sliding helix* model of gating (Catterall, 1986; Guy and Seetharamulu, 1986; Yarov-Yarovoy et al., PNAS, 2006). We used the disulfide locking method to analyze intramolecular protein-protein interactions in mutants of the bacterial sodium channel NaChBac in which E70 in the S2 segment and the fourth gating charge of S4 (R4) were replaced with cysteines. As previously reported for R3:D60 (DeCaen et al. PNAS, 2008), activation of the E70C:R4C channel reduced I_{Na} irreversibly but had no effect on WT or single mutants. Application of the reducing agent β -mercaptoethanol restored I_{Na} , suggesting reversal of disulfide bond formation between E70 and R4. The voltage dependence of disulfide locking matched the voltage dependence of activation ($V_{1/2} \approx -75$ mV). Fast deactivation was blocked, and the loss of current upon repolarization was slowed to the rate of inactivation (≈ 330 ms). Evidently, depolarization drives outward movement of the S4 segment that allows disulfide locking of R4C and E70C, and this activated state of the voltage sensor signals opening of the pore and then inactivation of the channel. These data suggest that gating charge R4 forms an ion pair with E70 during activation and that the side chains of these residues approach within ~ 2 Å, as required for rapid formation of disulfide bonds in the E70C:R4C mutant. Comparison of the rate and voltage dependence of disulfide locking shows sequential formation of the ion pairs R4:E70, R3:D60, and then R4:E60. This new information on molecular interactions allows further refinement of the ROSETTA sliding helix model of gating and is incompatible with the paddle model of gating in which the gating charges move through the lipid bilayer.

P71. Knock-Down of CLOCK in the VTA Modifies Dopaminergic Activity and Mood-Related Behavior in Mice

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Abnormalities in circadian rhythms and mood related disorders occur together, and certain treatments for mood stabilization rely upon stabilizing daily rhythms. However, the exact role of circadian genes in mood regulation is still elusive. Previously, our lab found that mice with a mutation in the Clock gene display a behavioral profile that is markedly similar to the bipolar patients in the manic state. These mice show signs of hyperactivity, less anxiousness and less depression-related behavior. These mice also showed higher reward seeking behavior. We developed a Clock shRNA to specifically knock-down CLOCK. To determine the precise function of CLOCK in the dopaminergic pathway, we knocked down the expression of Clock specifically in the VTA of mice and found that the dopaminergic activity was increased following in cells expressing the Clock shRNA. Furthermore, these mice were hyperactive and showed reduced anxiety-related behavior, and these behavioral phenotypes were similar to that of Clock mutant mice. However, unlike the Clock mutant mice which display a decrease in depression-like behavior, knock-down in the VTA increases depression-like behavior. Clock knock-down also alters circadian rhythms and the gene expression profile in the VTA, but these changes differ from those seen in the Clock mutant mice. Taken together, these results suggest an important role for CLOCK in the VTA in the regulation of both manic and depressive-like behavior, and that both are associated with increased dopaminergic activity. These studies help define the role of the Clock gene in complex mood regulation and the development of bipolar disorder.

P72. Control of Glutamate Spillover by Transporters in the Hippocampus

*Katie Hoffmann, Emily Stone, Weinan Sun, Michael Kavanaugh**

Prompt removal of synaptic glutamate is necessary for terminating transmitter action and controlling spillover to maintain synapse specificity. Some studies suggest that glutamate transporter block has negligible effects on EPSC kinetics in hippocampus (e.g. Isaacson and Nicoll, 1993), although other work indicates that selective block of neuronal transporters can lead to prolonged synaptic responses in conditions allowing NMDA channel opening (Diamond, 2001). To investigate this further we utilized a panel of glutamate analogs that varied in transporter subtype selectivity. Non-selective block showed little effect on

single EPSPs recorded in acute hippocampal slices from 3–5 wk old CD1 mice. However, with brief trains of activity (2–5 stimuli, 50 ms interval), a marked prolongation of the EPSP is seen that is blocked by the NMDAR antagonist APV. EAAT2-selective blockers did not cause this effect, nor was it seen in the neuronal EAAT3 knockout mouse, suggesting that during repetitive activity the glial transporter EAAT1 plays a role in limiting synaptic NMDAR activity. Even without without transporters blocked, we found evidence that glutamate spillover/pooling occurs as the density of active inputs is increased, leading to a decrease in paired-pulse facilitation that can be prevented by blocking AMPAR desensitization. In summary, we find that glutamate spillover induced by strong and/or repetitive activity in the hippocampus is limited by transporters. We propose that heterosynaptic AMPA desensitization can modulate short-term plasticity as reflected by spillover-induced changes in paired-pulse facilitation.

P73. Mechanical Conflict System (MCS): A Novel Operant Method for Assessing Acute and Chronic Nociception

Thomas Morrow, Steven Harte*

Measures of innate reflexes remain the cornerstone of preclinical pain research, primarily due to their technical simplicity and efficiency. However, reflex measures are flawed because they fail to adequately represent the motivational and cognitive dimensions of pain. Furthermore, reflex tests are neither sensitive nor specific predictors of drug efficacy in clinical trials. The widespread adoption of paradigms that measure complex pain behaviors requiring supraspinal processing has been argued for by many researchers. To this end, we developed a motivational “conflict” pain assessment device, termed the Mechanical Conflict System (MCS). The MCS consists of two compartments connected by an enclosed alley. One compartment is brightly illuminated with LED lights and the other compartment is dark. The alley contains an adjustable array of tapered pins that serves as a nociceptive stimulus. Animals are trained to escape the light by crossing the alley to the preferred dark compartment. During testing, animals experience a cognitive conflict in that the motivational drive to acquire a reward (escape to darkness) is pitted against the negative consequence of experiencing pain. Pain is assessed by measuring the latency to exit the light chamber and total time spent on the stimulus array. The MCS possesses the characteristics of a valid and reliable pain measure. MCS behaviors differentiate acute and chronic pain, and change as a function of stimulus intensity. There is no evidence of learning or testing effects. Lastly MCS behaviors differentiate neuropathic and inflammatory pain models and are sensitive to analgesic treatments.

P74. Rapid Optimization of AMPA Receptor Kinetics and Role of Subunit Independence

*Allison Gehrke, Katie Rennie, Ilkyeun Ra, Tim Benke**

Regulation of the activation of AMPA-type glutamate receptors (GluR1-4) is critical for modulation of complex neuronal signaling as these receptors mediate most fast excitatory transmission in the central nervous system and at many sensory synapses. The kinetic properties of these receptors are reportedly altered under both normal conditions that may mediate sensory integration, learning and memory and in pathological conditions such as epilepsy. Detailed kinetic descriptions are useful for both understanding their function and implementation into accurate mathematical models of these processes. Numerous studies have demonstrated that these receptors activate, deactivate and desensitize in a complex fashion. These receptors are thought to be composed of tetramERICALLY arranged subunits. Studies suggest that the interactions between subunits are complicated: agonist binding and desensitization may proceed sequentially while channel opening may be dependent on resulting agonist dependent binding conformations. Previously published kinetic schemes are unable to simultaneously describe the effects of partial agonists on channel conductance and related shifts in conductance due to phosphorylation which preserve affinity and desensitization /deactivation. We used a parallel implementation of a genetic algorithm to rapidly optimize rate constants describing previously published and hybrid kinetic schemes. Optimization was measured by a template extracted from data describing recombinant GluR1 receptors. Data were best described by a hybrid kinetic scheme with cooperative agonist binding. Newer models incorporating subunit independence are being implemented that describe the data more completely. Implementation can be altered to incorporate the effects of TARPs on GluR function.

P75. Opioid and Cannabinoid Actions within the Amygdala-Striatal Systems Differentially Contribute to Palatability-Driven Feeding Behaviors

Matthew Will, Kyle Parker, Jordan McCall, Dennis Miller*

Opioid activation of the nucleus accumbens produces a robust consumption of preferentially palatable diets such as those high in fat and/or sugar. Interestingly, the endocannabinoid system has been shown to contribute to many of the same behavioral effects as the opioid system, such as increased feeding behavior, hypolocomotion, and reinforcement of drug self-administration behavior. Recent evidence has shown that these behavioral effects produced by the endocannabinoid system interact with the opioid system. The present

experiments investigated the central interactions of the cannabinoid and opioid systems within an established model of binge eating of a high-fat diet. Therefore, near sub-threshold doses of both the mu opioid agonist D-Ala², NMe-Phe⁴, Glyol⁵-enkephalin (DAMGO) and the selective cannabinoid CB1 agonist, O-2545, were administered into the accumbens and feeding behavior associated with a high-fat diet was assessed. The results demonstrated that opioid and cannabinoid systems synergize to increase both food consumption and activity. The second series of studies examined whether intra-accumbens opioid driven feeding behaviors were dependent on cannabinoid and/or opioid activity within the basolateral amygdala (BLA). The cannabinoid antagonist, AM-251, or the opioid antagonist, naltrexone, were administered into the BLA prior to intra-accumbens DAMGO. The results showed feeding responses following intra-accumbens DAMGO are dependent on both cannabinoid and opioid activation within the BLA, however the influence on approach vs. consummatory responses were differentially affected. These data support endogenous opioid and cannabinoid interaction and suggest they also maintain distinct roles in this model of opioid-driven feeding of a high-fat diet.

P76. Subthalamic Neurons Recorded in Humans Exhibit Agent Selective Responses to Sedatives

M. Bruce MacIver, John G. Brock-Utne, Richard A. Jaffe*

Patients receiving STN electrode implants were given low-dose propofol or remifentanyl and effects on neuronal discharge activity were studied. Bolus IV injections of either propofol (0.3 mg/Kg) or remifentanyl (0.8 µg/Kg) were given and STN action potential discharge activity was recorded before (2 min) and after (10 to 15 min) injections. Only minor effects on discharge activity of STN neurons were observed, including no change in spike amplitude, rise time or undershoot potential. However, action potentials of STN neurons with short inter-spike intervals (less than 10 ms) were markedly reduced by propofol, even though overall discharge rates (5 s bin widths) remained stable. Similarly, little change in discharge frequency was produced by remifentanyl, and no change in fast spiking activity was seen, however, discharge patterns became some what more burst-like. Whole cell recordings of STN neurons in rat brain slices demonstrated that propofol prolonged GABA-mediated synaptic currents, similar to effects seen in other types of neurons. This occurred with no change in membrane conductance or evoked action potential discharge responses—consistent with the lack of depression seen in human recordings. Remifentanyl did not appear to increase the duration of inhibition, and may even depress inhibition somewhat, leading to increased burst firing. Neither agent appeared to produce tonic depression of STN discharge. Thus both propofol and/or remifentanyl could be useful as sedatives during DBS implant surgeries.

P77. Opioid Reward and Withdrawal in Methadone Maintained Patients: Modulation by a Neurokinin 1 (NK1) Receptor Antagonist

Malcolm S. Reid, Wade Berretini, Vatsal Thakkar*

Pre-clinical studies indicate that the NK1 receptor is critical in the expression of opioid reward and withdrawal. We therefore tested the effects of a clinically available NK1 antagonist, aprepitant, on the acute response to methadone, and on prolonged methadone withdrawal, in stable methadone maintained patients (40-130 mg/day). A placebo-controlled, within-subjects, crossover study design was employed. During each 3 day treatment phase participants received aprepitant (80 mg, po, QD) or placebo, separated by a 5-day washout period. Days 1-2 participants received study medication at 9 AM, consumed their methadone maintenance dose 60 min later, and then acute responding was assessed for the following 90 minutes. On Day 3 participants received study medication at 9 AM and then symptoms of opioid withdrawal were assessed for the following 7 hours (up to 30 hr since their last methadone dose). Participants were also genotyped for the opiate mu receptor 1 (OPRM1) gene polymorphism A118G, which is associated with greater sensitivity to beta-endorphins and opioid withdrawal. Thus far 10 patients have completed testing, demonstrating moderate effects. On Day 2 methadone induced morphine-like subjective ratings (ARCI) and desire for another dose were attenuated in the aprepitant group. On Day 3, 30 hour since last methadone dose, observer-rated and self-reported withdrawal symptoms were reduced in the aprepitant group. These data indicate a potential non-opioid medication for opioid detoxification and relapse prevention treatment in opioid dependent patients. Data from a larger set of patients (n=15), including A118G genotyping and plasma cortisol and ACTH levels, will be presented.

P78. Status Epilepticus: Therapeutic Implications of the Receptor Trafficking Hypothesis

Claude Wasterlain, Roger Baldwin, Roland Eavey, Viet Huong Nguyen, Jerome Niquet*

Rationale: During experimental SE, self-sustaining seizures and pharmacoresistance to benzodiazepines develop progressively, and may reflect seizure-induced movement of synaptic GABA_A receptors (GABA_AR) from synapses to the cytoplasm and of "spare" NMDA receptors (NMDAR) from cytoplasm to synapses. Since both changes are proconvulsant, the traditional treatment of SE with GABA agonists leaves glutamatergic excitation unchecked, and polytherapy is needed to simultaneously stimulate GABA_AR and reduce the activity of NMDAR. We treated SE by combining benzodiazepines with NMDAR

antagonists, in order to mitigate the consequences of changes in receptors, or with benzodiazepine antagonists, in order to reverse GABAAR internalization. Methods: We used a very severe model of SE (5 mEq/kg lithium, 320 mg/kg pilocarpine), and treated after the second convulsive seizure. Video-EEG telemetry was used to measure EEG seizure frequency and severity. Results: Seizures refractory to an anesthetic doses of diazepam (20 mg/kg), could be stopped without depressing consciousness, using a low dose of diazepam (1 mg/kg), combined with an NMDA antagonist (dizocilpine, in a dose which had no measurable anticonvulsant effect when given alone). Treatments aimed at reversing GABAAR receptor trafficking failed to alter the course of SE. Conclusions: These results suggest that initial treatment with a combination GABAAR agonist/NMDAR antagonist is more effective and less toxic than monotherapy, and reverses some physiological changes resulting from receptor trafficking. Supported by VHA Research Service, by grants NS13515 and NS 059704 from NIH/NINDS, and by the Cho Family Foundation.

P79. Blocking PSD95 Interactions Provides Neuroprotection by Maintaining Cortical Function and Neurotrophic Signalling

*Luka Srejc, Karen Bell, William Hutichson, Michelle Aarts**

There are currently few treatment options available for stroke, a leading cause of death and morbidity in Western Society. We have previously shown that selective blockade of PSD95 interactions can prevent in vitro excitotoxicity via NMDA receptors and more importantly provide significant neuroprotection from acute neuronal injury in vivo. Despite this exciting advance we still have limited knowledge of the cellular and neurophysiological events that determine cell survival following stroke onset. Our current research shows that PSD95 inhibition does not simply block neurotoxic NMDAR signals as originally hypothesized; rather it maintains or enhances key calcium-dependent neurotrophic signals to the nucleus as an early event following acute neuronal injury. In addition we have recently developed an in vivo neurophysiological model to study cortical function and recovery following acute stroke. We have found that small cortical infarcts cause dramatic loss of EEG power and evoked potentials across the cortex in control animals and that PSD95 inhibition prevents loss of cortical function and restores evoked potentials to >80% of baseline. These combined results indicate that the preservation of trophic signalling and a rapid recovery of cortical function, rather than blockade of an early excitotoxic event, are critical for stroke neuroprotection. Thus, manipulating neuroprotective signalling (i.e. normal NMDA receptor function) in combination with uncoupling PSD95 may yield new therapeutic strategies for neuroprotection in brain injury.

P80. A Novel Biomarker for Parkinson's Disease: The Purine Connection

Peter LeWitt

While Parkinson's disease (PD) has several systemic manifestations outside of the CNS and affects multiple brain regions, the focus for biomarker discovery has been degeneration in the dopaminergic nigrostriatal system. For the neuronal population of the substantia nigra pars compacta, more than half are lost before even the first symptoms of PD arise. Hence, the pathology of the disease is already advanced at the time that PD is typically diagnosed. Improved methods are needed for early recognition of the disease if effective neuroprotective treatments are developed. Our high-performance liquid chromatography studies of CSF have recognized several compounds from untreated PD subjects differentiating them from healthy controls. Among these is xanthine, an intermediate in purine metabolism. Xanthine is the immediate product of hypoxanthine by the action of xanthine oxidase, and xanthine formation represents the pathway of degradation of all of the purine nucleotides (whose roles include energy transfer molecules, signaling transmitters, and components of nucleic acids). In CSF collected in a standardized manner from the lumbar region in 288 PD patients, mean xanthine concentration was increased by 17% as compared to healthy controls in an aliquot collected from ml 18-20 ($p < 0.05$). Furthermore, when xanthine was indexed to the CSF concentration of homovanillic acid, their ratio provided a high degree of discrimination for PD from controls ($p < 0.001$). The overall correlation of homovanillic acid and xanthine was approximately 77%. Since there was no change in CSF [xanthine]/[homovanillic acid] between the initial and subsequent lumbar puncture conducted up to 2 years later, we regard this quotient as a PD trait marker and are currently exploring whether it might serve as a systemic marker useful in PD diagnosis.

P81. Pre- and Postsynaptic Regulation of Proopiomelanocortin Neurons via Multiple Opioid Receptor Subtypes

*Reagan L. Pennock, Shane T. Hentges**

Proopiomelanocortin (POMC) neurons produce the opioid beta-endorphin which modulates reward, nociception, and other physiologic responses. In addition to releasing endogenous opioids, it is clear that these neurons are also regulated by opioids. However the role of specific pre- and postsynaptic receptors has not been clearly determined. In the present study whole cell voltage clamp recordings were made in hypothalamic POMC neurons in brain slices prepared from POMC-egfp transgenic mice to analyze the effect of the selective opioid receptor agonists U69593 (κ), DPDPE (δ), and DAMGO (μ) on

preand postsynaptic regulation of POMC neurons. All three agonists reduced the amplitude of the evoked and spontaneous GABA mediated inhibitory postsynaptic currents (IPSCs). Application of U69593 and DAMGO resulted in the reduction of the amplitude of evoked glutamate mediated excitatory postsynaptic currents (EPSCs), but DPDPE had no effect. Only the mu receptor-specific agonist DAMGO induced an inhibitory postsynaptic current. The EC50 for DAMGO induced inhibition of IPSCs was ~50 nM whereas the EC50 for the postsynaptic outward current was ~360 nM. While the postsynaptic response to high concentrations of mu receptor agonist declined quickly, the presynaptic inhibition was much less sensitive to desensitization. It remains to be determined whether the presence of other opioid receptor subtypes on presynaptic terminals has a role in preventing desensitization. Together the results indicate that POMC neurons are regulated by various pre- and postsynaptic opioid receptors which may alter POMC neuron activity differently upon acute or prolonged exposure to opioids.

P82. Glial Fibrillary Acidic Protein and Vimentin Are Negative Regulators of the Neurogenic Niche

Tulen Pekny, Maryam Faiz, Ulrika Wilhelmsson, Milos Pekny*

Adult neurogenesis is regulated by a number of cellular players within the neurogenic niche. Previously, we showed that ablation of the astrocyte intermediate filament proteins glial fibrillary acidic protein (GFAP) and vimentin created an environment more permissive to transplantation of neural grafts or neural stem cells (Kinouchi et al., 2003; Widstrand et al., 2007) and improved axonal and synaptic regeneration after neurotrauma (Cho et al., 2005; Wilhelmsson et al., 2004). More recently, we have investigated the role of GFAP and vimentin in the regulation of endogenous neurogenesis. Ablation of GFAP and vimentin increased the number of newly born hippocampal neurons and this correlated with enhanced learning and memory and greater plasticity in the adult hippocampus in response to injury and running (Faiz et al; unpublished). Here we used an in vitro neurosphere system and demonstrate that ablation of GFAP and vimentin in astrocytes increases neural stem/progenitor cell differentiation and that this increase is at least partially mediated by decrease in Notch signaling from astrocytes to stem/progenitor cells.

P83. Analysis of the Role of Trace Amine Associated Receptor 1 (TAAR1) in the Movement Control in Parkinson's Disease Models

Tatyana D. Sotnikova, Marc G. Caron, Raul R. Gainetdinov*

Trace amines are endogenous monoamines of unknown function that are structurally related to classical monoamines and normally found at low concentrations in the brain of mammals. Recently, specific GPCR receptors for trace amines, designated as Trace Amine Associated Receptors (TAARs), have been discovered. The best characterized TAAR1 is particularly interesting since it can be activated by a variety of monoaminergic compounds including trace amines, amphetamines and monoamine metabolites. These receptors represent attractive potential mediators of certain aspects of movement control. By using various experimental paradigms aimed to model Parkinson's disease (PD) in mice lacking TAAR1 we investigated role of TAAR1 in movement control. In particular we used three experimental approaches: 1) pharmacological model of PD (haloperidol catalepsy); 2) novel model of acute dopamine deficiency, DDD mice; 3) 6-OH-DA model of PD. In all these models TAAR1-KO mice demonstrated significantly altered responses thus indicating important role of TAAR1 in movement control and actions of antiparkinsonian drugs. These investigations suggest that targeting TAAR1 may be a novel approach in the pharmacology of Parkinson's disease.

P84. GLP-1 Receptor Stimulation Reduces Amyloid- β Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease

Harold Holloway, Yazhou Li, Mary Ann Ottinger, Debomoy Lahiri, Nigel Greig*

Type 2 (T2) diabetes mellitus (DM) has been associated with an increased incidence of neurodegenerative disorders, including Alzheimer's disease (AD). Several pathological features are shared between diabetes and AD, including dysfunctional insulin signaling and a dysregulation of glucose metabolism. It has therefore been suggested that not only may the two conditions share specific molecular mechanisms but also that agents with proven efficacy in one may be useful against the other. Hence, the present study characterized the effects of a clinically approved long-acting analogue, exendin-4 (Ex-4), of the endogenous insulin releasing incretin, glucagon-like peptide-1 (GLP-1), on stress-induced toxicity in neuronal cultures and on amyloid- β protein (A β) and tau levels in triple transgenic AD (3xTg-AD) mice with and without streptozocin (STZ)-induced diabetes. Ex-4 ameliorated the toxicity of A β and oxidative challenge in primary neuronal cultures and human SH-SY5Y cells in a concentration-

dependent manner. When 11 to 12.5 month old female 3xTg AD mice were challenged with STZ or saline, and thereafter treated with a continuous subcutaneous infusion of Ex-4 or vehicle, Ex-4 ameliorated the diabetic effects of STZ in 3xTg-AD mice, elevating plasma insulin and lowering both plasma glucose and hemoglobin A1c (HbA1c) levels. Furthermore, brain levels of A β precursor protein and A β , which were elevated in STZ 3xTg-AD mice, were significantly reduced in Ex-4 treated mice. Brain Tau levels were unaffected following STZ challenge, but showed a trend toward elevation that was absent following Ex-4 treatment. Together, these results suggest a potential value of Ex-4 in AD, particularly when associated with T2DM or glucose intolerance.

P85. Antisocial Substance-Dependent Boys' Processing of Rewards and Punishments after Risky Behaviors

Thomas Crowley, Manish Dalwani, Susan Mikulich-Gilbertson, Yiping Du, Marie Banich*

Adolescent conduct disorder, co-occurring with substance dependence, sometimes is called "antisocial substance dependence (ASD)." "Risky behaviors" are behaviors that may result unpredictably in rewarding and/or adverse outcomes, and ASD adolescents, pursuing exciting reinforcers despite potential adverse outcomes, excessively engage in risky behaviors (e.g., substance intoxications, fighting, thefts, unprotected sex). At WCBR 2009 we reported that pre-response deliberation before repeated forced choices to do either a risky or a cautious behavior generated in ASD youths very different (from controls) event-related BOLD patterns of neural activity. We here examine the additional hypothesis that after responses those ASD youths' brains differently (from controls' brains) process the rewards and punishments from risky behaviors. Subjects: 20 adolescent boys in treatment for ASD, drug free (mean 38 days); 20 control boys. In 90 decision trials in a 3T scanner subjects chose between a cautious behavior (always gain \$.01) or a risky behavior (unpredictably gain \$.05 or lose \$.10); odds of losing increased as the game progressed. Ninety comparison trials presented the same visual/auditory stimuli, required no decision, and always predictably earned \$.02. Considering activation differences [decision trial—comparison trial], we examined controls' vs. patients' activation patterns during the 3.5 sec presentation of wins, and separately of losses. During wins controls had greater activity: ACC, temporal, parietal, and cerebellar regions. During losses patients had greater activity: pons; DL and medial PFC; and cingulate, temporal, parietal, and cerebellar regions. We speculate that these surprising findings partially may reflect inhibition-driven fMRI activation. Support: DA-009842, DA-011015. Kane Family Foundation.

P86. Looking BAC Carefully: Altered Dopaminergic Signaling in BAC D2-GFP Transgenic Mice

Paul F. Kramer, Yolanda Mateo Gonzalez, Lisa A. Hazelwood, Alice Dobi, Christine H. Christensen, David R. Sibley, Veronica A. Alvarez*

Transgenic mice carrying bacteria artificial chromosomes (bac) contain several hundreds of thousands of base pairs of regulatory sequences for the gene of interest and thus they recapitulate the regulation of endogenous genes much better than shorter transgenes. Over the past years, bac transgenic mice expressing the fluorescent reporter GFP under the D1 or D2 dopamine receptor promoters have become very popular tools for studies of striatal function because they allow for the easy and reproducible identification of medium spiny neurons (MSN) from direct striatonigra pathway (D1-GFP mice) and the indirect striatopallidum pathway (in the D2-GFP mice). We performed behavioral studies and found that D2-GFP mice have increased locomotor activity when compared to wild type Swiss Webster and D1-GFP mice and showed a paradoxical response to acute cocaine exposure: a dose dependent decrease in locomotor activity. When exposed to the D2 agonist quinlorane, D2-GFP mice showed hypersensitivity to the agonist actions ($EC_{50} = 1 \mu\text{g}/\text{kg}$) in comparison to wild type and D1-GFP mice ($EC_{50} = 6 \mu\text{g}/\text{kg}$). Electrophysiological recordings from midbrain dopaminergic neurons, which express high levels of D2 dopamine receptors, revealed a left-shifted dose response to D2-agonist application in D2-GFP mice ($EC_{50} = 60$ and 260 nM for D2 and D1 GFP mice, respectively). To evaluate whether dopamine release, uptake and/or modulation by autoreceptors was affected in these mice, we performed fast-scan cyclic voltammetry in nucleus accumbens slices from the three mouse strains. We found that cocaine inhibition of dopamine uptake is diminished in Drd2-GFP mice, in agreement with the behavioral data. Even more interesting, bath application of sulpiride (D2 antagonist) caused an increase in the basal stimulated dopamine release in slices from D2-GFP mice, revealing a tonic inhibition of release, possible through autoreceptors, that was not observed in slices from either Swiss Webster or D1-GFP mice. Together these results suggested that D2-GFP mice could have elevated expression of D2-dopamine receptors. Radioactive binding experiments confirmed that striatal tissue from D2-GFP mice has ~50% higher concentration of binding sites for D2-specific ligand ($B_{\text{max}} = 440 \text{ fmol}/\text{mg}$ and $260 \text{ fmol}/\text{mg}$ for D2 and D1-GFP mice). In conclusion, the data from this study shows that bac transgenic D2-GFP mice express higher levels of D2 dopamine receptors and display behavioral, electrophysiological and neurochemical alterations in dopaminergic signaling. Section on Neuronal Structure, NIAAA and Molecular Neuropharmacology Section, NIND- NIH. Bethesda, MD 20892
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P87. Constitutively Active Mu Opioid Receptors: A Novel Therapeutic Target for Pain?

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The “Holy Grail” of opioid research has been to develop opioid drugs for the treatment of pain without triggering reward, tolerance, and withdrawal that clearly can contribute to drug addiction. Our previous studies in mouse neonatal primary afferent dorsal root ganglion (DRG) neurons showed that in the absence of either β -arrestin 2 or c-Src signaling, constitutive mu-receptor activity is upregulated. The constitutive mu-receptor mediated inhibitory coupling to Ca²⁺ channels in β -arrestin 2 knockout (β arr2^{-/-}) DRG neurons could be reversed by naloxone and naltrexone (consistent with inverse agonist activity), but not by 6 α - and 6 β -naloxol or 6 β - naltrexol that acted as neutral antagonists since they were able to block agonist-induced signaling. Similar results were obtained in adult DRG neurons. The tail withdrawal assay of thermal pain revealed that constitutive mu receptor activity accounts for the increased analgesic threshold observed in mice lacking β arr2^{-/-}. Thus the increased nociceptive threshold in β arr2^{-/-} mice could be blocked by naloxone and naltrexone but not by 6 α - and 6 β -naloxol or 6 β - naltrexol. Interestingly, the aversive properties of naloxone were unaffected in the β arr2^{-/-} suggesting that constitutive activity of the mu-receptor does not measurably perturb basal hedonic homeostasis. These studies suggest that upregulation of mu-receptor constitutive activity by perturbation of mu- β -arrestin 2 interaction may provide a novel therapeutic target for maintaining sustained analgesia without major adaptation of reward circuitry.

P88. Pseudo-Bayesian Analysis of Alzheimer’s Disease Genetic Association Data

*C. Harker Rhodes**

A typical late-onset Alzheimer’s disease (LOAD) genetic association study is a case-control study in which the genotypes of several hundred Alzheimer’s disease patients are compared to those of matched control subjects. These studies contain individuals who have a wide range of *a priori* risks of AD based on their age, gender, and APOE genotype. However, this subject-to-subject variation in *a priori* risk of AD is usually ignored in the data analysis with the data from all subjects being weighted equally. It seems intuitively obvious that this is not the most efficient use of the available data. For example the presence of a putative risk allele in a 65 y/o ϵ 3/ ϵ 3 man with AD is much stronger evidence for the association of that allele with LOAD than the presence of the allele in an 85 y/o ϵ 4/ ϵ 4 woman who was likely to develop AD no matter what her genotype at

the candidate locus. This report describes statistical techniques which incorporate information about the subject-specific *a priori* risk of AD in genetic association studies to increase their statistical power with a fixed number of subjects. Note that we are *not* proposing a Bayesian analysis which would take into account an *a priori* probability that some specific genotype is associated with the risk of LOAD. The “*a priori* risk” to which we refer is based on confounder genotypes and is not the *a priori* probability distribution of a Bayesian analysis.



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