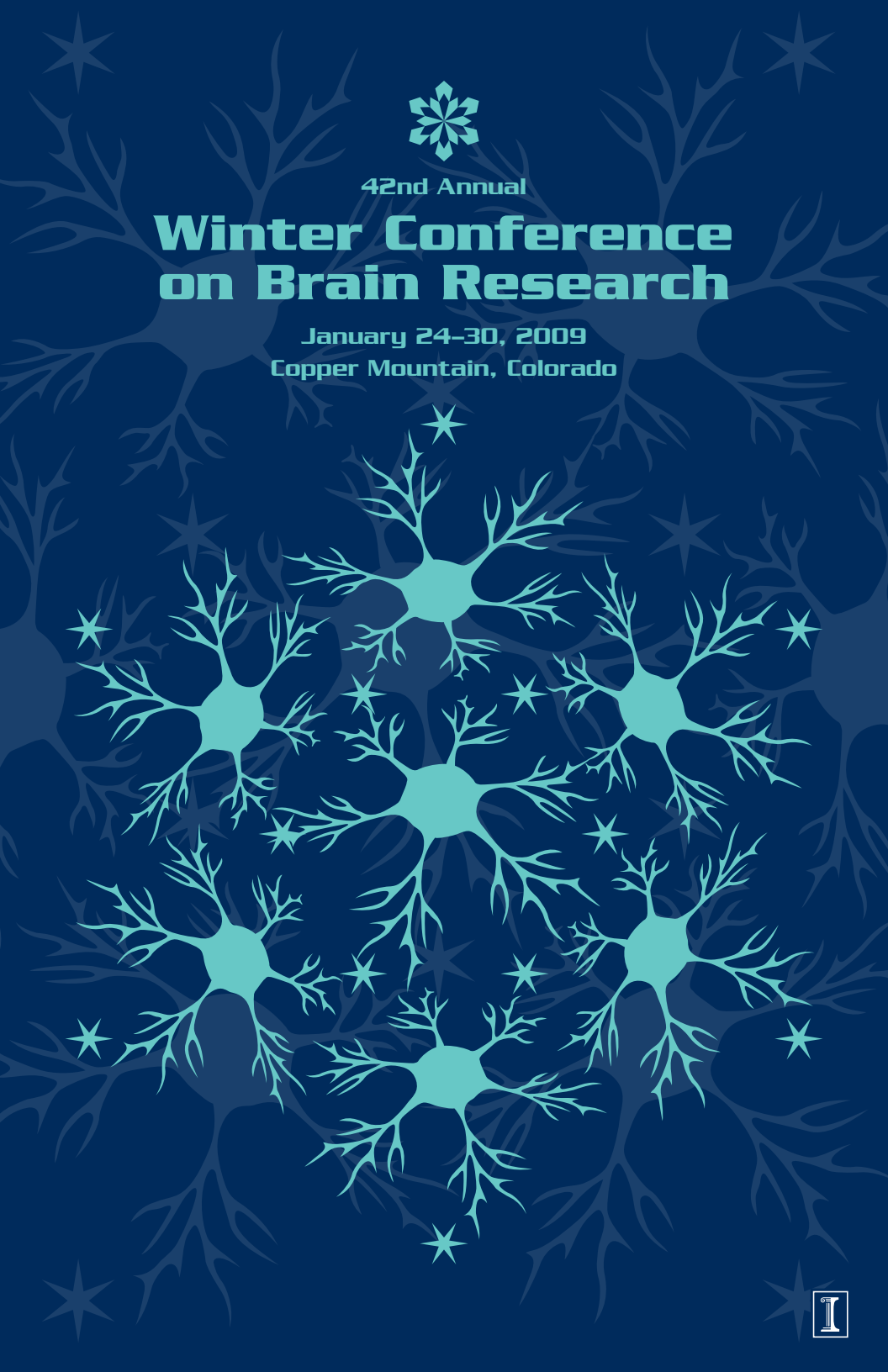
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Winter Conference
on Brain Research
January 24–30, 2009
Copper Mountain, Colorado

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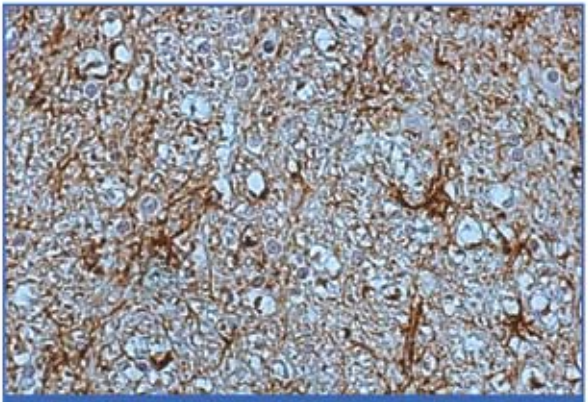

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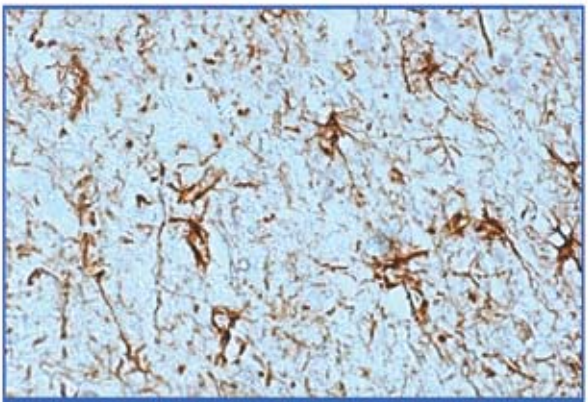

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Welcome to the 42nd Annual Winter Conference on Brain Research!

Greetings to those of you who are returning to WCBR, and a sincere welcome to first-time attendees. The Winter Conference on Brain Research 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, providing a vehicle for scientists with common interests to discuss current issues in an informal setting. The conference 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 meet 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 (light blue badges) and Travel Fellows (badges with blue dots) into your scientific discussions, ski/snowboard trips, and meals throughout the week.

The **Opening Breakfast** on Sunday will feature our keynote speaker, **Michael Selzer, MD, PhD**. Dr. Selzer is Professor of Neurology at the University of Pennsylvania and Director of Rehabilitation Research and Development at the US Department of Veterans Affairs. He studies the regenerative abilities of neurons in the CNS, using the lamprey spinal cord as an experimental model. In his talk, **"Traumatic Brain Injury–Impact and Innovation,"** he will discuss traumatic brain injury in civilian and military populations and describe recent advances in imaging that may shed light on the subtle cognitive deficits of TBI.

Taking on the important responsibility of educating the lay public, on Tuesday night, WCBR sponsors a **Town Meeting Lecture**, organized by Karen Greif, to be held at Copper Mountain. Martha Bohn will speak on **"Viruses Offer Cures! Gene Therapy for Parkinson's Disease and Other Brain Diseases."** All WCBR attendees and their families are welcome to attend. WCBR scientists also provide **School Outreach** sessions, organized by Frank Welsh, throughout the week in the local elementary, middle, and high schools. This year we have scheduled a **Special Poster Session** on Tuesday evening, featuring top poster abstract submissions and light refreshments. You are encouraged to engage in discussions with poster presenters as well as with corporate exhibitors. Exhibitors also sponsor the afternoon breaks; please visit exhibitor booths throughout

the week. Plan to join us at Wednesday's **Mountain Lunch** to be held at Solitude Station. The **Smitty Stevens Memorial (NASTAR) Ski Race** will occur on the Copperopolis slope on Wednesday. Please be sure to attend the **Business Meeting** on Wednesday as well, following the afternoon sessions, as we will be holding elections and discussing 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, cellular/developmental , or systems/behavioral neuroscience. We will close the week on Friday night with the **Annual Banquet**, at which we will announce awards for the special poster session and the ski race, as well as let our hair down dancing to live music.

We are an all-volunteer organization, so please join me in thanking Program Chair Patricio O'Donnell and his committee members for an outstanding scientific program. We welcome Program Chair-Elect Barbara Lipska, who will be taking over next year. We thank Facilities Chair Tom Swanson and welcome Facilities Chair-Elect Janet Finlay for the meeting venue and organization. Thanks also to Paula Dore-Duffy and John Mendelson, who 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 WCBR mentors. Jacqueline McGinty keeps us on solid financial ground as WCBR treasurer. Lastly, we thank Barry Levin, past WCBR conference chair, 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

Contents

Don't forget to visit the exhibits

General Information

Headquarters are the Copper Conference Center. All scientific activities will be held there.

The WCBR Information Desk and Message Center are in the Registration area, upper level.

The desk hours are as follows:

	Morning	*Afternoon*
Saturday 1/24	8:00–10:00 AM	3:30–9:00 PM
Sunday 1/25	6:30–10:00 AM	3:30–7:00 PM
Monday 1/26–Thursday 1/29	7:00–9:45 AM	3:30–7:00 PM
Friday 1/30	7:00–9:45 AM	

The telephone number for messages 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 Bighorn B, upper level.

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 their 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 will be awarded to the best poster, and first prizes will also be given to the best poster in the cellular/developmental, systems/behavioral, and clinical/human studies categories. *Presenters will be with their posters on Tuesday and Wednesday from 3:30 to 4:30 PM.*

Poster Session 3, Thursday
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.*

Please refer to pages 25–30 for a listing of poster sessions.

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

Exhibits and Lounge are in Bighorn B, upper level. Exhibitor setup is Sunday, January 25, 12:00–3:00 PM. Refreshments are provided from 3:30 to 4:30 PM, Sunday through Thursday. Exhibits close after 10:30 AM on Friday, January 30. Friday's afternoon break will be in the Ballroom lobby.

Breakfast is served to all registrants on Sunday, from 7:30 to 8:30 AM, in the Bighorn Lobby & Ballroom, and on Monday through Friday, from 6:00 to 10:00 AM, at Jack's Slopeside Grill. 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 and tickets can be picked up during information/registration desk hours.

Banquet table sign-up sheets will be posted next to the registration area, from Monday to Wednesday. Attendees will be able to reserve a table for 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 registration area.

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We thank the individuals and organizations who have generously supported the travel fellowship program.

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Champaign, IL 61820
Contacts: Michelle Chappell,
Karen Nichols
Phone toll free: 877-455-2687
Fax: 217-333-9561
E-mail: winterbrain@ad.uiuc.edu

IN MEMORIAM

Victor Denenberg 1925–2008

We are sorry to have lost this year a long-time WCBR friend, colleague, and mentor, Dr. Victor Denenberg. Vic had a BA in Psychology from Bucknell University and a PhD in Experimental Psychology from Purdue University. He held a faculty position in Psychology at Purdue University from 1954 to 1969, and at University of Connecticut from 1969 to 2000. Vic retired as Professor Emeritus, and accepted a position as Visiting Professor at the University of Washington. Over the course of his career, Vic published nearly 400 manuscripts and chapters, including several statistical texts; received federal and private research support for studies of early development of the brain and behavior; and trained more than 70 MS and PhD students. Vic was a founding/charter member of the Society for Neuroscience, and a long-time member of WCBR. He was a visionary and philosopher, and he will be deeply missed.

Exhibitors

Association Book Exhibit
9423 Old Mt. Vernon Road
Alexandria, VA 22309
Contact: Mark Trocchi
Phone: 703-619-5030
Fax: 703-619-5035
E-mail: info@bookexhibit.com

Fine Science Tools
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Contact: Christina Callanta
Phone: 650-281-4557
E-mail: ccallanta@finescience.com

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Williston, VT 05495
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Phone: 802-288-9290
Fax: 802-288-9002
E-mail: info@mbfbioscience.com

Nature Publishing Group
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Contact: Kim Mesman
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Fax: 303-730-1966
E-mail: kim@novusbio.com

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Special Events

Saturday, January 24

Welcome Wine and Cheese Reception • 6:00–7:30 PM, Bighorn Ballroom
Newcomers, fellows, and mentors only from 6:00 to 6:30 PM; all attendees from 6:30 to 7:30 PM

Sunday, January 25

Conference Breakfast and Opening Address • 7:30 AM, Bighorn Lobby & Ballroom

The plenary keynote speaker will be **Michael Selzer, MD, PhD**, Professor of Neurology at the University of Pennsylvania, and Director of Rehabilitation Research and Development at the US Department of Veterans Affairs.

"Traumatic Brain Injury—Impact and Innovation"

It is estimated that there are about 1.4 million cases of traumatic brain injury (TBI) in the United States each year. Most of these are mild and the patients recover fully, but between 5 percent and 10 percent are left with long-lasting neurological symptoms and deficits. The wars in Iraq and Afghanistan have seen an increased use of improvised explosive devices, and these have led to a great increase in the frequency of TBI due to the effects of the blast wave and secondary impact. There is now a great need to understand the pathophysiology of TBI, which has been called the "signature injury" of the wars, and to develop means of preventing and treating it. Dr. Selzer will review the epidemiology of TBI in civilian and military populations, explore its pathophysiology and neurological sequellae, and discuss recent advances in imaging that may shed light on the subtle cognitive deficits often not detected in the immediate aftermath. Finally, he will explore some recent approaches to the treatment of TBI.

Meeting of Panel and Workshop Organizers • 9:30–10:30 AM, Bighorn Ballroom immediately after breakfast. The meeting will be brief but important. Organizers and WCBR staff are requested to attend.

Monday, January 26

First Meeting of the Board of Directors • 6:30–8:30 AM, Village Square—Ponderosa

Tuesday, January 27

Breakfast for Travel Fellows Meeting • 6:30–7:30 AM, Jack's Slopeside Grill

Special Poster Session • 6:30–8:30 PM, Bighorn B

The 30 top-ranked posters submitted by junior investigators will be on display on Tuesday from 6:30 to 8:30 PM in a special session with wine and cheese. Awards will be given, including a "Best Poster" award made possible by a generous donation by Wyeth, and one "First Prize" award in each thematic category (cellular/developmental, systems/behavioral, clinical/human studies). The awards will be announced at the Closing Banquet on Friday, January 30.

Town Meeting • 7:00 PM, Village Square—Ponderosa

Attendance is open to all.

"Viruses Offer Cures! Gene Therapy for Parkinson's Disease and Other Brain Diseases"

Martha C. Bohn, PhD
Medical Research Institute Council Professor; Director, Neurobiology Program, Children's Memorial Research Center (CMRC), Northwestern University

Wednesday, January 28

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 AM, Copperopolis

NASTAR registration cards to be completed no later than Monday, January 26, 8:00 AM at WCBR Information Desk.

Mountain Lunch • 11:30 AM–2:00 PM, Solitude Station

Outdoor lunch; required lunch ticket is in your registration packet. Non-skiers requiring transportation should sign up at the WCBR Information Desk by Monday, January 26.

Business Meeting • 6:30 PM, Bighorn C1

Attendees will vote on the Conference Chair-Elect, four members of the Board of Directors, and discuss locations of future meeting sites, along with other business items.

Friday, January 30

Second Meeting of the Board of Directors • 6:30–8:30 AM, Village Square—Ponderosa

Banquet and Dance • 7:30 PM, Bighorn Ballroom

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

Preamble to the Program

The 2009 WCBR Program consists of panels, workshops, and posters. Please consult the program booklet and posted announcements for details regarding the scientific presentations as well as information regarding the School Outreach program and the Town Meeting.

Sunday, January 25

7:30 AM

Breakfast • Bighorn Lobby & Ballroom

8:00 AM

Plenary Session • Bighorn Ballroom

Michael Selzer, MD, PhD, Professor of Neurology at the University of Pennsylvania, and Director of Rehabilitation Research and Development at the US Department of Veterans Affairs

3:30–4:30 PM

Exhibits and Posters • Bighorn B

4:30–6:30 PM

1. Panel • Bighorn C1

Regulation of the Dopamine System: Neurodevelopmental Perspectives and Its Impact on Psychiatric Disorders Models

Susan Andersen, Patricio O'Donnell, Alain Gratton, **Yukiori Goto (Chair)**

2. Panel • Bighorn C2/C3

New Aspects of Dopamine Receptor and Transporter Structure/Function Identified Using Novel Proteomics Approaches

Kim Neve, **David Sibley (Chair),** Christine Wu, Fang Liu

3. Panel • Hasty's

Estrogen Receptor Signaling in the Brain: A Trip Down Memory Lane

Nick Brandon (Chair), Eniko Kramar, Peter Puenzes, Feng Liu, John Morrison

4. Panel • Ptarmigan A

Allostatic Dysregulation of Emotions: Is It CRF, the HPA Axis, or Cytokines?

George Koob, **Fulton Crews (Chair),** Friedbert Weiss, Gunter Schumann

5. Panel • Ptarmigan B

Therapeutic Perspective of Adenosinergic Drugs in the Brain

Susan Masino, Michael Schwarzschild, **Felicita Pedata (Chair),** Sergi Ferre

6. Panel • Ptarmigan C

Novel Signaling Mechanisms Involved in Ischemic Injury and Ischemic Preconditioning

John Weiss (Chair), Elias Aizenman, Claude Shuttleworth, Raymond Swanson

8:30–10:00 PM

7. Panel • Bighorn C1

Risky Research: Advances in Understanding the Drive to Gamble from Both Clinical and Preclinical Perspectives

Marc Potenza, Robert Rogers, **Catharine Winstanley (Chair)**, Christopher Olsen

8. Panel • Bighorn C2/C3

Androgens and the Brain: New Functions for an Old Hormone

Kathie Olsen, Josep Nunez, Rae Silver, **Robert Handa (Chair)**

9. Panel • Hasty's

Subcellular Receptor Interactions in Analgesia and Tolerance

George Wilcox (Chair), Aaron Overland, Catherine Cahill, Dennis Paul, Lakshmi Devi

10. Panel • Ptarmigan A

Oxidative Stress as a Target for Treatment of Neurovascular and Traumatic CNS Disorders: Why Hasn't This Worked?

Gregory DelZoppo, Dale Pelligrino, Edward Hall, **Jaroslaw Aronowski (Chair)**

11. Panel • Ptarmigan B

Parkinson Disease: Genetic Influences on Organelle Function and Dysfunction

Anurag Tandon (Chair), David Park, Angus McQuibban, Philipp Kahle, Haung Yu

12. Panel • Ptarmigan C

Translational Opportunities in Epilepsy: Tales of Transporters and Tangles

Kevin Staley, **Thomas Sutula (Chair),** Frances Jensen, Jeff Noebels

Don't forget to visit the exhibits

Monday, January 26

7:30–9:30 AM

13. Panel • Bighorn C1

VTA Dopamine Neuron Heterogeneity: Can It Help Us Understand Addiction and Other Psychiatric Disorders?

Susan Volman (Chair), Elyssa Margolis, Stephan Lammel, Gary Aston-Jones, Wenlin Sun

14. Panel • Bighorn C2/C3

DISCo Dancing: Genetic and Molecular Interactions in the DISC1 Pathway and the Risk for Schizophrenia

Nick Brandon, David Porteus, Katherine Burdick, **Barbara Lipska (Chair**)

15. Panel • Hasty's

Facial Processing—What Is New and Different

Robert Morecraft, **Elliott Ross (Chair**), Jason Barton, Alice O'Toole

16. Panel • Ptarmigan A

New Insights into the Role of Leucine-Rich Repeat Kinase 2 in Parkinson's Disease

Peter Reinhart (Chair), Warren Hirst, Andrew West, William Dauer, Zhenyu Yue

17. Panel • Ptarmigan B

NMNAT and Wallerian Slow Proteins in Neuronal Protection and Repair

Michael Coleman, Grace Zhai, **Hui-Chen Lu (Chair**), Robia Pautler

18. Panel • Ptarmigan C

Excitation or Dysinhibition: Novel Modes of Regulation of Excitability and GABAergic Neurotransmission in Epilepsy

George Richerson, Kai Kaila, **William Catterall (Chair**), Kevin Staley

3:30–4:30 PM

Exhibits and Posters • Bighorn B

4:30–6:30 PM

19. Panel • Bighorn C1

Dopamine and Hippocampal Function: A Neglected Relationship?

Elizabeth Tunbridge (Chair), Paul Harrison, Robert Greene, Yukiori Goto, Daniel Weinberger

20. Panel • Bighorn C2/C3

PDEs in the Brain: What Are They Good For? Apparently Everything!

Frank Menniti (Chair), Arjan Blokland, Gretchen Snyder, Christopher Schmidt

21. Panel • Hasty's

Viral Vectors to Investigate the Mechanisms of Pain and to Produce Analgesia

Luc Jasmin (Chair), Michel Pohl, Andrease Beutler, David Fink, Carolyn Fairbanks

22. Panel • Ptarmigan A

The Fountain of Youth: Is Adolescent Plasticity Part of the Story?

Beatriz Luna, **Kyle Frantz (Chair),** Michela Marinelli, Mary Cain

23. Panel • Ptarmigan B

Neurogenesis and Neurological Disease: Can the Brain Repair Itself?

Henriette van Praag (Chair), Xinyu Zhao, Brian Christie, Kunlin Jin, Paul Lucassen

24. Panel • Ptarmigan C

Calcium Permeable AMPA Receptors in Synaptic Plasticity and Neuronal Death

Suzanne Zukin, Camilla Bellone, Thomas Soderling, **John Isaac (Chair)**

8:30–10:00 PM

25. Panel • Bighorn C1

The Behavioral Genetics of Co-Morbidity: More Than Just Overlapping Phenotypes

Minda Lynch (Chair), Alexander Niculescu, Gregory Miller, Edgardo Falcon, Elissa Chesler

26. Panel • Bighorn C2/C3

GABA Signaling: From Excitatory to Inhibitory. The Roles of Cotransporters, NKCC1 and KCC2, in Brain Development, Seizures and Schizophrenia

Joel Kleinman (Chair), Darwin Berg, Kevin Staley, Eric Delpire, Thomas Hyde

27. Panel • Hasty's

Sensible Neural Prosthetics

Doug Weber (Chair), Arthur Prochazka, Jerry Loeb, John Chapin, Joseph Francis

28. Workshop • Ptarmigan A

One Model Doesn't Fit All—Partial DA Loss and Striatal Function

Marjorie Ariano, Jesus Angulo, Jean-Lud Cadet, **Kristen Keefe (Chair)**

29. Panel • Ptarmigan B

The Pathogenic Role of A-beta Oligomers in the Progression of Alzheimer's Disease

Peter Reinhart (Chair), Dennis Selkoe, William Klein, Charles Glabe, Lennart Mucke

30. Panel • Ptarmigan C

Defining the Line between Pain Relief and Extra-Analgesic Reward

Carolyn Fairbanks (Chair), Lisa Schrot, Carrie Wade, Thomas Martin, James Zadina

Tuesday, January 27

7:30–9:30 AM

31. Panel • Bighorn C1

New Gene Discoveries from Genome-Wide Association Studies: Carving Up the Genetics of Bipolar Disorder and Schizophrenia Phenotypes

John Kelsoe (Chair), Nick Craddock, Michael O'Donovan, Pamela Sklar

32. Panel • Bighorn C2/C3

Understanding How Cocaine Withdrawal May Trigger Relapse

Mehmet Sofuoglu, **Deanne Buffalari (Chair**), Robert Wheeler

33. Panel • Hasty's

Seeing Is Believing? Visual Deprivation-Induced Plasticity

William Guido, Elizabeth Quinlan, Ania Majewska, **Hey-Kyoung Lee (Chair**)

34. Panel • Ptarmigan A

Spinal Cord Injury: Determinants of Degeneration, Regeneration, and Recovery Processes

Kimberly Topp (Chair), Sang Mi Lee, Dale Bredesen, Michael Shifman, Ephron Rosenzweig

35. Panel • Ptarmigan B

GnRH and GnIH: To Reproduce or to Eat!

Mary Ann Ottinger, Harry Jean (Co-Chairs), Yonathan Zohar, George Bentley, Gregory Fraley, Ramesh Ramachandran

36. Panel • Ptarmigan C

Of the Subthalamic Nucleus: How to Use It for Parkinsonism or Addictive Behavior?

Michael Frank, **Christelle Baunez (Chair),** Claire Cannon, Kuei-Yuan Tseng

3:30–4:30 PM

Exhibits and Posters • Bighorn B

4:30–6:30 PM

37. Panel • Bighorn C1

Neuronal Ensembles in the Nucleus Accumbens

Patricio O'Donnell, Cyriel Pennartz, **Bruce Hope (Chair**)

38. Panel • Bighorn C2/C3

Models of Autism and Related Disorders: Molecules, Mechanisms, and Treatment

Luis Parada, Eric Klann, **Craig Powell (Chair),** Edwin Weeber

39. Panel • Hasty's

Vestibular Physiology on Earth and in Space

Richard Boyle, Richard Rabbit, Floris Wuyts, **Larry Young (Chair)**

40. Panel • Ptarmigan A

Steroid Hormones and the Brain: Multiple Mechanisms for Rapid Signaling

Paul Mermelstein, **Jill Becker (Chair),** Paul Micevych, Jeffrey Tasker

41. Panel • Ptarmigan B

Emerging Concepts in Neurotoxicity and Neuroprotection: Zinc, Fatty Acids, AMPA and K^+ Channels, and Metabolism

Nicolas Bazan, Elias Aizenman, Michael Bennett, **Christian Sheline (Chair)**

42. Panel • Ptarmigan C

AKAP Signaling Complexes in Regulation of Neuronal Ion Channels

Mark DellAcqua (Chair), Johannes Hell, William Sather, Todd Scheuer

6:30–8:30 PM

Special Poster Session • Bighorn B

7:00 PM

Town Meeting • Village Square—Ponderosa

Wednesday, January 28

7:30–9:30 AM

43. Panel • Bighorn C1

Phasic Release of Neurotransmitters: What Does Phasic Do to Your Tonic?

Paul Phillips, Martin Sarter, John Bruno, **Greg Gerhardt (Chair)**

44. Panel • Bighorn C2/C3

Neurodevelopment and Neurodegeneration in Neuropsychiatric Disorders: from Genotype to Phenotype

Anil Malhotra (Chair), Christopher Ross, Katherine Karlsgodt, Katherine Burdick

45. Panel • Hasty's

Regulation of GABA-A Receptor Alpha4 Subunits: From Transcription to Membrane Trafficking

Leslie Morrow (Chair), Igor Spigelman, David Werner, Neil Harrison, Patricia Janak

46. Panel • Ptarmigan A

Hypoglycemia and the Brain: The Life, Death, and Specialized Functions of Neurons and Glia That Respond to Glucoprivation

Barry Levin (Chair), Dianne Lattemann, Robert Sherwin, Nicole Sanders, Raymond Swanson

47. Panel • Ptarmigan B

Resveratrol and Other Polyphenols—Are they Worth "Wine-ing" About?

James Joseph (Chair), Donald Ingram, Giulio Pasinetti, Fulton Crews, Tom Kuhn

48. Panel • Ptarmigan C

Synaptic Transmission and Intrinsic Neuronal Properties Underlying Postsynaptic Mechanisms of Plasticity System

Conny Kopp-Scheinpflug, Karl Kandler, **Ian Forsythe (Chair),** Leonard Kaczmarek

3:30–4:30 PM

Exhibits and Posters • Bighorn B

4:30–6:30 PM

49. Panel • Bighorn C1

Neuropeptide Regulation of Behavior

Charles Chavkin, Mitchell Roitman, **Matthew Wanat (Chair),** Gary Aston-Jones

50. Minicourse • Bighorn C2/C3

Frontiers in Genomics and Neurogenetics

Robert Williams (Chair), Robert Hitzemann, Wolfgang Sadee, Abraham Palmer

51. Panel • Hasty's

The Many Faces of Norepinephrine

Elisabeth Van Bockstaele (Chair), Sergey Kalinin, Barry Waterhouse, Patricia Szot, David Morilak

52. Panel • Ptarmigan A

Cognitive Modulation of Sensory Processing

Carl Petersen, Leslie Kay, Marshall Hussain Shuler, **Alfredo Fontanini (Chair)**

53. Panel • Ptarmigan B

Understanding the Role of APP and Cholesterol Metabolism in the Etiology of Alzheimer's Disease

Menelas Pangalos (Chair), Cheryl Wellington, Tobias Hartmann, Liu Qiang, David Riddell

54. Panel • Ptarmigan C

Under Construction: Phospho-Bridges Integrate Dopamine and Glutamate Signaling in the Striatal Cytoskeleton

Gretchen Snyder, Christopher Pierce, David Sibley, **Jacqueline McGinty (Chair)**

6:30–7:30 PM

Business Meeting and Elections • Bighorn C1

Thursday, January 29

7:30–9:30 AM

55. Panel • Bighorn C1

Impulsivity and Psychopathology: From Animal Models to Humans

Pier Vincenzo Piazza, Jill Becker, **Jon-Kar Zubieta (Chair),** Larry Siever

56. Panel • Bighorn C2/C3

Disease Models of Genetic Susceptibility for Complex Brain Disorders

Ron McKay, Francesco Papaleo, Inga Deakin, **Amanda Law (Chair)**

57. Panel • Hasty's

Four Views of Brain Development and Plasticity: From Progenitors to Matrix Molecules

Joel Levine, **William Freed (Chair),** Herbert Geller, James Fawcett

58. Panel • Ptarmigan A

Food for Thought: Adenosine, Metabolism, and Brain Activity

Susan Masino (Chair), Masahito Kawamura, Detlev Boison, Robert Greene, Kelly Drew

59. Panel • Ptarmigan B

Translational Therapeutics: The Quest Progresses

John Sladek (Chair), Krys Bankiewicz, Kimberly Bjustad, Lotta Granholm-Bentley

60. Panel • Ptarmigan C

Structural and Functional Determinants of Synaptic Transmission and Plasticity at Central Synapses

Ora Ohana, **Joachim Lübke (Chair)**, Francesco Ferraguti, Silvio Rizzoli

3:30–4:30 PM

Exhibits and Posters • Bighorn B

4:30–6:30 PM

61. Panel • Bighorn C1

Mesocorticolimbic Processing of Decisions in Health and Mental Disease

Matthew Roesch, **Aaron Gruber (Chair),** Michael Frank, Jonathan Cohen

62. Panel • Bighorn C2/C3

Stop Yawning and "See" What's New at D2

Amy Newman (Chair), Gregory Collins, Bruce Jenkins, Jeffrey Dalley

63. Panel • Hasty's

Circadian Organization of the Retina: Genes, Neuromodulators, and Networks

Gianluca Tosini, Robert Lucas, Douglas McMahon, **Michael Iuvone (Chair)**

64. Minicourse • Ptarmigan A

Novel Strategies for CNS Regeneration and Modern Rehabilitation, *Part 1*

Milos Pekny, Pablo Celnik (Co-chairs), Klas Blomgren, Maurice Curtis, Georg Kuhn

65 Panel • Ptarmigan B

Membrane Protein Trafficking within in Distinct Neuronal Compartments

Michael Tamkun (Chair), Jeffrey Martens, Don Arnold, Jose Esteban

66. Panel • Ptarmigan C

Mechanisms of Neuron-Glia Interaction in Myelination

Elior Peles, Jonah Chan, Matthew Rasband, **Timothy Kennedy (Chair)**

8:30–10:00 PM

67. Panel • Bighorn C1

Making Better Scientists through Chemistry: Norepinephrine, Psychostimulants, and Cognitive Enhancement

Barry Waterhouse (Chair), Kong Fatt Wong-Lin, Jill McGaughy, Kara Agster, Craig Berridge

68. Panel • Bighorn C2/C3

Neurodevelopment of Cognitive Systems: Toward a Specification of Risk Trajectories for Child and Adolescent Mental Disorders

Kathleen Anderson (Chair), Beatriz Luna, Bradley Schlaggar, Bruce McCandliss, Silvia Bunge

69. Panel • Hasty's

Descending Pathways and the Modulation of Pain and Body Functions by Mental States

Hayley Foo, Donna Hammond, **Juan Carlos Marvizon (Chair)**

70. Panel • Ptarmigan A

"Rac"ing Up Dendritic Spines

Thomas Soderling (Chair), Takeo Saneyoshi, Peter Penzes, Scott Soderling, Gary Wayman

71. Minicourse • Ptarmigan B

Novel Strategies for CNS Regeneration and Modern Rehabilitation, *Part 2*

Milos Pekny, Pablo Celnik (Co-chairs), Michael Nilsson, Hubert Dinse, Friedhelm Hummel

72. Workshop • Ptarmigan C

Rural and Global Health: Does Intellectual Property Reduce or Increase the Disparity?

Carol Stratford, Joseph Belanoff, **Phuong Pham (Chair)**

Friday, January 30

7:30–9:30 AM

73. Panel • Bighorn C1

Too Much Excitement? Role of Glutamate Signaling in Relapse to Drug Seeking

Taco De Vries (Chair), Peter Kalivas, Chris Pierce, Marina Wolf, Sabine Spijker

74. Panel • Bighorn C2/C3

Cannabinoids and the Brain: Behavioral Functions of Endocannabinoids in Motivation and Cognition

Ken Mackie, Larry Parsons, **Tommy Pattij (Chair),** Kornelia Kamprath

75. Panel • Hasty's

Trials and Tribulations on the Translational Research Trail

John Steeves, Andrew Blight, **James Fawcett (Chair),** Dan Lammertse

76. Panel • Ptarmigan A

A Look into Long-Term Potentiation of GABAergic Synapses

Melanie Woodin, Freshteh Nugent, **Arianna Maffei (Chair),** Michela Fagiolini

77. Panel • Ptarmigan B

OPRM1 Variation and Reward Sensitivity—Translation across Species and Situation

Christina Barr (Chair), William Copeland, Lara Ray, Annika Thorsell

78. Panel • Ptarmigan C

Molecular Regulators of Presynaptic Vesicle Cycling and Behavior

Maria Bykhovskaia(Chair), Katrin Engisch, Gyorgy Lonart, Craig Powell

4:30–6:30 PM

79. Panel • Bighorn C1

NMDA Receptor Modulation in Health and Disease

Robert Zaczek (Chair), Joseph Coyle, Robert Schwarcz, Richard Bergeron, Robert Greene

80. Panel • Bighorn C2/C3

Clinical Models of Drug Reward and Craving: Tools to Identify Therapeutic Potential in the Treatment of Addiction

Malcolm Reid (Chair), Thomas Newton, John Mendelson, Charles O'Brien

81. Panel • Hasty's

How Would We Perceive the World without Endocannabinoids?

Cecilia Hillard, Thanos Tzounopoulos, David Lovinger, **Kuei-Yuan Tseng (Chair)**

82. Panel • Ptarmigan A

Rolling, Sleeping and Breathing: Serotonin Connection?

George Ricaurte (Chair), James Leiter, George Richerson, Dietrich Richter, Una McCann

83. Panel • Ptarmigan B

Stem Cell-Based Clinical Strategies

Hans Keirstead (Chair), Alan Lewis, Jane Lebkowski, Chris Airriess, Donald Fink

84. Panel • Ptarmigan C

Nanoscale Protein Assembly and the Pathogenesis of Amyloid-Related Neurodegenerative Disease

William Bunney (Chair), Christopher Ross, Judith Frydman, Charles Glabe, Steven Potkin

Poster Session 1

Sunday–Monday • Bighorn B

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. Understanding Resting Neurotransmitter Levels in the CNS: Second-by-Second Measurements Using Microelectrode Arrays

Peter Huettl

P2. Pharmacological Characterization of Plasma Membrane-Expressed Human Trace Amine-Associated Receptor 1 (TAAR1) by a Novel Bioluminescence Resonance Energy Transfer (BRET) cAMP Biosensor

Raul Gainetdinov

P3. Antisocial, Substance Dependent Boys: Hypofunction in a Neural Network for Processing Risky Decisions

Thomas Crowley

P4. Role of NADPH Oxidase in the Pathobiology of Traumatic Brain Injury

Alan Faden

P5. Dopamine D1 and D2 Modulation of Glutamatergic Transmission in Adult Rat Nucleus Accumbens Recorded *In Vitro*

Fred Huppe-Gourgues

P6. Does the H5N1 Influenza Virus Induce Neurodegeneration and the Development of Post-encephalitic Parkinsonism?

Richard Smeyne

P7. Mapping and Identification of GABAergic Neurons That Project to Cardiac Vagal Neurons in the Nucleus Ambiguus Using Photo-Uncaging

David Mendelowitz

P8. Adolescent Seizures and Loss of Dentate Granule Neurons: Neuroinflammation and Neurogenic Capability

Gaylia Jean Harry

P9. Oxidative Stress and Synaptic Decline in Mild Cognitive Impairment

Stephen Scheff

P10. Posiphen and Analogs: Experimental Alzheimer Agents That Reduce Amyloid-beta Peptide by Lowering Amyloid Precursor Protein Levels in Culture and *In Vivo*

Harold Holloway

P11. Distinct AMPA-type Glutamatergic Synapses in Developing Rat CA1 Hippocampus

Elizabeth Stubblefield

P12. Contributions of Hindbrain GLP-1 Receptor Acti… the Control of F…e: Role of the Er… Ligand and Mediation by …everal Intracellular Pathways

Matthew Hayes

P13. An Essential Role for Dopamine in Fear Conditioning

Jonathan Fadok

P14. Tetanus Toxoid Vaccination Induces Acute Spinal Cord Neuroinflammation and Accelerates Onset of ALS-like Disease in hmSOD1 Transgenic Rat Model

Brent Harris

P15. Serotonin Receptors of the Nucleus Accumbens Shell Differentially Affect Feeding in the Rat

Wayne Pratt

P16. Integrated Neurochemical and EEG Measurements in Freely Moving Rodents

Daniel Aillon

P17. Polyinosinic:Polycytidylic Acid Elicits NF-kappa B Activation and IL-6 Production in CNS-derived Cells

Frederick Franken

P18. Organization and Reorganization of Forepaw Barrelettes in Cuneate Nucleus in Juvenile Rats

Robert Waters

P19. Loss of Peptidergic and Nonpeptidergic Intradepidermal Nerve Fibers in an STZ-induced Mouse Model of Insensate Neuropathy

Douglas Wright

P20. Elevated Potassium Associated with Ischemia Produces Neuronal Damage Independent of Calcium Influx into Hippocampal CA1 Cells

Bruce MacIver

P21. The Food Intake Inhibition of Leptin: Amplification of t… Satiating Effects … intestinal Signals … eurons with A… …ase Activity as a Putative Common Signal

Harvey Grill

P22. PKC Regulation of Intraneuronal Zinc Mediates Neuronal Survival during Preconditioning

Mandar Aras

P23. Ultrastructural Investigation of Synaptic Vesicle Pools in *Drosophila melanogaster*

Annette Denker

P24. MR Imaging of Beta-A… …id Plaques and H… …Analysis in Bot… …lzheimer's … and APP/PS1 Transgenic Mice

Qing X Yang

P25. Ephrin-A2 Localization in Primary Somatosensory Cortex during the Early Postnatal Period

Cynthia Kenmuir

P26. Angiogenesis and Exercise-Induced Neuroprotection in the Substantia Nigra of MPTP-Treated Mice

Michelle Smeyne

P27 The Development of Excitatory and Inhibitory Intracortical Circuits in the Reorganized Somatatosensory Cortex of Neonatally Amputated Rats

Richard Lane

P28 Reinstatement of Drug-Seeking Behavior in Adolescent and Adult Male Rats

James Doherty

P29 Effect of Sleep on Working and Long-Term Memory

Katya Potkin

P30 Clinical and Neurocognitive Correlates of Suicidal Behavior in Bipolar I Disorder

Raphael Braga

Poster Session 2

Tuesday–Wednesday • Bighorn B

This is a special session with highest ranked posters by young investigators. A grand prize to the best poster, and first prizes to the best poster in the cellular/developmental, systems/behavioral, and clinical/human studies categories will be awarded. Presenters will be with their posters on Tuesday and Wednesday from 3:30 to 4:30 PM.

P31 Fluorescence Activated Cell Sorting: A Novel Method to Study Neurons Selectively Activated during Context-Specific Cocaine Sensitization

Danielle Guez

P32. Probing Afferent Specific Synaptic Strength and Transmission in the Nucleus Accumbens

Garrett Stuber

P33. Medial Amygdalar Nucleus: A Novel Limbic Hypoglycemia-Sensing Region in the Rodent That Communicates Directly with the Glucose-Sensing Ventromedial Hypothalamic Nucleus

Ligang Zhou

P34. Mapping of Active Inputs on Thalamorecipient Neurons in the Auditory Cortex Revealed a Novel Mechanism of Effectiveness of Thalamocortical Pathways

Stanislav Zakharenko

P35. Daun02 Lesions Neuronal Ensembles That Encode Learned Associations Between Cocaine and Its Administration Environment

Eisuke Koya

P36. Phasic Dopamine Deficiency Impairs Cue-Dependent Learning

Larry Zweifel

P37. Orbitofrontal Cortex Inactivation Impairs Reversal of Pavlovian Learning by Interfering with Disinhibition of Responding for Previously Unrewarded Cues

Kathryn Burke

P38. Risky Decision Making Following Adolescent Alcohol Exposure

Nicholas Nasrallah

P39. Evidence for the Role of Dopamine D3 Receptors in Mediating Methamphetamine Addiction

Amanda Higley

P40. Prior Cocaine Exposure Occludes Potentiation of Basolateral Amygdala-Evoked Responses in Medial Prefrontal and Orbitofrontal Cortices but Not Nucleus Accumbens

Clinton McCracken

P41. Effects of Differential Rearing on Amphetamine-Induced *c-fos* Expression in the Basolateral Amygdala and Nucleus Accumbens

Margaret Gill

P42. Methamphetamine Neurotoxicity and the Ubiquitin Proteasome System

Anna Moszczynska

P43. Role of Phasic Nucleus Accumbens Dopamine in Effort-Related Decision Making

Jeremy Day

P44. Neurons in the vSub Are Activated by Noxious Stimuli and Are Modulated by NE Afferents

Witold Lipski

P45. Changes in Reward-Related Signaling in the Basolateral Amygdala—Attention or Error Signaling?

Donna Calu

P46. Expression Genetics of Neurocognitive Genes

Audrey Papp

P47. Tumorigenicity, Allodynia, Biodistribution, and Toxicity Study of Human Embryonic Stem Cell (hESC) Derived-Motor Neuron Progenitors Following Transplantation into the Spinal Cord in NOD/SCID Mice

Monica Siegenthaler

P48. Dichotomous Dopaminergic Control of Striatal Synaptic Plasticity

Weixing Shen

P49. Tumor Characteristics of Neural Stem Cells

Olle Lindberg

P50. Learning Deficits, Impaired LTP, and Altered Synaptic Excitation-Inhibition Ratio in Mice Over-Expressing Neuroligin 1

Regina Dahlhaus

P51. NG2 Glial Cells Are Targets for Neurovirulent Murine Retroviruses: Implications for Differentiation and Spongiform Neuropathogenesis

Ying Li

P52. Evidence for a Neuromodulatory Role of the Dopamine Metabolite 3-Methoxytyramine

Tatyana Sotnikova

P53. Hypoxia-Ischemia Induces an Endogenous Reparative Response by Local Oligodendrocyte Progenitors in Postnatal Mice

Maria Dizon

P54. A Zn^{2+}-Dependent Dual Phosphorylation Checkpoint in Kv2.1 Regulates the Apoptotic Surge of K^+ Currents

Patrick Redman

P55. Accelerating Spongiform Neurodegeneration: Pushing the Limits Using Neural Stem Cell-Based Brain Chimeras

Sandra Cardona

P56. Genetic Variation in GRM7 Predicts Amygdala and Hippocampal Response to Emotional Stimuli

Kristin Bigos

P57. Mild Cognitive Impairment Gene Expression Profile is Unique from Normal Aging and Alzheimer's Disease

Nicole Berchtold

P58. Methylene-Tetrahydrofolate Reductase A1298C Polymorphism Modulates Brain Function

Fabio Sambataro

P59. Polymorphism in the Fibroblast Growth Factor-20 Gene Modulates Grey Matter Volume in the Medial Temporal Lobe

Herve Lemaitre

P60. A Link between the Systems: Functional Differentiation and Integration within the Human Insula Revealed by Meta-analysis

Florian Kurth

Poster Session 3

Wednesday–Thursday • Bighorn B

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. Why Do So Many Parkinson's Disease Medications Fail?

Peter LeWitt

P62. Endothelin-1 Receptor A Antagonists Improve Neurologic and Cognitive Outcome Following TBI

Christian Kreipke

P63. Surface Accumulation of NR2B-containing NMDA Receptors during Status Epilepticus Increases Both Phasic and Tonic Excitatory Currents

David Naylor

P64. Distributed Representation of Single Touches in Somatosensory and Visual Cortex

Michael Beauchamp

P65. Cerebral Neuronal Calcium Sensor 1 Is Altered After Methylphenidate Exposure in Young and Adult Brain Rats

Renan Pedra Souza

P66. Multiple Treatment Protocols: Optimizing Functional Outcomes for Traumatic Brain-Injured Patients

Jacob VanLandingham

P67. AMPA Receptor Potentiators Differentially Modulate Glutamate Binding Affinity

Hong Yu

P68. Virus-Induced Spongiosis Is Associated with Spontaneous Firing in Specific Neuronal Cell Types

William Lynch

P69. Mesolimbic Dopamine and the Costs of Future Rewards

Jerylin Gan

P70. Environmental Modulation of Haloperidol-Induced Fos Expression in Rat Nucleus Accumbens Following Repeated Drug Administration in a Novel Environment

Sam Golden

P71. The Effects of Selective Cannabinoid Receptor 1 Antagonist in Various Rodent Models of Cognition

Philip Iredale

P72. Precise Dissection of Human Postmortem Brain Tissue and Nucleic Acid Quality

Ross Buerlein

P73. Spatial Uncertainty Associated with Stereotaxic Coordinates of Neuroimaging Results

Simon Eickhoff

P74. Serum Prolactin Gender Difference and Psychopathology in First Episode Non-medicated Schizophrenia

Amresh Shrivastava

P75. Neuroprotective Role of Lithium in Aluminium-Induced Behavioral and Functional Alterations in Rats

Punita Bhalla

P76. Neuroprotective Effect of Piperine on Dopaminergic System Modulation, Behavioral Changes, and Oxidative Stress after Intrastriatal Administration of 6-OHDA for Hemi-Parkinsonian Rat Model

Pallavi Shrivastava

P77. MEG Response Reconstruction via Variational EM Algorithm

Jing Kan

P78. Navigating Drug Development Moguls for Potential Biotechnology Moguls

Eric Harris

Session Abstracts

Panel • Sunday 4:30–6:30 PM • Bighorn C1

1. Regulation of the Dopamine System: Neurodevelopmental Perspectives and Its Impacts on Psychiatric Disorders

Yukiori Goto, Susan Andersen, Patricio O'Donnell, Alain Gratton

The dopamine (DA) system is neurodevelopmentally regulated, and does not fully mature up until adulthood. Disruptions of developmental process in the DA system have been implicated in a number of psychiatric disorders such as schizophrenia and attention deficit/hyperactivity disorders (ADHD). In this session, we will discuss recent findings of the neural mechanisms of the DA system regulation, and how developmental compromises on this regulation may cause abnormalities mimicking pathological conditions of psychiatric disorders in animal models. First, Dr. Andersen will present studies showing dynamic changes within the normal DA system in the juvenile, adolescent, and adult brain, ranging from dopamine innervation patterns, receptor expression, second messenger systems, and behavior. Then, Dr. O'Donnell will talk about the post-pubertal emergence of abnormalities in the prefrontal cortex DA system that could be associated with the pathophysiology of schizophrenia in neurodevelopmental rodent models. Third, Dr. Gratton will talk about his studies showing the impacts of various perinatal anoxia events on development of the mesolimbic and mesocortical DA systems and its potential relation to psychiatric disorders. Finally, Dr. Goto will present the study showing that a neonatal damage on the habenula causes DA-related abnormalities that are consistent with those observed in ADHD.

Panel • Sunday 4:30–6:30 PM • Bighorn C2/C3

2. New Aspects of Dopamine Receptor and Transporter Structure/Function Identified Using Novel Proteomics Approaches

David Sibley, Kim Neve, Christine Wu, Fang Liu

As we move from the era of the genome and into the proteome, critical questions include how are protein interacting networks organized and who are the players involved. Neurotransmitter receptors and transporters are not singular units in the membrane, but rather exist as large macromolecular complexes comprised of multiple interacting proteins. In this panel, we explore interacting

protein networks involving D1 and D2 dopamine receptors (DARs) and the dopamine transporter (DAT). Kim Neve will show that the D2 DAR directly interacts with S100B, a novel Ca2+ binding protein. This interaction is specific for the D2 DAR and is found to occur in striatal neurons where S100B positively regulates D2 DAR-mediated signaling. David Sibley will show that sorting nexin-25 (SNX25) directly interacts with both D1 and D2 DARs. SNX25 increases the cell surface expression of D1/D2 DARs along with a corresponding increase in signaling; however, there is also an accumulation of receptors intracellularly. This suggests that SNX25 modulates receptor trafficking leading to an overall increase in function. Christine Wu will present work characterizing the membrane topology of the DAT using shotgun proteomics. This approach characterizes the topology of integral membrane proteins in their native environment by distinguishing between protease accessible and membrane embedded domains. Finally, Fang Liu will report that D2 DARs directly interact with DATs, enabling recruitment of DATs to the plasma membrane and enhancement of dopamine uptake. Disrupting D2-DAT coupling, using an interfering peptide, results in DAT down-regulation and decreased dopamine uptake, possibly accounting for the hyperactivity of mice injected with the peptide. Interestingly, post-mortem brain tissues of schizophrenics show a decrease in D2-DAT coupling, which may contribute to hyperdopaminergia in some neuropsychiatric disorders.

Panel • Sunday 4:30–6:30 PM • Hasty's

3. Estrogen Receptor Signaling in the Brain: A Trip Down Memory Lane

Nick Brandon, Eniko Kramar, Peter Penzes, Feng Liu, John Morrison

Actions of estrogens are mediated via estrogen receptor ERα and ERβ, both of which are widely expressed in the CNS. Estrogens have long been implicated in influencing memory processes, yet the molecular mechanisms underlying these effects and the roles of the estrogen receptors alpha (ERα) and beta (ERβ) remain unclear. Enikö A. Kramár (UCI) will indicate how estrogen rapidly modifies the spine cytoskeleton. Acute infusions of β-estradiol cause a rapid modest, and reversible increase in the size of field EPSPs and promote theta burst-induced long-term potentiation in hippocampal area CA1. These acute effects on synaptic responses and LTP involve signaling pathways leading to actin polymerization within dendritic spines. Peter Penzes (Northwestern, Chicago) will discuss how estrogen and NMDA receptor signaling mediate novel forms of two-step wiring plasticity in the cortex. He will report that acute estrogen treatment results in a rapid, transient increase in spine density, accompanied by temporary formation of silent synapses through reduced surface-GluR1. Feng Liu (Wyeth, Princeton) will show that the effects of

estrogen on hippocampal synaptic plasticity and memory are mediated through ERβ. Selective ERβ agonists increase key synaptic proteins and induce morphological changes in hippocampal neurons in vivo, enhance LTP and improve performance in hippocampus-dependent memory tasks. Complementing the data from Dr Liu, Nick Brandon (Wyeth, Princeton) will focus on the differential impact of ERα and ERβ activation on AMPA-receptor subunit GluR1 trafficking in primary hippocampal cultures. ERβ activation elevates GluR1 levels at the surface while ERα activation looks to have different effects. The session will conclude with John H. Morrison (Mount Sinai), who will present new insights from studies of young and aged female non-human primates on the interactive effects of aging and estrogen treatment on neuronal architecture and synaptic organization in hippocampus and prefrontal cortex. These data have important implications for the neurobiological basis of cognitive aging and also demonstrate the potential for protection against these age-related synaptic alterations and the related cognitive decline. This session will show the importance of estrogen signaling for memory formation and start to describe recent advances in dissecting out the pathways underlying these effects. This research should have a profound impact on how we consider estrogen-based therapies for diseases with memory deficits.

Panel • Sunday 4:30–6:30 PM • Ptarmigan A

4. Allostatic Dysregulation of Emotions: Is it CRF, the HPA Axis, or Cytokines?

Fulton Crews, George Koob, Friedbert Weiss, Gunter Schumann

George Koob will introduce CRF systems in brain and how they regulate aspects of emotional allostasis. He will focus on the dysregulation of CRF in the extended amygdala during stress and excessive drug taking. Fulton Crews will present findings on the synergistic interaction of ethanol and cytokines on neuropeptide expression and neurogenesis in specific brain regions associated with mood. Both human and rodent studies will be presented. Cytokine regulation of HPA axis and CRF as well as other key neuropeptides could underlie progressive changes in affect and allostasis associated with chronic ethanol consumption. Friedbert Weiss will present studies on CRF-dependent allostatic changes in behavioral models of abuse and dependence. Studies will include an overview of pharmacotherapies that could contribute to reversal of addictive behaviors. Gunter Schumann will present studies investigating stress-induced gene x environment interactions associated with risky alcohol intake and alcohol dependence. Particular emphasis will be placed on HPA-axis genes and circadian rhythm genes. Neurobiological mechanisms underlying the observed associations will be discussed. In total, how these multiple factors interact in the regulation of mood will be discussed.

Panel • Sunday 4:30–6:30 PM • Ptarmigan B

5. Therapeutic Perspectives of Adenosinergic Drugs in the Brain

Felicita Pedata, Susan A. Masino, Michael A. Schwarzschild, Sergi Ferré

Adenosine is a crucial link between metabolism and brain activity. It is a powerful endogenous anticonvulsant, neuroprotective molecule. To date attempts to harness its clinical potential have been thwarted by its short half life, broad receptor distribution, and peripheral side effects. New evidence on the endogenous regulation of adenosine and related purine molecules and their receptors, new techniques which can measure adenosine levels in real time in living tissue, and a battery of genetically modified animals are breathing new insight and life into therapeutic strategies involving adenosine. Adenosine acts on four receptor subtypes: A1, A2A, A2B and A3. Adenosine receptors are now coveted for their therapeutic potential in a variety of neurological conditions such as Parkinson's disease, epilepsy, stroke. First, Susan Masino (Trinity College, Hartford CT) will discuss how increasing the influence of adenosine acting at the A1 receptor subtype is particularly relevant for epilepsy, stroke and traumatic brain injury. Michael Schwarzschild (Harvard Medical School, Charlestown MA) will speak about A2A antagonists that are emerging as promising non-dopaminergic therapeutic candidates for Parkinsons disease (PD). Felicita Pedata (University of Florence, Italy) will discuss evidence that A2A antagonists are therapeutic implements in the treatment of stroke. Sergi Ferrè (National Institute on Drug Abuse, Baltimore MD) will present data showing how psychostimulant effects of caffeine depend on its ability to release the pre- and postsynaptic brakes that adenosine imposes on dopaminergic neurotransmission by acting on different adenosine receptor heteromers.

Panel • Sunday 4:30–6:30 PM • Ptarmigan C

6. Novel Signaling Mechanisms Involved in Ischemic Injury and Ischemic Preconditioning

John Weiss, Elias Aizenman, Claude Shuttleworth, Raymond Swanson

The high metabolic demands of CNS tissue mean that even relatively brief periods of brain ischemia can cause devastating neuronal loss. However, it is notoriously difficult to prevent neuronal death following stroke, and there are currently no treatments in use to protect brain and diminish ischemic neuronal injury in humans. This panel addresses recent insights into ischemic cell death signaling which may highlight new strategies for neuroprotective intervention. A range of in vitro models will be discussed, which are used to examine

aspects of ionic signaling and activation of mitochondrial and extramitochondrial pathways. John Weiss (University of California, Irvine), will provide an overview of subcellular mechanisms of ischemic neuronal injury, and will describe ionic and mitochondrial changes during acute phases of simulated ischemia (slice oxygen glucose deprivation) and their relationship to cell death. Elias Aizenman (University of Pittsburgh) will then describe in vitro studies of mechanisms of ischemic preconditioning, the phenomenon whereby sublethal ischemia greatly reduce cell death following subsequent ischemic insults. Bill Shuttleworth (University of New Mexico) will present data on novel mechanisms underlying spreading depression, profound waves of depolarization that are linked to the enlargement and extension of ischemic infarcts. Finally, Ray Swanson (University of California, San Francisco) will describe new signaling pathways leading to activation of microglia after ischemia, a mechanism that is strongly implicated in the evolution of injury.

Panel • Sunday 8:30–10:00 PM • Bighorn C1

7. Risky Research: Advances in Understanding the Drive to Gamble from both Clinical and Preclinical Perspectives

Catharine Winstanley, Marc Potenza, Robert Rogers, Christopher Olsen

Opportunities to gamble are increasing in number, variety and popularity. However, for some, gambling is more than an entertaining pastime. The growth of the gambling industry is associated with an increase in problem and pathological gambling, yet treatment options are limited and not empirically validated. This panel will highlight the progress being made in understanding the neurobiological basis of gambling and the impact of such research on treatment interventions. Dr. Potenza will discuss neuroimaging experiments and genetic investigations examining pathological gambling and theoretically related disorders (e.g. substance abuse). Findings suggest similar involvements of fronto-striatal circuits across disorders. Dr. Rogers will discuss the brain systems underpinning the cognitive and behavioral biases central to problem gambling, such as the continual engagement in gambling to recover losses ("loss-chasing"). Both presentations will highlight how such research can stimulate the development of hypothesis-driven treatments, and might explain individual differences in the response to therapy. Dr. Winstanley will consider the issues involved in modeling recreational and pathological gambling in

animals, and why such models could be useful. Experiments investigating the role of serotonin in gambling using a rodent loss-chasing paradigm and a rodent version of the Iowa Gambling Task will be discussed. Dr. Olsen will present data on operant sensation-seeking, whereby mice "self-administer" varied visual stimuli. This phenomenon resembles aspects of drug self-administration, and demonstrates the importance of sensation-seeking in the addictive-like aspects of gambling. Collectively, these presentations illustrate how synergy between clinical and preclinical research is improving our understanding of gambling disorders and their treatment.

Panel • Sunday 8:30–10:00 PM • Bighorn C2/C3

8. Androgens and the Brain: New Functions for an Old Hormone

Robert Handa, Kathie Olsen, Joseph Nunez, Rae Silver

Throughout life, our brains are constantly bathed in a milieu rich with sex steroid hormones. The brain not only responds to hormones made peripherally, but it also possesses the ability to synthesize these same hormones de novo. Given the distribution of steroid hormone receptors in the brain, it is apparent that estrogen and testosterone can modulate all facets of brain function, and from birth through senescence, and should no longer be regarded as simply hormones of reproduction. This panel will address and discuss a number of novel roles for testosterone and its metabolites in the control of brain function. First, Kathie Olsen (National Science Foundation) will provide a perspective for research on the neural effects of androgens and androgen receptors, brain loci mediating some of androgens unique actions and animal models that are useful to study this hormone's functions. Joseph Nunez (Michigan State University) will present exciting new evidence that androgens and androgen receptor activation are critical mediators of normal hippocampal development and can act to influence the sensitivity of the developing brain to excitotoxicity. Rae Silver (Columbia University) will present and discuss interesting new findings that androgens can act on their receptors located in specific compartments of the brain's internal clock, the suprachiasmatic nucleus of the hypothalamus, to control basic circadian regulated physiology and behaviors. Bob Handa (University of Arizona) will discuss brain mechanisms that underlie the recent observations that androgens and androgen metabolites can regulate stress reactivity, anxiety, depressive-like behaviors and cognitive function.

Panel • Sunday 8:30–10:00 PM • Hasty's

9. Subcellular Receptor Interactions in Analgesia and Tolerance

George Wilcox, Aaron Overland, Catherine Cahill, Dennis Paul, Lakshmi Devi

Recent decades have delineated the signaling cascades invoked by the activation of monomeric GPCRs, but few studies have investigated receptor-receptor interactions in detail. This panel explores several mechanisms of on a subcellular receptor interactions producing synergistic drug effects, which promise enhanced efficacy and reduced side effects. Some synergistic interactions appear to be restricted to single subcellular compartments, for example primary afferent terminals. Four receptors co-localize in nociceptive terminals: alpha2-adrenergic (AR), delta-opioid (DOR), mu-opioid (MOR) and 5HT3-serotonergic. Synergy among these receptors contributes importantly to spinal analgesia particularly in chronic pain states. Changes in receptor trafficking from intracellular compartments to plasma membrane may account for increased functional competence, including formation of heteromeric complexes contributing to synergism. Overland will present anatomical and functional data showing that alpha2-AR and DOR co-localize in peptidergic terminals and synergize ~100-fold in reducing neuropeptide release and producing analgesia. Surprisingly, this synergism is dependent on PKC activation. Paul will show that co-administration of 5HT3 agonists with the alpha2-AR/DOR combination further enhances this synergy (1000-fold synergy) and evidence that divalent cations conducted by 5HT3-receptors mediate this synergy. Cahill will present data suggesting that DORs targeted to sensory neuron plasma membranes following peripheral nerve injury correlates with the pharmacology of opioid receptor hetero-oligmers. Devi will present data indicating MORs and DORs dimerize and that chronic morphine treatment increases expression of MOR-DOR heterodimers in sensory neurons. Surprisingly, this up-regulation of heterodimer expression on plasma membranes contributes to the manifestation of opioid analgesic tolerance.

Panel • Sunday 8:30–10:00 PM • Ptarmigan A

10. Oxidative Stress as a Target for Treatment of Neurovascular and Traumatic CNS Disorders: Why Hasn't This Worked?

Jaroslaw Aronowski, Gregory del Zoppo, Dale Pelligrino, Edward Hall

Recent experience with the free radical trapping agent, NXY-059, showing no effect vs placebo in patients with acute ischemic stroke raised question about the validity of anti-free radical therapy as treatment for cerebral ischemia and

possibly other neurological disorders namely intracerebral hemorrhage and spinal cord injury. During this panel discussion, we will attempt to reconcile past experience with anti-free radical strategies and also attempt to discuss where the field is going now, and what the future directions are? Gregory del Zoppo will discuss the role(s) of free radical generation in the early development of the ischemic lesion and its subsequent maturation in ischemic stroke, and the relationship of pre-clinical intervention studies to the two major clinical intervention trials of free-radical quenchers/scavengers in ischemic stroke. The possible reasons for the failure of translation from pathobiological observation to clinical outcome in this setting will be examined. Dale Pelligrino will present the work on RAGE (receptor for advanced glycation endproducts) and its contribution to neutrophil infiltration and oxidative stress. RAGE, a multiligand receptor that is activated by glycated proteins seen in aging and diabetes, and s100-B, HMGB1, and Mac-1. RAGE has been linked to ischemic and Alzheimer-associated brain damage. Ed Hall will examine the major role of the reactive nitrogen species peroxynitrite in traumatic spinal cord and brain injury, its interaction with other secondary injury factors and the relative benefits of single vs. multiple pharmacological approaches for inhibition of post-injury neurovascular oxidative damage. Jaroslaw Aronowski will discuss the role of transcription factors PPAR-gamma and Nrf2, two master regulators of expression of numerous anti-oxidative enzymes such as catalase, superoxide dismutase or heme oxygenase-1 and their potentials as target for therapies for ischemic stroke and in intracerebral hemorrhage.

Panel • Sunday 8:30–10:00 PM • Ptarmigan B

11. Parkinson Disease: Genetic Influences on Organelle Function and Dysfunction

Anurag Tandon, David Park, Angus McQuibban, Philipp Kahle, Haung Yu

It is increasingly apparent that pathophysiological mechanisms in Parkinson disease (PD) involve communication and interactions between multiple subcellular organelles. Mutations in 7 genes are known to account for 2-3% of all cases of PD, and the clinical manifestations of familial and idiopathic PD are often indistinguishable. The proteins encoded by these PD genes are alpha-synuclein (synaptic vesicles), parkin and LRRK2 (cytoplasm), and DJ-1 and Pink1 (mitochondria). Recently, the involvement of two lysosomal proteins (ATP13A2 and beta-glucocerebrosidase) in levodopa-responsive Parkinsonism was also reported. The panelists will discuss the relationships between the affected gene products that are normally expressed in very diverse subcellular compartments, yet induce overlapping pathology that includes Lewy bodies and the degeneration of dopaminergic neurons. While the organelle association of each PD protein offers some clues to its function, our understanding of the

biochemical pathways which all converge upon alpha-synuclein accumulation are poorly understood. Anurag Tandon (U Toronto) will give brief overview on the relevant PD genes and the affected organelles. Next, David Park (U Ottawa) will link mitochondrial stress and DJ-1 function to cell death pathways. Angus McQuibban (U Toronto) will discuss the protective role of Pink1 and its proteolytic processing in maintaining normal mitochondrial function. Philipp Kahle (U Tubingen) will describe the role of parkin, which acts downstream of Pink1, and the ubiquitin-proteasome system in clearing oxidation-modified proteins. Finally, Haung Yu (Columbia U) will present some recent work on the role of lysosome-mediated autophagy in PD and how ATP13A2 and beta-GBA might be involved.

Panel • Sunday 8:30–10:00 PM • Ptarmigan C

12. Translational Opportunities in Epilepsy: Tales of Transporters and Tangles

Thomas Sutula, Kevin Staley, Frances Jensen, Jeff Noebels

Epilepsy is caused by diverse molecular, cellular, and systems alterations, and repeated seizures induce alterations at every level of brain organization from transcription to higher cognitive functions. With this rich diversity of cellular alterations contributing to both the development and consequences of epilepsy, investigation of epilepsy in experimental models offers translational opportunities potentially relevant not only for epilepsy, but for other CNS disorders sharing similar molecular and pathological processes. One translational strategy commonly employed in epilepsy research is to investigate how a given molecular or cellular system which plays a role in normal function may contribute to epileptic phenomena in neural circuitry. If involved in epiletogenesis, therapeutic targeting of this system can potentially provide new treatment possibilities for epilepsy. A second translational strategy is to investigate whether epileptic phenomena are observed in association with mutations or models linked to other CNS diseases. If accompanied by epileptic activity, anticonvulsant treatment of these mutations or models may offer new therapeutic possibilities. This panel discussion will provide examples of how these strategies may yield promising translational opportunities. Tom Sutula, Kevin Staley, and Frances Jensen will provide examples of how members of the ubiquitous family of electroneutral ion co-transporters, specifically NKCC1 and KCC2, contribute to alterations in [Cl-]i that have important functional consequences on GABAa inhibition and are now leading to clinical trials of the co-transporter blocker

bumetanide as an anticonvulsant. Jeff Noebels will present studies in a mutant mouse overexpressing beta-amyloid that develops tangles and plaques and prominently demonstrates epileptic network activity, suggesting that anticonvulsant treatment might provide therapeutic opportunities to improve cognitive function. The discussion will critically examine the possibility that anticonvulsants may be therapeutically useful in a variety of CNS disorders.

Panel • Monday 7:30–9:30 AM • Bighorn C1

13. VTA Dopamine Neuron Heterogeneity: Can It Help Us Understand Addiction and Other Psychiatric Disorders?

Susan Volman, Elyssa Margolis, Stephan Lammel, Gary Aston-Jones, Wenlin Sun

Dopamine neurons in the ventral tegmental area have been implicated in a bewildering variety of normal brain function and psychiatric disorders. Recent research has shown that subpopulations of dopamine neurons in the VTA that project to different target differ in their electrophysiological properties, their complement of ligand- and voltage-gated ion channels, their release properties, and other characteristics. These findings have the potential for high impact in research on drug abuse and other psychiatric disorders both conceptually and because they are leading to new research approaches for pharmacological manipulation of separate pathways. Elyssa Margolis (Gallo Research Center) will show how subpopulations of DA neurons that project to n. accumbens, prefrontal cortex, and the amygdala differ in their electrophysiological and pharmacological properties, and revisit the question of whether there is an electrophysiological marker for DA neurons. Stephan Lammel (Stanford University) will describe the unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system and discuss the functional implications of this heterogeneity for understanding DA function in health and disease. Gary Aston-Jones (Medical University of South Carolina) will talk about the differential innervation of DA neurons by orexin neurons in the hypothalamus and discuss their function in arousal and motivational processes. And Wenlin Sun (University of Tennessee) will demonstrate how he has exploited the distinct properties of mesocortical DA neurons to investigate neural circuits involved in cue-induced relapse to drug seeking behavior.

Panel • Monday 7:30–9:30 AM • Bighorn C2/C3

14. DISCo Dancing: Genetic and Molecular Interactions in the DISC1 Pathway and the Risk for Schizophrenia

Nick Brandon, David Porteous, Katherine Burdick, Barbara Lipska

Since the discovery of DISC1, multiple genetic studies have supported a role for DISC1 in schizophrenia, bipolar disorder and major depression. There has however been little consensus as to the specific functional variants operative, although recent evidence points to allelic interplay and allelic heterogeneity. Genetic evidence has also emerged for several DISC1 protein interactors, being independent or co-dependent genetic risk factors. The biology of DISC1 and DISC1 interactors, and the phenotypes of Disc1 transgenic mouse mutants paint a compelling picture of DISC1 as a hub around which key processes including neuronal migration and integration, synaptic function and cAMP regulation are organised and which collectively impact on brain function to precipitate major mental illness. Nick Brandon will introduce DISC1 as a hub protein with multiple neurodevelopmental functions and binding partners with a focus on synaptic DISC1, and show that Ndel1 is critical for neuritogenesis and affected by interactions with DISC1. David Porteous will present data on the complex genetics and neurobiology of DISC1 and PDE4. Kate Burdick will present data suggesting that genetic interactions among binding partners, including NDEL1 and NDE1, influence risk for schizophrenia and are validated by biological evidence of competitive binding at the protein level. Barbara Lipska will present novel DISC1 splice variants identified in human brain and lymphoblasts, presumably encoding truncated DISC1 proteins, and show that they are expressed at higher levels in patients with schizophrenia and in subjects with risk-associated genetic variations. This panel will attempt to elucidate molecular mechanisms of genetic risk associated with DISC1.

Panel • Monday 7:30–9:30 AM • Hasty's

15. Facial Processing—What Is New and Different?

Elliott Ross, Robert Morecraft, Jason Barton, Alice O'Toole

The face is a crucial region for psychosocial interactions that has specialized and multiple representations in the brain. The panel will explore new data and concepts concerning the anatomical and functional aspects of face motor control and perceptual processing in primates and humans. Morecraft will summarize the different cortical areas controlling facial movement in monkey, emphasizing

differences between corticofugal projections to the facial nuclei from the lateral and medial hemisphere and the unique patterns of corticocortical and amygdalocortical inputs to the various facial motor areas. These observations will be related to clinical deficits in facial expression following medial versus lateral cortical injury. Ross will present complimentary behavioral research in humans suggesting that human facial expressions and their perception are organized predominantly across the upper-lower rather than the (traditional) right-left facial axis and relate the research to the concept that primary and social emotions are differentially lateralized in brain. Barton will discuss current and classic models proposing that there are divergent perceptual processing streams for extracting information about facial identity versus expressions. Using a variety of techniques, including behavioral adaptation, fMRI and human lesion studies, he will show that the relationship between these two types of face processing is more complex than currently envisaged. OToole will present research that explores how the brain recognizes faces under suboptimal conditions. For facial recognition to be useful, neural representations must operate robustly over changes in three-dimensional viewpoint. She will present fMRI experiments examining the neural codes for view-invariant face recognition and face-invariant view recognition.

Panel • Monday 7:30–9:30 AM • Ptarmigan A

16. New Insights into the Role of Leucine-Rich Repeat Kinase 2 in Parkinson's Disease

Peter Reinhart, Warren Hirst, Andrew West, William Dauer, Zhenyu Yue

Parkinson's Disease (PD) is the second most common neurodegenerative disease affecting an estimated 6 million people worldwide, and for which there is no disease-modifying treatment. Mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene cause late-onset PD clinically and pathologically indistinguishable from sporadic cases. The most prevalent mutation in LRRK2, G2019S, increases the kinase activity of LRRK2 and enhances neurotoxicity suggesting that LRRK2's kinase activity plays a key role in PD susceptibility. However, the physiological substrates of LRRK2 and its regulation in cells remain undescribed. The LRRK2 gene encodes a large, multi-domain protein. In addition to the kinase domain that harbors most common PD-linked mutations, there is a GTPase domain that regulates kinase activity, and two protein-protein interaction domains. Peter Reinhart will provide an overview of the panel which is focused on new data on the enzymological, cellular and physiological roles of LRRK2, making it an interesting target for developing novel therapeutics to treat PD. Warren Hirst will describe the enzymological characterization of LRRK2, identification of the phosphorylation motif and

novel substrates and the development of high throughput assays that will allow for the rapid identification of LRRK2 inhibitors. Andy West will present data on LRRK2 quaternary structure that may underlie kinase activity regulation and interactions with protein kinase substrates. Bill Dauer will discuss LRRK2 signaling in relation to the extrinsic cell death machinery, specifically FADD and caspase-8. Finally, Zhenyu Yue will present on the development and characterization of novel transgenic models (BAC-mediated) expressing LRRK2. Overall, this panel will provide an update on our understanding of LRRK2.

Panel • Monday 7:30–9:30 AM • Ptarmigan B

17. NMNAT and Wallerian Slow Proteins in Neuronal Protection and Repair

Hui-Chen Lu, Michael Coleman, Grace Zhai, Robia Pautler

Neurodegeneration can be triggered by a variety of genetic, epigenetic, or environmental factors. Despite the differences in cause or age at onset, many human neurodegenerative disorders share similar pathological manifestations, such as neuronal loss, memory loss, and cognitive deficits. Wallerian Slow (WldS) mice, a spontaneous mutant mouse strain, exhibit much delayed neurodegeneration compared to wild type mice upon injury or in other neurodegenerative conditions. The protective effects occurring in these mice are attributed to a chimeric gene, Ube4b/Nmnat (WldS), which contains the entire coding region of nicotinamide mononucleotide adenylytransferase (nmnat), leading to increased NMNAT expression. Drosophila contains only one nmnat gene, whose over-expression delays axonal degeneration protects neurons in diverse neurodegenerative conditions, including injury induced nerve degeneration and a Drosophila model of spinocerebellar ataxia type 1 (SCA1). In this panel we will discuss the therapeutic potential of WldS and NMNATs to delay neurodegeneration in various neurodegenerative models and discuss the mechanisms underlying the protection afforded by these proteins. Dr. Michael Coleman, from Univ. of Cambridge will introduce the literature on WldS, and discuss the potential neuroprotective mechanism of WldS on axon degenerations in mammalian peripheral nerves. Dr. Grace Zhai from Univ. of Miami will report on the role of NMNAT in the maintenance of in neural connections with loss-of-function studies and discuss how the chaperone activity of NMNAT proteins may protect neurons against various insults. Dr. Hui-Chen Lu, Baylor College of Medicine, will talk about the therapeutic effect of the over-expression of WldS in preventing the neuronal loss in Tau mice, an animal model of Alzheimer's. Dr. Robia Pautler from Baylor will report on in vivo MRI studies that allow for

precise quantitation of NMNAT's role in neuronal protection and repair. In addition to the detail anatomical analysis, physiological changes detected with molecular MRI will also be presented. These four talks will provide a thorough overview of our current understanding of the actions and the therapeutic potential of WldS and NMNATs in models of neurodegeneration.

Panel • Monday 7:30–9:30 AM • Ptarmigan C

18. Excitation or Dysinhibition: Novel Modes of Regulation of Excitability and GABAergic Neurotransmission in Epilepsy

William A. Catterall, George Richerson, Kai Kaila, Kevin Staley

Mutations in sodium channels and GABA receptors cause inherited forms of epilepsy, and alterations in excitability and GABAergic neurotransmission likely contribute to more common non-genetic forms of this complex disease. This panel will consider novel forms of GABAergic neurotransmission and modulation of cellular excitability that may contribute to epilepsy. Catterall will introduce the program. Richerson will present his recent work showing that reversal of GABA transporters provides both tonic and phasic components of GABA release and inhibitory transmission, impinging on extrasynaptic GABA receptors in postsynaptic neurons. Inhibitory GABAergic neurotransmission depends crucially on chloride transport and homeostasis. Kaila will present his work on regulation of chloride transport by the potassium-chloride co-transporter KCC2 and its role in temporal lobe epilepsy. Effective inhibitory GABAergic neurotransmission also depends on generation of trains of action potentials in inhibitory neurons that drive phasic GABA release. Catterall will present studies of a mouse model of severe myoclonic epilepsy of infancy showing that loss-of-function mutations of the Nav1.1 channel specifically impair action potential generation in GABAergic inhibitory neurons and thereby cause thermally induced seizures, epilepsy, and co-morbidities such as ataxia. Inhomogeneous loss of sodium-dependent action potentials and resulting glutamate release can cause hyperexcitability in excitatory neurons. Staley will present work showing that phasic depression of glutamate release leads to burst firing in hippocampal CA3 neurons, and he will discuss experimental and computational models of loss of sodium channel function, with an emphasis on the implications for network activity. A general discussion will conclude the session.

Panel • Monday 4:30–6:30 PM • Bighorn C1

19. Dopamine and Hippocampal Function: A Neglected Relationship?

Elizabeth Tunbridge, Paul Harrison, Yukiori Goto, Daniel Weinberger

The hippocampus is a critical structure for memory and anxiety behaviours, and a key site of dysfunction in schizophrenia. Abnormalities in dopaminergic signalling are also strongly implicated in schizophrenia and, whilst much is known of the role of dopamine in prefrontal cortex, its importance in the hippocampus remains relatively neglected. This panel will review recent progress in our understanding of the interactions between dopaminergic signalling and hippocampal function. Paul Harrison will give an overview of the dopaminergic innervation of the hippocampal formation, its implications for hippocampal function, and its alterations in schizophrenia. Robby Greene will then present recent data demonstrating D1/D5-mediated long-term potentiation of AMPA-mediated field potentials of the Schaffer collaterals, which is independent of stimulated neural activity. He will also discuss the potential mechanisms underlying this effect. Yukiori Goto will discuss evidence for hippocampal modulation of dopamine systems. Danny Weinberger will conclude the panel by showing that polymorphisms in dopaminergic genes are associated with activation differences in the hippocampus during fMRI paradigms. Thus these presentations will highlight the importance of reciprocal interactions between the hippocampus and the dopaminergic systems at the molecular, cellular and systems levels, and will discuss the relevance of these findings for schizophrenia.

Panel • Monday 4:30–6:30 PM • Bighorn C2/C3

20. PDEs in the Brain: What Are They Good For? Apparently, Everything!

Frank Menniti, Diego Golombek, Arjan Blokland, Gretchen Snyder, Christopher Schmidt

During the last decade neuroscientists have become increasingly interested in phosphodiesterases (PDEs) as regulators of cyclic nucleotide signaling. Molecular studies have elucidated 11 PDE families encoded by 21 genes transcribed into more than 60 functionally unique enzymes. Not surprisingly, the brain, as a signaling organ, contains the highest and most complex expression pattern of these enzymes in the body. This session will focus on our growing understanding of the functions of these enzymes in regulating information processing in the brain. Frank Menniti (Pfizer Inc.) will give a brief overview of the physiology and regulation of the PDEs. Presentations will focus on the roles of specific PDEs in brain function deduced by studying the effects of selective inhibitors.

He will also describe the involvement of PDE5 in regulating the entrainment of the circadian clock. Arjan Blokland (Univ Maastricht) will present data showing that different PDEs (type 2, 4 and 5) are differently involved in memory consolidation, via LTP-related and a novel non-LTP-related mechanism. Gretchen Snyder (Intra-Cellular Therapies) will discuss the role of PDE1 in striatal motor function and its potential role in dopamine signaling and neurotransmission. Finally, Christopher Schmidt (Pfizer, Groton) will present data on the role of PDE10A in the regulating striatal function pertaining to the treatment of schizophrenia. These presentations illustrate the diversity of involvement of PDE-regulated cyclic nucleotide signaling in information processing in the brain, and the tremendous therapeutic potential of targeting this class of enzymes for the treatment of neuropsychiatric diseases.

Panel • Monday 4:30–6:30 PM • Hasty's

21. Viral Vectors to Investigate the Mechanisms of Pain and to Produce Analgesia

Luc Jasmin, Michel Pohl, Andreas Beutler, David Fink, Carolyn Fairbanks

Dr. Pohl has developed strategies based on local intraspinal delivery of lentiviral-derived vectors driving targeted expression of endogenous regulatory proteins or interfering shRNA in spinal glial cells. Aiming on a selective modulation of the activity of various signal transduction pathways in glial cells, these approaches allow in vivo exploration of their role in the modification of glial cell activity and their participation in pathological pain development. Intrathecal gene therapy is attractive for chronic pain because of its potential for spinal targeting and the ease of performing lumbar punctures clinically. Dr. Beutler has developed effective intrathecal gene transfer to the primary sensory neurons using self-complementary rAAV8. A single administration of vectors expressing either pre-pro-b-endorphin or interleukin-10 controlled chronic neuropathic pain in rats for ≥3 mo. Drs. Fink and Mata show that local release of a soluble truncated form of the p55 TNF receptor in spinal cord, achieved by inoculation of a nonreplicating HSV vector expressing the truncated p55 TNF receptor, results in a reduction in spinal membrane-associated TNF and concomitant reductions in interleukin-1beta and phosphorylated p38 MAP kinase that correlate with reductions in mechanical post nerve injury allodynia and thermal hyperalgesia. These results suggest a novel "reverse signaling" mechanism through glial mTNF which may be exploited to down-regulate the neuroimmune reaction and to reduce neuropathic pain. Dr. Fairbanks's group has achieved substantial spinal cord and DRG transduction of the marker green GFP by direct lumbar puncture injection of AAV5 in mouse and rat. She will describe optimization of delivery to the spinal cord and DRG and characterize the distribution of the AAV5-GFP construct throughout the CNS.

Panel • Monday 4:30–6:30 PM • Ptarmigan A

22. The Fountain of Youth: Is Adolescent Plasticity Part of the Story?

Kyle Frantz, Beatriz Luna, Michela Marinelli, Mary Cain

Adolescence is a developmental stage known for heightened novelty-seeking and risk-taking across multiple species. In humans, recreational drug use might exemplify the new and exciting experiences sought by adolescents, and teenagers are often labeled as highly "vulnerable" to drug abuse. However, recent reports reveal less robust drug effects in adolescent compared with adult subjects. These outcomes are not surprising if adolescence is considered as a transitional phase characterized by ongoing neural plasticity, some of which could confer resistance, rather than vulnerability, to drug effects. Panelists in this session will explore clinical studies and animal models of reward-processing in adolescence, as well as the maturation of relevant brain regions and the impact of environmental enrichment on brain and behavior. Dr. Bea Luna (University of Pittsburgh) will present studies examining brain system immaturities in reward-processing and their effects on cognition, using oculomotor tasks, fMRI, and DTI. Dr. Kyle Frantz (Georgia State University) will review animal models of reward and reinforcement, with focus on adolescent resistance to acute and long-term drug effects. Dr. Micky Marinelli (Rosalind Franklin University) will consider developmental changes in cellular and molecular activity of mesocorticolimbic circuits in rats, and their dependence on social environments. Dr. Mary Cain (Kansas State University) will discuss potential palliative effects of environmental enrichment during adolescence, in terms of reducing drug-related behaviors via changes in neural substrates. Collectively, these presentations and facilitated discussion with attendees will consider evidence that ongoing developmental plasticity during adolescence results in resistance to some drug effects.

Panel • Monday 4:30–6:30 PM • Ptarmigan B

23. Neurogenesis and Neurological Disease: Can the Brain Repair Itself?

Henriette van Praag, Xinyu Zhao, Brian Christie, Kunlin Jin, Paul Lucassen

Forty years ago it was discovered that the adult brain can generate new neurons. Subsequent research showed that neurogenesis can be regulated by both intrinsic genetic and epigenetic programs, as well as by extrinsic environmental factors. The functional significance of neurogenesis remains unclear. However,

there is evidence that the new cells may be important for learning, mood and brain repair in disease or injury. This panel will review the role of newborn neurons in neurological disorders. Alterations in neurogenesis have been implicated in conditions that manifest during postnatal brain development such as Fragile X Syndrome and Fetal Alcohol Syndrome, as well as aging associated neurodegenerative disorders such as stroke and Alzheimer's Disease. In particular, changes in the molecular mechanisms underlying cell genesis and alterations in new cell morphology associated with these conditions will be presented. Xinyu Zhao will discuss how adult neurogenesis is affected by Fragile X mental retardation protein (Fmrp), an RNA binding protein that regulates protein translation, in Frmp deficient mice and in neural stem cells. Brian Christie will examine the detrimental effects of prenatal alcohol exposure on hippocampal cell proliferation and synaptic plasticity in the mature brain, and strategies that may ameliorate these deficits. Kunlin Jin will discuss the functional significance of neurogenesis in animal models of ischemic stroke and in patients with stroke. Paul Lucassen will discuss adult neurogenesis in relation to stress and dementia and present data on neurogenic changes in human brain material of Alzheimer's patients and related animal models.

Panel • Monday 4:30–6:30 PM • Ptarmigan C

24. Calcium-Permeable AMPA Receptors in Synaptic Plasticity and Neuronal Death

John Isaac, Suzanne Zukin, Camilla Bellone, Thomas Soderling

The objective of the symposium is to highlight recent developments in the area of Ca2+-permeable AMPARs in synaptic plasticity and neuronal death. AMPARs mediate fast synaptic transmission at excitatory synapses and are critical to neuronal development, synaptic plasticity and structural remodeling. AMPARs lacking the GluR2 subunit are permeable to Ca2+. Ca2+ permeation through AMPARs is crucial to several forms of synaptic plasticity and neurodegeneration. Exciting new research shows that AMPAR subunit composition and Ca2+ permeability are not static, but are dynamically remodeled during development and in response to neuronal activity, sensory experience and insults. These changes arise not only due to regulated GluR2 expression, but also RNA editing, receptor trafficking and dendritic protein synthesis. Isaac will present findings that AMPAR GluR2 content at CA1 synapses is regulated during long-term potentiation (LTP) and is dependent upon PICK1. Luscher will present evidence that cocaine promotes synaptic insertion of GluR2-lacking AMPARs at synapses on dopamine neurons of VTA, altering network activity. Zukin will discuss findings that neuronal activity/insults promote epigenetic remodeling

of AMPAR phenotype at CA1 synapses and that aberrant Ca2+ flux through GluR2-lacking AMPARs elicits cell death. Soderling will discuss recent work on the role of CaM kinases and the regulation of GluR2-lacking AMPARs in the expression of hippocampal LTP.

Panel • Monday 8:30–10:00 PM • Bighorn C1

25. The Behavioral Genetics of Co-morbidity: More Than Just Overlapping Phenotypes

Minda Lynch, Alexander Niculescu, Gregory Miller, Edgardo Falcon, Elissa Chesler

The etiology of co-morbidity is complex and may involve self-medication for psychiatric symptoms, common neurobiological substrates, or psychiatric vulnerability unleashed by substance abuse. Using behavioral genetics, researchers have identified gene variants that suggest similar neurobiological mechanisms in these co-morbid disorders. Mutations that express phenotypes with characteristics of both addiction and other psychiatric diseases suggest that common neuropathological mechanisms, under genetic control, give rise to diagnostic entities with overlapping features that can be characterized along dimensions of abnormal behavior. In this session, Alexander Niculescu (Indiana University School of Medicine) will present findings from behavioral, genomic, biomarker and treatment studies that have contributed to the development of an animal model for bipolar disorder and co-morbid substance abuse. Gregory Miller (Harvard Medical School) will discuss how rhesus monkeys can serve as a highly translational research model for studying the genetics that underlie co-morbidity of addiction and other mental health disorders and present new data on genotype/phenotype modeling of serotonin transporter (SERT) and tryptophan hydroxylase 2 (TPH2) polymorphisms associated with cognitive flexibility and addictive behavior. Edgardo Falcon, a graduate student with Colleen McClung (UT Southwestern Medical Center), will present findings on the unique role of circadian genes in the regulation of the dopaminergic reward circuit, mood disorders and co-morbid drug addiction. Lastly, Elissa Chesler (University of Tennessee College of Medicine) will present a multi-dimensional analysis of drug abuse susceptibility phenotypes and co-morbidities from a large-scale systems genetic analysis in a mouse genetic reference population.

Panel • Monday 8:30–10:00 PM • Bighorn C2/C3

26. GABA Signaling: From Excitatory to Inhibitory (The Roles of Cotransporters, NKCC1, and KCC2 in Brain Development, Seizures, and Schizophrenia)

Joel Kleinman, Darwin Berg, Kevin Staley, Eric Delpire, Thomas Hyde

Although GABA is a major inhibitory neurotransmitter in the brain, early in development its action on GABA receptors is excitatory. The switch from an excitatory to an inhibitory response is determined by the relative protein levels of two cotransporters, NKCC1 and KCC2. This panel will cover when and how this switch occurs as well as its implications for brain development and risk for seizure disorders and schizophrenia. Darwin Berg will present how nicotinic innervation helps drive the conversion of GABAergic transmission from excitatory to inhibitory focusing on the roles of NKCC1 and KCC2. These genes also play a part in glutamate synapse formation and neurogenesis in the adult hippocampus. Kevin Staley will focus on the role of NKCC1 in the plasticity of GABA signaling in neonatal neurons and the implications of this process for early onset/pediatric seizures. Eric Delpire will use KCC2 knockout and heterozygous mice to establish the role of KCC2 in preventing brain hyperexcitability. He will also discuss a number of novel compounds that affect KCC2 function. Lastly, Thomas Hyde will present data on how expression of NKCC1 and KCC2 in prefrontal cortex (PFC) varies across the human lifespan (from week 14 in the fetus to 78 years). He will also discuss the role of both cotransporter genes in schizophrenia with data from both PFC and hippocampus.

Panel • Monday 8:30–10:00 PM • Hasty's

27. Sensible Neural Prosthetics

Doug Weber, Arthur Prochazka, Jerry Loeb, John Chapin, Joseph Francis

A new generation of prosthetic limbs are being developed to look, feel, and function just like the native limb. For these devices to feel and function naturally, a somatosensory neural interface is needed to convey limb-state information to the neural networks supporting perception and feedback control in the central nervous system (CNS). Designing such an interface requires choosing both a location and a method for activating neurons to deliver the body-state information, with careful consideration of the anatomy and physiology of the potential target and its projections to other regions of the CNS. This panel will discuss different approaches to designing a somatosensory neural interface,

ascending the sensory hierarchy from receptor to primary sensory cortex (S1). Arthur Prochazka will introduce this topic with a brief review of the role and function of muscle afferents in motor control. Jerry Loeb will describe biomimetic tactile sensing technology for prosthetic hands, injectable BIONic spindles to sense posture and movement in reanimated limbs, and spinal-like regulators for their closed-loop control. Doug Weber will describe a method for stimulating groups of primary afferent neurons with natural patterns of afferent input, evoking movement-like responses in S1 cortex. Similarly, John Chapin will show that thalamic (VPL) microstimulation produces response patterns in S1 cortex that emulate closely the responses to natural touch. Finally, Joseph Francis will describe proprioceptive activity in the rat rVPL and results from cortical proprioceptive stimulation in area 2 of monkeys. Collectively, these efforts span several levels of the sensory hierarchy, and the panel members will discuss the capabilities and limitations of each approach in providing touch and movement sense for prosthetic limbs.

Workshop • Monday 8:30–10:00 PM • Ptarmigan A

28. One Model Doesn't Fit All—Partial DA Loss and Striatal Function

Kristen Keefe, Marjorie Ariano, Jesus Angulo, Jean-Lud Cadet

The impact of large, dopamine-depleting brain lesions on striatum has been extensively examined. Much less is known about the impact of partial dopamine (and/or serotonin) loss. Studies from several labs have reported contradictory effects of partial loss induced by 6-hydroxydopamine or methamphetamine on indices of striatal function. Ariano has reported increased expression of caspase-3, fractin, and components of the apoptosome in striatopallidal efferent neurons despite an absence of striatal cell loss. Angulo has shown increased TUNEL staining in subsets of striatal efferent neurons, cholinergic interneurons and parvalbumin interneurons. Similarly, Cadet has reported apoptosis and expression of Fas Ligand in striatopallidal efferent neurons. Conversely, Keefe has shown a preferential impact on basal and behaviorally evoked gene expression in striatonigral neurons. Each participant will be allowed one slide and 5 min to present their data. The workshop then will focus on discussion of the following questions (and others raised by the audience): 1) Does the toxin selected influence the post-synaptic impact in striatum and, if so, what interpretations can we draw from different models for human partial monoamine loss? 2) Is the time point examined important for determining the post-synaptic impact of partial monoamine loss in striatum? 3) What do different dependent measures tell us about the post-synaptic impact of partial monoamine loss in striatum? 4) What

role, if any, does the loss of serotonin play in the post-synaptic effects? 5) What questions remain to be addressed to understand the impact of partial monoamine loss on striatal and basal ganglia function?

Panel • Monday 8:30–10:00 PM • Ptarmigan B

29. The Pathogenic Role of A-beta Oligomers in the Progression of Alzheimer's Disease

Peter Reinhart, Dennis Selkoe, William Klein, Charles Glabe, Lennart Mucke

Much evidence supports the hypothesis that the amyloid β-protein (Aβ) plays an initiating pathogenic role in Alzheimer's disease (AD), however, the specific neurotoxic species giving rise to these effects remain to be identified. Much recent data indicates that diffusible oligomers of Aβ, containing between 2 and 24 Aβ monomers arranged in an undefined structure, may give rise to the initial intermittent impairment of memory which precedes the development of AD dementia. This session, introduced by Dr. Peter Reinhart (Wyeth Research), will review our current understanding of Aβ oligomers and their role in AD pathology. Dr. Dennis Selkoe will discuss evidence for a role of naturally secreted Aß dimers and trimers, but not monomers, in giving rise to a progressive loss of hippocampal synapses and dendritic spines. Dr. Bill Klein will discuss the association of oligomers ranging from trimers to 12-24-mers with postsynaptic density complexes resulting in a rapid decrease in the expression of membrane receptors and a significant decrease in spine density. Dr. Charles Glabe (UCAL, USA) will discuss advances in antibody and vaccine mediated approaches targeting a number of different oligomer and fibrillar forms of Aβ for the treatment of AD. Dr. Lennart Mucke will discuss the extraction and role of Abeta oligomers from transgenic animals. The session will provide an overview of the evidence supporting the role of specific oligomers in the initiation and development of AD pathology.

Panel • Monday 8:30–10:00 PM • Ptarmigan C

30. Defining the Line between Pain Relief and Extra-Analgesic Reward

Carolyn Fairbanks, Lisa Schrott, Carrie Wade, Thomas J. Martin, James Zadina

The mechanistic relationships among drug addiction, chronic opioid exposure, and chronic pain have been widely recognized in terms of neuronal adaatation. In contrast, the separation of addiction from analgesia under conditions of chronic opioid exposure in the presence of chronic pain conditions has only

recently been investigated. There has emerged increasing interest as to how models of operant conditioning can be applied to models of chronic pain states to advance our understanding of this separation between opioid-seeking responses for analgesic outcomes versus reward. The panel will present four approaches to this question. Lisa Schrott (U of Louisiana-Shreveport) will profile the long term outcomes of rodents prenatally exposed to opioids when as adults they are evaluated in the conditioned place preference (CPP) test and for thermal withdrawal thresholds. Carrie Wade (U of Minnesota) will compare the opioid responding performance of subjects representing four models of chronic hypersensitivity in a model of oral opioid self-administration. Thomas Jeff Martin (Wake Forest Medical School) will describe mechanisms of neuromodulation of drug seeking behavior following nerve-injury. James Zadina (Tulane University) will present an observed favorable analgesia versus reward profile for endomorphin-1 and novel analogs. The panel will present the following concepts: 1) how the neuroplasticity of chronic opioid exposure and chronic hypersensitivity influences the motivation for opioid reward. 2) how several newly identified neuromodulators interact with established pain and addiction systems and 3) how these investigations might be uniquely informative to other areas of neuroscience.

Panel • Tuesday 7:30–9:30 AM • Bighorn C1

31. New Gene Discoveries from Genome-Wide Association Studies: Carving Up the Genetics of Bipolar Disorder and Schizophrenia

John Kelsoe, Nick Craddock, Michael O'Donovan, Pamela Sklar

Though the role of genetics in psychiatric disorders has been firmly established, identifying the specific genes involved has proven challenging. Human genetics is now in the midst of a revolution fueled by microarray technology. It is now possible to genotype one million SNP markers in an individual at low cost. This paired with large sample sizes has resulted in the ability to test for association comprehensively throughout the genome. This enables the detection of genes of small effect consistent with polygenic transmission. The first of these results are now becoming available. Dr. John Kelsoe will briefly introduce this technology and then discuss the results of the GAIN/BiGS study of 1,000 bipolar cases from the NIMH Bipolar Genetics Initiative. This study has identified two novel genes, NAP5 and DPY19L3. Dr. Nick Craddock will present the result of the Welcome Trust study of 2,000 bipolar subjects and the identification of PALB2 as a novel candidate. Dr. Michael O'Donovan will present a study of schizophrenia that has identified a zinc finger transcription factor ZNF804. Lastly, Dr. Pamela Sklar will present an analysis of the STEP-BD sample and a combined

analysis with the Welcome Trust sample. Together these data obtained genome-wide significant evidence for association for two genes, ANK3 ($p<10-9$) and CACNA1C ($p<10-9$). The strong significance and independent replication argue that real gene effects are now being discovered and may soon lead to novel ideas about pathways and mechanism of disease.

Panel • Tuesday 7:30–9:30 AM • Bighorn C2/C3

32. Understanding How Cocaine Withdrawal May Trigger Relapse

Deanne Buffalari, Mehmet Sofuoglu, Robert Wheeler

Relapse to drug use after periods of abstinence is a major impediment to successful treatment in cocaine users. Cocaine withdrawal is one of the primary triggers for renewed drug use. This panel will describe recent advances examining cocaine withdrawal from the clinical to the cellular level, and how it may contribute to relapse. Talks will focus on how a better understanding of the processes underlying withdrawal may promote more effective treatment and relapse prevention. Dr. Sofuoglu will show data from clinical populations demonstrating how cocaine withdrawal symptom severity is predictive of more severe dependence and poorer treatment outcomes. These data also suggest withdrawal severity may be predictive of treatment response to GABA and adrenergic medications. Dr. Buffalari will describe an animal model using cocaine self-administration and extinction to measure withdrawal anxiety and its underlying neural circuitry. This model may be extended to screen potential pharamacotherapies for their ability to alleviate withdrawal anxiety and attenuate or prevent reinstatement in an animal model of relapse. Dr. Wheeler will discuss how cocaine-associated taste cues elicit a conditioned aversive state in rats which predicts motivation to self-administer cocaine. This state is reflected in neurophysiological activity and dopamine signaling in the nucleus accumbens, providing insight into how negative affective states may drive drug seeking.

Panel • Tuesday 7:30–9:30 AM • Hasty's

33. Seeing Is Believing?: Visual Deprivation-Induced Plasticity

Hey-Kyoung Lee, William Guido, Elizabeth Quinlan, Ania Majewska

Vision plays an important role in our ability to interpret and interact with the external environment, and normal vision is also required for the proper development of the visual system. Emerging evidence suggests that visual experience is not only critical for the initial formation of proper connectivity in the visual

system, but is also required for the proper maintenance of mature circuits. Much of what we know about the role of visual experience in development has been gleaned from deprivation paradigms, which continue to be powerful approaches. This session will present exciting new data demonstrating that visual deprivation induces a diverse set of plastic changes throughout the visual system and beyond. William Guido (Virginia Commonwealth University) will present evidence for a novel role of retinal activity in establishing and maintaining segregation of newly refined retinogeniculate circuitry. Elizabeth Quinlan (University of Maryland) will present evidence that visual deprivation can "rejuvenate" the adult visual cortex to allow ocular dominance plasticity. Her work suggests that visual deprivation may allow the recovery of visual function in adult amblyopes. Ania Majewska (University of Rochester) will present her work using in vivo imaging approaches to demonstrate how rapid structural changes at cortical synapses occur in response to visual deprivation. Her work underscores the close relationship between synapse structure and network function. Lastly, Hey-Kyoung Lee (University of Maryland) will demonstrate that visual deprivation triggers synaptic changes in several primary sensory cortices, which may be a basis for cross-modal sensory compensation.

Panel • Tuesday 7:30–9:30 AM • Ptarmigan A

34. Spinal Cord Injury: Determinants of Degeneration, Regeneration, and Recovery Processes

Kimberly Topp, Sang Mi Lee, Dale Bredesen, Michael Shifman, Ephron Rosenzweig

Among the most exciting frontiers in medicine is the repair of traumatic injuries to the spinal cord. Improvements in treatment are helping people survive spinal cord injury (SCI), yet most injuries still cause lifelong disability. A quarter of a million Americans are currently living with spinal cord injuries and the annual cost of managing their care approaches $4 billion. Following injury, axons in the mammalian spinal cord do not regenerate across the trauma zone and are unable to re-connect to their appropriate targets. This failure to regenerate is caused by 1) lack of growth-promoting substances; 2) lack of permissive bridges for axon growth; 3) deficiency of strong signals for the cell to re-enter an active growth state; and 4) blockade of growth by inhibitors in the injured region. Moreover, retrograde degeneration in the lesioned pathways induces neuronal death or severe atrophy, limiting functional recovery. This panel will discuss determinants of degeneration, regeneration and recovery processes in the injured spinal cord, addressing the wound healing environment, axonal

guidance molecules, and strategies to support regeneration. Dr. Topp will briefly describe the clinical problem of SCI and introduce the panel. Dr. Lee will consider how macrophages modulate the wound healing environment including their contribution to early oxidative stress. Dr. Bredesen will discuss the involvement of trophic factors and dependence receptors in cell death pathways. Dr. Shifman will present data on the role of axonal guidance molecules in mechanisms of neuronal death after SCI and whether preventing neuronal death could enhance axon regeneration. Finally, Dr. Rosenzweig will discuss how combinatorial therapeutic strategies can enhance axonal plasticity and regeneration after acute and chronic SCI.

Panel • Tuesday 7:30–9:30 AM • Ptarmigan A

35. GnRH and GnIH: To Reproduce or to Eat?

Mary Ann Ottinger, Harry Jean, Yonathan Zohar, George Bentley, Gregory Fraley, Ramesh Ramachandran

Hypothalamic regulation of the reproductive axis has focused on mechanisms that dictate the release and action of gonadotropin releasing hormone (GnRH); yet the control mechanisms for balancing reproductive function with nutrient status remain unclear. A recently characterized hypothalamic hormone may have a key role, in combination with other regulatory mechanisms governing the interplay of reproductive and metabolic endocrine functions. Appropriately termed gonadotropin inhibiting hormone (GnIH), this hormone inhbits gonadotropin synthesis and release, as well as sexual behaviors. The action of this newly discovered hormone appears to be highly conserved across vertebrate classes, similar to GnRH. Additionally, intriguing potential links to the modulation of feed intake are emerging as more is learned about GnIH. Session contributors will overview our current understanding of the function of GnRH and GnIH, and examine neural mechanisms that optimize reproductive function while protecting metabolic endocrine responses. Yonathan Zohar will discuss the multiple forms of GnRH in terms of phylogenetic differences in form and function, as well as the use of zebrafish as a vertebrate model for the study of the GnRH system. George Bentley will summarize our current understanding of the action GnIH, including discovery and characterization of function, again from a comparative viewpoint. Greg Fraley will address the newly characterized mammalian form of GnIH in the context of multiple functions, including reproductive function and the control of feed intake. Ramesh Ramachandran will consider the role of GnIH in ovarian and pituitary gland function with seasonal cycles in reproduction.

Panel • Tuesday 7:30–9:30 AM • Ptarmigan C

36. Dysfunction of the Subthalamic Nucleus: How to Use It for Parkinsonism or Addictive Behavior?

Christelle Baunez, Michael Frank, Claire Cannon, Kuei-Yuan Tseng

How dysregulation of the subthalamic nucleus (STN) functioning contributes to the motor and non-motor behavioral outcomes associated with Parkinsons disease (PD) and cocaine addiction is not clearly understood. Here, we will provide a mechanistic analysis of the role of the STN in mediating the pathophysiological changes associated with these diseases. First, Michael Franck will describe his computational model of the fronto-subthalamic interactions and will present how these interactions regulate high conflict situations based on performance of PD patients with STN deep-brain stimulation (DBS). Next, Christelle Baunez will highlight the role of STN in coding reward values based on electrophysiological data and how STN DBS could be proposed as a possible surgical treatment for cocaine addiction based on her recent behavioral studies in rats. Claire Cannon will then present data showing how inhibition of the STN influences feeding activity, locomotion and reversal learning in the context of both PD and addiction to psychostimulants in mice. Finally, Kuei Tseng will summarize series of results demonstrating how chronic deficits of the mesocorticolimbic DA system resulting from MPTP-induced DA cell loss in the ventral tegmental area, and in association with frontal cortical hyperactivity, could play an important role in the pathophysiology of STN hyperactivity in PD. We will conclude by proposing an integrated functional model coupling the mesocorticolimbic DA system and the STN functioning in the regulation of different forms of cognitive and motivational behavioral neuroadaptations and disruptions.

Panel • Tuesday 4:30–6:30 PM • Bighorn C1

37. Neuronal Ensembles in the Nucleus Accumbens

Bruce Hope, Patricio O'Donnell, Cyriel Pennartz

Learning requires association of highly detailed information about an animal's environment and internal state to produce similarly highly detailed alterations in behavior. The nucleus accumbens in the ventral striatum is hypothesized to encode this information in ensembles of sparsely distributed medium spiny neurons selected by external and internal stimuli. Excitatory glutamatergic afferents from amygdala, prefrontal cortex, and hippocampus converge on the

nucleus accumbens to convey highly detailed information that determines which specific neuronal ensembles are activated. Other neurotransmitters such as dopamine from the midbrain convey more general information such as salience or motivational value that modulates activity of the selected neuronal ensemble. Combinations of stimuli present during learning can selectively activate neuronal ensembles unique to that stimuli combination. Under the right conditions, responsivity of these ensembles may be altered to produce learned associations. Disruptions in the functioning of these neuronal ensembles in the nucleus accumbens can affect learned behaviors associated with this brain region, such as feeding, sex, and drug abuse. First Patricio O'Donnell (University of Maryland) will introduce accumbens neuronal ensembles based on his in vivo electrophysiology studies. Cyriel Pennartz (University of Amsterdam) will then describe the anatomical inputs that convey specific environmental information to the accumbens. Bruce Hope (NIDA/NIH) will describe Daun02 lesioning of context-specific neuronal ensembles to demonstrate a causal role in context-specific sensitization to cocaine.

Panel • Tuesday 4:30–6:30 PM • Bighorn C2/C3

38. Genetic Models of Autism and Related Disorders: Molecules, Mechanisms, and Treatment

Craig Powell, Luis Parada, Eric Klann, Edwin Weeber

Recent advances in human genetics of autism and related disorders have paved the way for remarkable insight into molecules, mechanisms, and potential treatment of human autism spectrum disorders. Genetic mouse models of these disorders are proving to be a useful strategy for elucidating the molecular and microcircuit-level brain pathology responsible for subtypes of autistic disorders. Once thought of as essentially irreversible neurodevelopmental disorders, exciting advances using these animal models are now paving the way for novel therapeutics as autism-related abnormalities in these models are proving to be reversible both genetically and pharmacologically. This panel will highlight recent advances in the molecular/genetic basis of autism by exploring 4 genetic animal models of autism including molecular and microcircuit level mechanisms and potential for reversal of the underlying defect. Dr. Luis Parada (U.T. Southwestern Medical Center) will present an autism model based on conditional deletion of the phosphatase and tensin homolog on chromosome 10 (PTEN). He will illuminate the role of PTEN in the PI3K/Akt/mTOR pathway, in dendritic spine density and growth, and autism-relevant behaviors. In addition, he will present data suggesting that these dramatic structural and behavioral changes are reversible with selective pharmacologic treatment. Dr. Eric

Klann (NYU) will present biochemical, electrophysiological, and behavioral data relevant to a genetic model of Fragile X Syndrome, a disorder associated with an inordinately high incidence of autism. Dr. Craig Powell (U.T. Southwestern Medical Center) will discuss genetic models of autism based on mutants of the transsynaptic cell adhesion molecules neuroligins including molecular, electrophysiological, and autism-relevant behavioral characterization and potential mechanism. Finally, Dr. Edwin Weeber (University of South Florida) will discuss biochemical mechanisms involved in mouse models of Angelman Syndrome including genetic rescue of neurologic and electrophysiologic abnormalities via manipulation of downstream effectors of ubiquitin protein ligase E3A.

Panel • Tuesday 4:30–6:30 PM • Hasty's

39. Vestibular Physiology on Earth and in Space

Larry Young, Richard Boyle, Richard Rabbitt, Floris Wuyts

It has been almost a century since the only Nobel Prize was awarded for vestibular research. Knowledge remained largely limited to diagnosis of vertigo by caloric testing of the horizontal semicircular canals. Space flight and hypergravity provide opportunites to study the nervous systems response to altered gravitational environments. Although 1G has remained constant throughout animal evolution, the vestibular system responds quickly to transitions between gravity states, including weightlessness. Richard Boyle will examine the invertebrate and vertebrate vestibular responses to altered gravity, focusing in large part on the neurovestibular adaptation in the statocyst and utricular organs. Getting down to the basic semicircular canal function, Richard Rabbitt will examine their adapting responses, which do not directly reflect the macromechanical displacement of the endolymph. By recording cupula motion, hair cell modulations, microphonics and afferent discharge he identifies multiple sources of adaptation including contributions from regional differences in the adaptation of hair bundle deflections, hair-cell currents and synaptic transmission. The current concentration on interactions between sensory signals from the otoliths organs and from the semicircular canals, will form the basis of the presentation by Floris Wuyts, who will examine the role of vestibular efferents as well as afferents, and the intra-vestibular conflict as related to motion sickness. Larry Young will summarize some newer otoliths test methods and attempt to pull the material together with the help of a multi-sensory model which includes estimation of motion based upon an internal model and expectation.

Panel • Tuesday 4:30–6:30 PM • Ptarmigan A

40. Steroid Hormones and the Brain: Multiple Mechanisms for Rapid Signaling

Jill Becker, Paul Mermelstein, Paul Micevych, Jeffrey Tasker

The actions of steroid hormones on brain function have classically been conceived as slow processes requiring activation of intracellular receptors which induce changes in gene expression and protein synthesis. Further, these effects were principally thought to be restricted in their ability to regulate a few behaviors. Recent discoveries, however, have demonstrated the profound influence of steroids on a broad spectrum of brain functions and behaviors. It is now well accepted that steroids have a global influence on the brain that involves both classical and membrane initiated signaling. What is also emerging is that steroid actions are not always slow and mediated through intracellular receptors that mediate gene transcription. Steroid hormones acting through membrane receptors can trigger rapid signaling events. This symposium will bring together four scientists who have made significant strides in delineating the mechanisms of rapid steroid action in brain. Dr. Mermelstein will describe estrogen receptors trafficking to the cell surface membrane of neurons. These studies reveal that estrogen receptor alpha and beta act on distinct intracellular signaling pathways. Dr. Becker will discuss mechanisms mediating estradiol modulation of striatum and nucleus accumbens dopamine and GABA function. Dr. Micevych will discuss the role of rapid steroid signaling in physiological processes once thought to involve only intracellular receptors. Dr. Tasker will detail mechanisms through which corticosteroids trigger retrograde neurotransmission mediated by endocannabinoids and nitric oxide, to both excite and inhibit neuronal function through surface receptors. The topics are specifically designed to foster lively discussion among the participants and attendees.

Panel • Tuesday 4:30–6:30 PM • Ptarmigan B

41. Emerging Concepts in Neurotoxicity and Neuroprotection: Zinc, Fatty Acids, AMPA and K+ Channels, and Metabolism

Christian Sheline, Nicolas Bazan, Elias Aizenman, Michael Bennett

Zn2+-mediated neurotoxicity now has been widely implicated in neuronal injury including in conditions such as ischemia, trauma, epilepsy, hypoglycemia, and target deprivation. Much of this injury is associated with apoptosis, the hallmarks of which include cell shrinkage, activation of kinase and caspase cascades, and metabolism impairment. We have assembled a panel that will bring us up

to date on critical new angles relating to neuronal cell death, particularly as it pertains to Zn2+-mediated injury. Nicholas Bazan will begin the session by presenting his recent work on the potent, stereospecific, neuroprotectin D1. This docosanoid mediator is an anti-inflammatory substance that up-regulates anti-apoptotic Bcl-2 members, and downregulates pro-apoptotic Bcl-2 members during injurious processes. Elias Aizenman will follow by characterizing Zn2+-mediated phosphorylation changes that occur in voltage-gated channels during neuronal apoptosis. He will focus on a newly-discovered dual phosphorylation regulatory process that Kv2.1 channels undergo during their apoptotic membrane insertion. Michael Bennett will then tell us about the role of epigenetic repression of GluR2 in global ischemia mediated death. He will show that the REST-CoREST-histone deacetylase complex forms specifically on the GluR2 promoter in CA1 sensitive neurons, but not in CA3 insensitive neurons. This leads to GluR2 repression in CA1 causing Ca2+ and Zn2+ permeable AMPA receptors and neuronal death in CA1 following ischemia. Christian Sheline will conclude the session by suggesting that Zn2+ toxicity negatively affects the levels of a key metabolic second messenger, NAD+, both in vitro and in vivo, and by showing us that conditions which increase NAD+ are neuroprotective. The panel will attempt to connect these various novel facets of neuronal injury within the general central framework of devising novel therapeutic strategies to prevent or ameliorate neuronal injury.

Panel • Tuesday 4:30–6:30 PM • Ptarmigan C

42. AKAP Signaling Complexes in Regulation of Neuronal Ion Channels

Mark Dell'Acqua, Johannes Hell, William Sather, Todd Scheuer

Signaling complexes organized by scaffold proteins are crucial for modulation of ion channels. This symposium will highlight the roles of AKAP scaffolds in regulation of AMPA glutamate receptors and L-type Ca2+ channels. AKAP79/150 anchoring of PKA and the Ca2+-calmodulin-activated phosphatase calcineurin is implicated in regulation of AMPAR phosphorylation and localization during LTP and LTD. Dr. Mark Dell'Acqua will present findings showing that AKAP79/150 regulation of AMPARs depends on targeting of the AKAP to lipid rafts through palmitoylation of its N-terminal targeting domain, interactions with MAGUK scaffolds, and calcineurin anchoring. Anchored basal PKA activity is thought to maintain elevated AMPAR responses as injection of inhibitory PKI or AKAP dissociating Ht31 peptides leads to run-down that appears to occlude LTD. Dr. Johannes Hell will present findings showing that while basal synaptic transmission in mutant mice lacking the AKAP150 PKA binding site is normal, LTD is absent indicating that PKA also plays an

active role in LTD. PKA phosphorylation and Ca2+-dependent inactivation (CDI) regulate open probability of L-type Ca2+ channels. AKAP79/150 binds neuronal CaV1.2 L-channels, localizing PKA and calcineurin to the channel. Dr. William Sather will present work showing that channel-bound Ca2+-calmodulin activates channel-localized calcineurin to mediate CDI through channel dephosphorylation. CaV1.2 channels also form a complex in which the proteolytically processed distal C-terminus containing an AKAP15 binding site and a key PKA phosphorylation site binds to and inhibits the channel. Dr. Todd Scheuer will describe regulation of this autoinhibitory complex by AKAP15-PKA and Mg2+ binding to a nearby EF-hand motif.

Panel • Wednesday 7:30–9:30 AM • Bighorn C1

43. Phasic Release of Neurotransmitters: What Does Phasic Do to Your Tonic?

Greg Gerhardt, Paul Phillips, Martin Sarter, John Bruno

Neurons are known to fire spontaneously and in bursts of activity. These two firing modes produce tonic release of neurotransmitters and phasic release of neurotransmitters, respectively. For two decades, investigators have used the technique of microdialysis, which is ideally suited for measures of tonic release of neurotransmitters. However, the phasic properties of neurotransmitter release have largely remained unstudied due to the time resolution of this method. More recently, methods have been developed using microelectrode techniques that allow for sub-second measures of neurotransmitters, such as dopamine, choline (as a measure of acetylcholine) and glutamate in awake animals. This panel will focus on recent studies of sub-second measures of neurotransmitter release in behaving animals showing evidence for phasic neurotransmitter release during certain behavioral events and as a consequence of pharmacological treatments. First, Paul Phillips will describe studies conducted using fast-scan cyclic voltammetry for measures of dopamine release in awake animals during classical conditioning. Martin Sarter will present recent data on measures of choline, as a marker for acetylcholine release in the prefrontal cortex of rats performing a task involving detection of cues. John Bruno will explain recent studies with a microelectrode array and measures of phasic release of glutamate in the prefrontal cortex of rats performing simple vs. complex behavioral tasks. Finally, Greg Gerhardt will introduce recent technology to record glutamate events in the striatum and cortical areas of non-human primates showing evidence for transient glutamate activity. All of these studies will contribute to an understanding of new methodology for the detection of neurotransmitters on a sub-second time scale and their utilization for understanding phasic release of neurotransmitters in the brain.

44. Neurodevelopment and Neurodegeneration in Neuropsychiatric Disorders: From Genotype to Phenotype

Anil Malhotra, Christopher Ross, Katherine Karlsgodt, Katherine Burdick

A number of neuropsychiatric disorders have been hypothesized to involve neurodevelopmental or neurodegenerative processes (or both). To date, however, the specific mechanisms underlying these processes have not been fully elucidated, and the sequelae of disruption in these processes are not well understood. Better explication of aberrations in neurodevelopment and neurodegeneration could be important in the development of new treatments for neuropsychiatric disorders, as well as provide data that could lead to the development of better animal models of illness. In this panel, we will present data from a number of distinct viewpoints and disciplines to help synthesize our understanding of the trajectory of neuropsychiatric disorders, and the biological bases of differential illness trajectories. Anil Malhotra (Zucker Hillside Hospital, NY) will present data from molecular genetic studies that seek to identify key genes involved in the putatively neurodevelopmental disorder, schizophrenia, including data suggesting that the DISC-1 gene influences neurodevelopment through interactions with binding partners that result in increased risk for illness, but also in neurocognitive and brain morphological abnormalities that occur before illness onset. He will also discuss data suggesting that variation in the brain derived neurotrophic factor (BDNF) gene may influence hippocampal development at the earliest phases of illness. Chris Ross (Johns Hopkins University, MD) will discuss novel animal models of illness, focusing on an animal model of a neurodevelopmental disorder, schizophrenia, and an animal model of a neurodegenerative disorder, Huntington's disease, to provide insights into critical distinctions between these two processes that may underlie the expression of illness. Katherine Karlsgodt (UCLA, CA) will present work examining the timing of onset of reduced myelination in schizophrenia, by examination of a unique data set of subjects prospectively studied during conversion to schizophrenia in adolescence and early adulthood with neuroimaging methodologies, including diffusion tensor imaging. Finally, Katherine Burdick (Zucker Hillside Hospital, NY) will present on the clinical phenotypes of neurocognitive dysfunction across the life span in patients with schizophrenia, including data from patients at risk for schizophrenia or in their first episode of illness and contrast this with data from bipolar disorder patients, another neuropsychiatric disorder that may prove to be neurodevelopmental in origin. At the conclusion of this panel, it is hoped that participants will have gained a fuller understanding of the underpinnings of brain development and neurodegeneration, and of the role of these two processes in the development and potential treatment of neuropsychiatric disorders.

45. Regulation of GABAA Receptor Alpha4 Subunits: From Transcription to Membrane Trafficking

A. Leslie Morrow, Igor Spigelman, David Werner, Neil Harrison, Patricia Janak

GABAA receptors (GABAA-Rs) play a major role in inhibitory signaling and have been shown to be a major target for many drugs of therapeutic use and abuse, endogenous neuroactive steroids, as well as the pathology of certain neuropsychiatric disorders. GABAA-Rs containing α4 and δ subunits exhibit extrasynaptic localization and contribute to tonic inhibition. GABAA-Rs containing α4 and γ2 subunits may contribute to negative modulation of synaptic responses. This panel will discuss the function and regulation of α4-containing receptors from transcription to membrane expression and phosphorylation. Neil Harrison will discuss transcriptional regulation of the gene Gabra4 that encodes the α4 subunit and undergoes rapid activation in responses to acute ethanol exposure. This effect is mediated by binding of the transcription factor HSF-1 to a unique sequence element in intron 2 of Gabra4, termed the alcohol response element. The signaling cascades that mediate this effect will be discussed. Igor Spigelman will present evidence for the preferential enhancement of α4-containing GABAA-Rs by ethanol, a reduction in ethanol enhancement in the α4 knockout model, as well as critical compensatory changes in GABAA-R plasticity following ethanol intoxication. A major role of α4-containing receptors in ethanol-dependence will be discussed. David Werner will describe the post-translational regulation of α4-containing GABAA-Rs. Using ethanol as an α4-containing GABAA-R activator, receptor regulation by intracellular trafficking, phosphorylation as well as the involvement of protein kinases and neuroactive steroids will be discussed. Sheryl Smith will focus on the α4β2δ GABAA-Rs as sensitive targets for steroids such as THP (3αOH,5αpregnan-20-one). The outcome of steroid effects at this receptor depend upon the direction of Cl- flux through the channel. In CA1 hippocampal pyramidal cells where Cl- flux is inward (outward current), α4βδ GABAA-R expression and function are altered by fluctuations in THP levels observed at the onset of puberty in female mice. The relevancy to anxiety disorders that first emerge after puberty will be discussed. By examining the role of α4-containing GABAA-R regulation, the presentations in this panel will convey the importance α4-containing GABAA-R homeostasis in response to development, drugs of abuse such as alcohol, and neuropsychiatric disorders.

Panel • Wednesday 7:30–9:30 AM • Ptarmigan A

46. Hypoglycemia and the Brain: The Life, Death, and Specialized Functions of Neurons and Glia That Respond to Glucoprivation

Barry Levin, Dianne Lattemann, Robert Sherwin, Nicole Sanders, Raymond Swanson

Hypoglycemia is a serious clinical problem which can lead to coma and death. Single bouts elicit a series of neurohumoral counterregulatory responses which can restore blood glucose levels. Recurrent bouts markedly dampen these responses and severe, sustained hypoglycemia can cause neuronal death. The panel will discuss the brain areas and cell types involved in mounting the counterregulatory responses, the mechanisms involved in dampening them and potential interventions to prevent such downregulation and neuronal death. Levin briefly introduce the issues involved in sensing and responding to hypoglycemia by specialized glucosensing neurons in the brain. Lattemann will discuss the contributions of limbic circuitry and CNS inputs to the hypothalamic paraventricular nucleus on the endocrine response to hypoglycemia. She will compare and contrast responses to a single bout of hypoglycemia and the impaired neuroendocrine responding seen following repeated bout of hypoglycemia. Sherwin will present studies demonstrating the critical role of the ventromedial hypothalamus and neurotransmitters/peptides and hormones such as GABA, glutamate, CRF, urocortin and insulin in mediating the counterregulatory responses to single and repeated bouts of hypoglycemia. Sanders will discuss novel data demonstrating a critical interaction between tanycytes that line the third ventricle, the hypothalamic neurons they support and the way their interactions alter and are altered by single and recurrent bouts of hypoglycemia. Swanson will discuss the intimate relationship between neurons and astrocytes with emphasis on the role of brain glycogen in forestalling neuronal dysfunction and death and the downstream events that lead from very severe hypoglycemia to neuronal death.

Panel • Wednesday 7:30–9:30 AM • Ptarmigan B

47. Resveratrol and Other Polyphenols—Are They Worth "Wine-ing" About?

James Joseph, Donald Ingram, Giulio Pasinetti, Crews Fulton, Tom Kuhn

The evidence is becoming increasing clear that diet plays an important role in increasing "health span" in aging. However, questions of which foods might be the most beneficial in preventing cognitive and motor behavioral deficits in aging remain. It has been shown that the inclusion of fruits (e.g., blueberries, strawberries, blackberries etc. and beverages (red wine) that contain high amounts of polyphenolic compounds with antioxidant/anti-inflammatory properties are likely to promote healthy brain aging. In fact, recent evidence suggest that polyphenolic compounds such as resveratrol (one of several pterostilbenes) which are found in red wine, grapes and berries may be especially important in this regard. This panel will discuss the mechanisms involved in the beneficial effects of these polyphenols and how they may prevent or forestall age-related behavioral and neuronal deficits. Jim Joseph will introduce the session and give a brief overview of the putative role of fruit and walnut polyphenols in stress signaling behavior in aging and show how pterostilbenes may also have similar effects. Don Ingram provide an overview of research claims of the "anti-aging" effects of resveratrol. Giulio Pasinetti, will present preclinical evidence suggesting that a recently characterized grape seed polyphenolic extract (GSPE) may also provide beneficial disease-modifying activities in tau-associated neurodegenerative disorders. He will show how these data in conjunction with recent demonstrations of bioavailability / bioactivity in vivo may lead to the development of the GSPE for the prevention and/or treatment of a myriad of these "tauopathies". Fulton Crews will discuss possible sites of action of many antioxidants in oxidative stress and neurodegeneration, including activation of Nrf2 anti-oxidant genes and induction of inflammatory cytokines and oxidative enzymes, particularly NADPHoxidase and NFkB transcription. He will show how anti-oxidants, oxidative enzyme inhibitors, ethanol and other agents that can alter the proinflammatory-oxidative stress loop. Tom Kuhn will continue this discussion concerning signaling by showing that individual molecular compounds in blueberries can act as specific inhibitors of neutral sphingomyelinase and NADPHoxidase, two enzyme activities key to inflammatory signal transduction and increased oxidative stress.

Panel • Wednesday 7:30–9:30 AM • Ptarmigan C

48. Synaptic Transmission and Intrinsic Neuronal Properties Underlying Postsynaptic Mechanisms of Plasticity

Ian Forsythe, Conny Kopp-Scheinpflug, Karl Kandler, Leonard Kaczmarek

All neuronal pathways exhibit activity-dependent adaptation of information transmission involving changes in synaptic strength over broad time-scales. These phenomena have been well characterised, but modulation of transmission can also be achieved by changing the target neuron's excitability; for example, by modulation of voltage-gated potassium channels. Such malleability is a prerequisite for homeostatic processes and the scaling or matching of synaptic input with neuronal output (action potential firing). This panel will describe recent insights into the mechanisms by which synaptic transmission can be regulated through changes in intrinsic excitability of target neurons (rather than by changes in synaptic strength of the inputs to those neurons). The work focuses on synapses in the brainstem auditory pathway concerned with the physiological function of sound source localization. Conny Kopp-Scheinpflug (Leipzig University, Germany) will discuss evidence for failures of transmission at brainstem auditory relay synapses and describe spontaneous, sound and activity-dependent modulation in vivo. Karl Kandler (University of Pittsburgh) will review evidence for experience and activity-dependent refinement in excitatory and inhibitory transmission. Ian Forsythe (University of Leicester, UK) will describe the role of nitric oxide in mediating an activity-dependent shift in postsynaptic excitability at the calyx of Held/MNTB synapse by modulation of Kv3 potassium channels. Len Kaczmarek (Yale University) will focus on the molecular mechanisms by which sound modulates Kv3 channel phosphorylation and activity. Together these phenomena provide clues to mechanisms of neuronal processing that can adjust transmission efficacy throughout the brain and particularly in regions where classical LTP-like phenomena have yet to be described.

Panel • Wednesday 4:30–6:30 PM • Bighorn C1

49. Neuropeptide Regulation of Behavior

Matthew Wanat, Charles Chavkin, Mitchell Roitman, Gary Aston-Jones

Since the first neuropeptides were discovered and chemically identified in the 1950s, hundreds of additional neuropeptides have been characterized in animals ranging from hydra to mammals. A growing body of literature highlights neuropeptide function in stress responses, food consumption, motivation, and addiction, though less is known regarding the specific neuropeptides,

signaling pathways, and brain structures responsible for these behaviors. This panel presents recent developments in how neuropeptides regulate these behaviors. Charley Chavkin will discuss how repeated swim stress causes corticotropin-releasing factor (CRF)/urocortin release, subsequent CRF receptor activation, dynorphin release, and finally kappa receptor activation in mouse brain. Mitch Roitman will describe experiments investigating peptidergic modulation of phasic dopamine release with a focus on neuropeptide Y - a peptide implicated in motivation and addiction. Effects of NPY on dopamine terminal release dynamics in the nucleus accumbens (NAcc) will be correlated with those on progressive ratio responding for sucrose reward. Matt Wanat will present his work examining the mechanism by which CRF in the ventral tegmental area (VTA) increases locomotor activity, inhibits motivation for food reinforcers, and affects phasic dopamine release in the NAcc. Gary Aston-Jones will describe findings that orexin (hypocretin) neurons in lateral hypothalamus (LH) are strongly activated by stimuli associated with cocaine, morphine or food rewards. These cells are critically involved in reinstatement of extinguished morphine or cocaine-seeking in rats, and the VTA may be an important site of action for these effects. Finally, his recent findings indicate that this neuropeptide system is also essential for initial learning of stimulus-reward associations.

Minicourse– Wednesday 4:30–6:30 PM • Bighorn C2/C3

50. Frontiers in Genomics and Neurogenetics: Trawling for Genes and Mechanisms of Addiction

Robert W. Williams, Robert J. HItzemann, Wolfgang Sadee, Abraham Palmer

The systematic mechanistic dissection of CNS function has been a great strength of neurophysiology and neuropharmacology. In contrast, behavioral genetics and human clinical neuroscience has often involved large scale correlative studies that are more exploratory and statistical in nature. Recent advances in genomics, large-scale genetics, and bioinformatics can now bridge between mechanistic and exploratory approaches. The four speakers in this workshop will provide provide examples of how massively parallel sequencing and genome-wide association studies in model organisms (mostly mice) and in human populations are beginning to blur the boundaries between hypothesis generation and hypothesis testing. Huge data sets that were once derided as parts of fishing expeditions are now proving to be a boon for those studying specific mechanisms of synaptic function, drug addiction, and behavioral variation. Rob Williams will introduce several of the major neurogenomics data resources, such as the Allen Brain Atlas, GeneNetwork, and several synapse databases. Robert Hitzemann will illustrate how large scale resequencing of both the genome and transcriptome are transforming our relatively naive views

of gene expression in the brain (the striatum, in particular). Wolfgang Sadee will highlight how advanced genetic and genomics methods are being used to study the dopaminergic system. Finally, Abraham Palmer will illustrate how neurogenetic and genomic data sets generated using mice can be exploited efficiently to identify major genes that modulate addiction in humans.

Panel • Wednesday 4:30–6:30 PM • Hasty's

51. The Many Faces of Norepinephrine

Elisabeth Van Bockstaele, Sergey Kalinin, Barry Waterhouse, Patricia Szot

Norepinephrine is known to participate in the control of mood, behavioral responses to stress and higher cognitive functioning. Moreover, recent evidence points to a neuroprotective role of norepinephrine in certain neurological disorders and a modulatory role of this transmitter in synaptic plasticity and neurogenesis. This panel will discuss the plurality of function of the catecholamine neurotransmitter, norepinephrine. First, Elisabeth Van Bockstaele (Thomas Jefferson University) will introduce the panel by reviewing important new developments and direction in norepinephrine research. Sergey Kalinin (University of Illinois, Chicago) will review cellular evidence for a neuroprotective role of norepinephrine in neurodegenerative disease. Barry Waterhouse (Drexel University) will elaborate on multiple lines of evidence that implicate the norepinephrine system in sustained attention and attention deficit disorder. Patricia Szot (VA Puget Sound Health Care System) will discuss the implications of norepinephrine in neuronal plasticity and hippocampal neurogenesis as well as discuss the implications of norepinephrine dysfunction in Parkinson's disease. Finally, David Morilak (University of Texas Health Science Center, San Antonio) will present how norepinephrine is dysregulated by chronic stress and how this contributes to the complex symptomatology of depression and anxiety disorders.

Panel • Wednesday 4:30–6:30 PM • Ptarmigan A

52. Cognitive Modulation of Sensory Processing

Alfredo Fontanini, Carl Petersen, Leslie Kay, Marshall Hussain Shuler

These are exciting times for sensory neuroscientists, as sophisticated recording methods make possible unprecedented spatial and temporal resolution in monitoring sensory systems in action. Recent results from multi-electrode and imaging techniques show a great richness in the sensory responses of behaving animals. In fact, neural responses in sensory areas have been shown to change depending on the moment-to-moment behavioral state of the animal, which itself is a function of environmental context, task demands, experience and

internal homeostasis. The sensory brain does more than simply coding for the invariant physical properties of stimuli, it adaptively keeps track of their meaning and their relationship with action, achieving this task by dynamically changing its state and functional connectivity with higher order cognitive areas according to the environmental context. This panel will discuss this integrative view of sensory processing. Carl Petersen (Ecole Polytechnique Federale de Lausanne) will present evidence showing state dependent modulation of somatosensory processing in the rodents barrel cortex. Leslie Kay (University of Chicago) will discuss how the nature of a task can modulate the functional connectivity of olfactory circuits. Marshall Hussain Shuler (Johns Hopkins University) will discuss evidence showing that pairing visual stimuli with subsequent reward leads to the emergence of reward-timing activity in the primary visual cortex. Finally Alfredo Fontanini (SUNY Stony Brook) will talk about anticipatory activity in the gustatory cortex of rats self-administering taste stimuli.

Panel • Wednesday 4:30–6:30 PM • Ptarmigan B

53. Understanding the Role of APP and Cholesterol Metabolism in the Etiology of Alzheimer's Disease

Menelas Pangalos, David Holtzman, Tobias Hartmann, Liu Qiang, David Riddell

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that affects the elderly. Amyloid plaques composed of β-amyloid peptide (Aβ) are the characteristic AD pathology. Aβ is generated by processing of a large transmembrane protein, APP, by two proteases; β and γ-secretase. Studies of familial AD (FAD) patients have identified mutations in both APP and γ-secretase that lead to an overproduction of Aβ. These observations form the basis of the "amyloid hypothesis", where increased production of Aβ leads to neurodegeneration and dementia. However, major gaps in our understanding of the link between Alzheimer's and APP remain: Unlike FAD, we do not understand the precipitating factors that lead to Aβ overproduction in the more common sporadic form of AD, nor have we identified a physiological role of APP processing. Recent data suggest that cholesterol metabolism may be a common pathway that links many of the genetic, epidemiological and environmental factors implicated in the etiology of AD. This panel, introduced by Mene Pangalos, will provide an update on our understanding of cholesterol and AD, as well as highlight new data that suggests that the physiological role of APP is to regulate cholesterol metabolism. David Holtzman will provide an overview of role of APP and cholesterol metabolism in AD. Tobias Hartmann will present recent data on how Aβ can directly regulate cholesterol biosynthesis. Liu Qiang will discuss how APP processing can regulate cholesterol receptor expression. Finally, David

Riddell will present data suggesting that FAD mouse models and patients have a dysregulated cholesterol biosynthetic pathway.

Panel • Wednesday 4:30–6:30 PM • Ptarmigan C

54. Under Construction: Phospho-Bridges Integrate Dopamine and Glutamate Signaling in the Striatal Cytoskeleton

Jacqueline McGinty, Gretchen Snyder, Christopher Pierce, David Sibley

Dopaminergic and glutamatergic neurotransmission in the striatum is integrated by phosphorylation and dephosphorylation of target proteins that alter spatial and temporal signaling in medium spiny neurons. In addition to activating the major kinase and phosphatase pathways in striatal neurons, dopaminergic stimulation activates multiple phosphodiesterase cascades that regulate cyclic nucleotide signaling within subcellular domains. The goal of this panel is to discuss interactions between the kinase, phosphatase, and phosphodiesterase cascades that are altered by and alter dopamine and glutamate signaling. Gretchen Snyder will discuss how the distinct cellular localization of two phosphodiesterases, PDE4 and PDE10A, dictates the regulation of distinct sets of phosphoproteins in the D1 receptor-enriched and D2 receptor-enriched medium spiny striatal neurons and in dopamine terminals. The functional impact of selective phosphodiesterase inhibitors on striatal dopaminergic tone will be discussed. Chris Pierce will discuss data indicating that CaMKII is an essential link between accumbens shell dopamine and glutamate systems involved in the neuronal plasticity underlying cocaine craving and relapse. David Sibley will discuss findings that ethanol treatment inhibits PKC and potentiates D1 receptor- mediated DARPP-32 phosphorylation in rat striatal slices, supporting the notion that ethanol enhances D1 receptor signaling in vivo. Jakie McGinty will discuss alterations in kinase and phosphatase cascades in the corticostriatal circuitry of rats after repeated exposure to cocaine or amphetamine. These studies strengthen the concept that constant modification of intracellular bridges regulate dopamine-mediated signal transduction and plasticity.

Panel • Thursday 7:30–9:30 AM • Bighorn C1

55. Impulsivity and Psychopathology: From Animal Models to Humans

Jon-Kar Zubieta, Pier Vincenzo Piazza, Jill Becker, Larry Siever

Impulsiveness has received substantial attention because of its association with risky behaviors, personality disorders and aggression, particularly in the

context of stressors. This panel will discuss its neurobiological substrates in animal models and humans. Pier Vincenzo Piazza has utilized an animal model, rodents with high rates of exploratory behavior under the mild stress of a novel environment (high reactivity, HR), that develops drug self-administration faster and at lower drug doses than rats exhibiting lower rates of locomotor activity (low reactivity, LR). He will discuss neurotransmitter systems and brain nuclei involved in these traits. Jill Becker has investigated the additional influences of sex and gonadal steroids individual on selectively-bred HR-LR phenotypes. HR females self-administered significantly more cocaine than all other groups and exhibit higher breaking points on a progressive ratio schedule of reinforcement. Jon-Kar Zubieta examined the contribution of endogenous opioid/μ-opioid receptors to trait impulsivity in healthy humans. High impulsiveness subjects demonstrated higher μ-opioid receptor concentrations and stress-induced endogenous opioid system activity in orbitofrontal cortex, anterior cingulate, thalamus, nucleus accumbens and basolateral amygdala, accounting for up to 40% of the variance in this personality trait. Larry Siever will discuss brain circuitry, genetic influences and neuromodulators involved in impulsive aggression, common in personality disorder patients. He found evidence for reduced activity of orbitofrontal, anterior cingulate cortex, increased amygdala activation by emotional stimuli and a loss of reciprocal modulation. Lower 5HTT and greater 5HT2a receptor concentrations were obtained in frontal regions. SNPs of TPH2 were further associated with impulsive agression.

Panel • Thursday 7:30–9:30 AM • Bighorn C2/C3

56. Disease Models of Genetic Susceptibility for Complex Brain Disorders

Amanda Law, Ron McKay, Francesco Papaleo, Inga Deakin

The validation of susceptibility genes for psychiatric and neurodegenerative disorders requires novel, more tailored approaches to transgenic model design. This panel will present data on innovative strategies focused on directly modeling genetic-risk and disease related changes in genes associated with schizophrenia or Parkinson disease (PD), along with assessment of the impact on neurodevelopment and behavior. Prof. McKay will present evidence that the forkhead transcription factor, Foxa2, is a critical gene implicated in dopamine neuron development and age-related degeneration in a mouse model of PD. Dr Papaleo will describe novel findings from genetically modified mice on the impact of increased or decreased COMT activity on cognitive function and adaptive stress responses which at the molecular level implicates prefrontal cortical CaMK signaling. Inga Deakin will present behavioral, electrophysiological and molecular data derived from a transgenic mouse model of NRG1,

type I isoform overexpression, modeling molecular changes seen in the brain in schizophrenia. Finally, Dr Law will present data derived from transgenic mice and in-vitro hippocampal neuronal work on the biological consequences of overexpression of a novel isoform of the NRG1 gene, type IV, which in humans is associated with genetic risk for schizophrenia. The creation of biologically relevant models of genetic susceptibility for complex human brain disorders is critical to understanding the mechanistic basis of disease and for the development of novel therapeutics.

Panel • Thursday 7:30–9:30 AM • Hasty's

57. Four Views of Brain Development and Plasticity: From Progenitors to Matrix Molecules

William Freed, Joel Levine, Herbert Geller, James Fawcett

Brain development and plasticity in the adult involve complex interactions between many disparate processes, which interact to produce an intricate and adaptable structure. Moreover, injury or drug intake can disrupt these events in ways that result in permanent functional defects. This panel will present overviews of new findings in four areas in developmental and regenerative neuroscience: 1) Generation of new glia and neurons in the brain from oligodendrocyte precursor cells (OPCs); 2) The effect of cocaine on neural progenitor proliferation and brain development; and the role of extracellular matrix in controlling 3) axonal sprouting and growth and 4) plasticity in the adult CNS. Joel Levine will describe OPCs, a class of glial cells that is capable of generating new OPCs, oligodendrocytes, astrocytes and neurons throughout the life of the organism. William Freed will describe a mechanism through which cocaine interferes with neural progenitor proliferation and brain development, involving P450 metabolism of cocaine, oxidative stress, and inhibition of cyclin A expression. Herb Geller will discuss the dependence of directional axonal growth on environmental cues, and the role of extracellular matrix, carbohydrate GAG chains and signaling mechanisms in shaping development. James Fawcett will speak on critical periods for plasticity as related to formation of extracellulur matrix structures surrounding neurons known as perineuronal nets, how these structures are formed, and the results of removing them. The session will conclude with a general discussion on how these events are potential targets for the effects of various categories of drugs which lead to permanent behavioral changes.

Panel • Thursday 7:30–9:30 AM • Ptarmigan A

58. Food for Thought: Adenosine, Metabolism, and Brain Activity

Susan Masino, Masahito Kawamura, Detlev Boison, Robert Greene, Kelly Drew

An interaction between metabolism and brain activity is well documented, and its broad clinical relevance continues to emerge. The purine molecules ATP and adenosine provide a unique link between cell energy and neuronal signaling, and adenosine was long ago termed a "retaliatory metabolite." This session explores the relationship among adenosine, metabolism and brain activity as it spans from behavior to cellular neurophysiology. S. Masino will introduce the session with new insights into the metabolic regulation of adenosine. M. Kawamura will highlight electrophysiological evidence of a novel autocrine regulation of hippocampal pyramidal neuron excitability via adenosine A1 receptors (A1Rs). This bidirectional regulation of neuronal excitability by intracellular ATP is relevant to clinical conditions such as stroke and epilepsy. D. Boison will discuss the relationship between adenosine dysfunction and hyperactivity in epilepsy, specifically the upregulation of the astrocyte-based enzyme adenosine kinase (ADK), a molecular link between astrogliosis and neuronal dysfunction. R. Greene will explore the role of A1Rs in sleep and cognition, and provide evidence that a conditional knockout of A1Rs results in reduced capacity for both enhancement of slow wave activity and maintenance of cognitive function during waking. K. Drew will present the role of adenosine in the deepest "sleep" - torpor during hibernation - where whole animal metabolic rate is as low as 2% of basal rate. This metabolic suppression is regulated, in part, by adenosine. These insights into the relationship among adenosine metabolism and brain activity have the potential to translate into novel therapies for a variety of clinical conditions.

Panel • Thursday 7:30–9:30 AM • Ptarmigan B

59. Translational Therapeutics: The Quest Progresses

John Sladek, Krys Bankiewicz, Kimberly Bjugstad, Lotta Granholm-Bentley

We have explored multiple approaches for neural repair and restoration of function including fetal cell grafts, gene therapy, and embryonic stem cell implantation. The availability of animal models permits translational therapy for neurological disorders with cognitive, motor and other deficits. Our panel will review the potential for repair of disorders that affect over 5 million Americans. Krys Bankiewicz will overview gene therapy approaches in movement deficits

that model Parkinson's disease and share recent data on the ability to protect residual neurons from further damage that can halt progression of a disease by stimulating neuritic growth and providing trophic support in the adult brain. Lotta Granholm will describe genetic and environmental events during early development that affect neural function with aging. Kim Bjugstad will discuss the ability of human embryonic stem cells to migrate long distances to reach neurons at risk in a primate model of parkinsonism, presumptively to provide trophic support to the substantia nigra. She also will discuss the ability of stem cells to mitigate against hippocampal tau clusters in a rodent model of Down syndrome (DS). DS children lose hippocampal neurons progressively postnatally, which accounts for cognitive decline, and show pathological features of Alzheimer's disease beginning in their fourth decade leading to further cognitive insult as adults. John Sladek will present data on the potential for co-grafts of tropic factor-laden tissue to stimulate neuritic extension over long distances in the primate brain to promote nigrostriatal circuit reconstruction. Together we will explore the potential for brain repair.

Panel • Thursday 7:30–9:30 AM • Ptarmigan C

60. Structural and Functional Determinants of Synaptic Transmission and Plasticity at Central Synapses

Joachim Lübke, Ora Ohana, Francesco Ferraguti, Silvio O. Rizzoli

Synapses are the key elements for synaptic transmission and plasticity. Although our knowledge about synapses has increased over the last years by the introduction of novel fluorescence, electron and molecular techniques, detailed information about their structure and function still remains limited. Synapses vary enormously, with no simple model being generally applicable. Many parameters differ among synapses, including the geometry of synaptic contacts, pools of synaptic vesicles, mode of release, content of pre- and postsynaptic signalling proteins, and the pattern of synaptic formation, consolidation and adaptation. A detailed description of different synapses, in both functional and morphological terms, is required for a better understanding of synaptic function. This panel will highlight and discuss different aspects concerning structural and functional determinants of synaptic transmission and plasticity at central synapses. First, Ora Ohana (ZMNH, Germany) will talk about the structural and electrical properties of recurrent cortical synapses and their functional consequences for information processing. Joachim Lübke (Research Centre Jülich, Germany) will focus on how structural parameters such as the number, size and distribution of transmitter release sites and the organization of synaptic vesicle pools determines the function of synapses. Francesco Ferraguti (Innsbruck Medical University, Austria) will compare the ultrastructure of excitatory and inhibitory

synapses and the spatial arrangement of glutamatergic and GABAergic receptors by means of freeze-fracture replica immunolabelling. Finally, Silvio Rizzoli (European Neuroscience Institute, Germany) will bridge the gap between synaptic morphology and activity by describing the behaviour of individual synaptic vesicles upon exocytosis by using a novel diffraction-unlimited fluorescence imaging technique (STED microscopy).

Panel • Thursday 4:30–6:30 PM • Bighorn C1

61. Mesocorticolimbic Processing of Decisions in Health and Mental Disease

Aaron Gruber, Matthew Roesch, Michael Frank, Jonathan Cohen

Good choices depend on the ability to estimate the outcomes of actions and to then perform actions that maximize future benefit, such as reward intake or injury avoidance. This process involves learning from past action-outcome experience and can engage cognitive processes such as attention and working memory to select appropriate responses in complex or ambiguous situations. This panel explores how mesocorticolimbic processing contributes to decision making, and how dysfunction in these circuits may play a role in poor decision making and cognitive control in psychiatric disease. Matthew Roesch will present data demonstrating differences in outcome-related information encoded by neurons in orbitofrontal cortex, amygdala and ventral tegmental area in rats performing a discounting task. Aaron Gruber will present data showing that synchronization of activity in nucleus accumbens with activity in prefrontal cortex and hippocampus depends on task context in healthy rats, and that neural signaling in these circuits as well as performance on a discounting task are disrupted in a rodent model of schizophrenia. Michael Frank will present results from a computational-based analysis of human behavior showing that polymorphisms within striatal and prefrontal genotypes are associated with modulation of independent parameters within a reinforcement learning framework. Lastly, Jonathan Cohen will present data from computational, behavioral and imaging studies that examine the role of prefrontal cortex for cognitive control in human subjects, and alterations that occur in subjects with schizophrenia.

Panel • Thursday 4:30–6:30 PM • Bighorn C2/C3

62. Stop Yawning and "See" What's New at D2

Amy Newman, Gregory Collins, Bruce Jenkins, Jeffrey Dalley

Dopamine is the primary neurotransmitter associated with the psychomotor stimulant effects and addictive liability of cocaine and other stimulant drugs

of abuse. Moreover, drugs that block dopamine D2-like receptors are used clinically to treat schizophrenia and other neuropsychiatric disorders, despite debilitating side effects. Recently, D2-like receptors have received particular attention in psychostimulant abuse as their availability is related to cocaine's pleasurable effects in both humans and nonhuman primates. In this panel presentation, Amy Newman will provide an introduction on the challenges of dissecting the roles of the D2 and D3 receptor subtypes in drug addiction and will describe D3-selective antagonists that are efficacious in animal models of drug abuse without incapacitating motor side effects. Greg Collins will describe additional models in rodents that have provided separation between D2, D3 and D4-mediated behaviors. Bruce Jenkins will present phMRI studies of D2 and D3 receptors that relate brain localization and function of these receptors to dyskinesia in rats and monkeys. Finally Jeff Dalley will describe studies that support a role for D2/D3 receptors in the nucleus accumbens in trait impulsivity, and the switch to compulsive cocaine taking.

Panel • Thursday 4:30–6:30 PM • Hasty's

63. Circadian Organization of the Retina: Genes, Neuromodulators, and Networks

Michael Iuvone, Gianluca Tosini, Robert Lucas, Douglas McMahon

The retina possesses an incredible capability to adapt to changes of light intensity over ~9 orders of magnitude between day and night. Some of this adaptive capability occurs by a form of synaptic plasticity referred to as network adaptation, which is subject to control by retinal circadian clocks. Two important mediators of network adaptation are melatonin and dopamine, which promote dark- and light-adaptation, respectively. The speakers in this panel will present new data on the organization of circadian clock networks in the retina, and the roles of specific clock genes and neuromodulators in the circadian control of retinal function. The first speaker will be Gianluca Tosini, who will describe recent studies on the role of melatonin receptors in the regulation of circadian rhythms and scotopic (dim light) visual processing. Rob Lucas will then describe rhythms in the photopic (bright light) and mesopic visual pathways of the mouse retina, and the intriguing new finding that these pathways are anomalously active in cry1-/- and cry2-/- mutant mice. Doug McMahon will present studies on the regulation of retinal circadian clocks by dopamine and GABA. Lastly, Mike Iuvone will discuss the role of dopamine and D4 receptors in generating circadian rhythms of metabolism and gene expression in photoreceptor cells of mouse retina, and new data on rhythms and adaptation in a mouse with retina-specific disruption of the tyrosine hydroxylase gene. Collectively, these

presentations will highlight significant recent advances in our understanding of circadian organization of the mammalian retina.

Minicourse– Thursday 4:30–6:30 PM • Ptarmigan A

64. Novel Strategies for CNS Regeneration and Modern Rehabilitation—Part 1

Milos Pekny, Pablo Celnik, Klas Blomgren, Maurice Curtis, George Kuhn

The brain is the most complex organ. It regulates a wide range of biological processes and controls most of the physical, emotional and cognitive functions. The ability to store information and to learn, as well as to adapt to a continuously changing environment, is critical for proper function of the central nervous system. Indeed, the human brain continuously undergoes structural and functional remodeling, which is the basis for brain plasticity. Plasticity is also the underlying mechanism for functional recovery following brain injury. This minicourse focuses on some novel strategies for CNS regeneration and modern neurorehabilitation. Dr. Blomgren will focus on the effect of tumor irradiation on the cognitive abilities of children and animal experimental subjects and on the ways this irradiation-induced cognitive deficit can be restored. Dr. Pekny will present the role of reactive astrocytes in CNS regeneration and will show data suggesting that some reactive astrocytes in adult human brain behave as neural stem cells. Dr. Curtis's talk will summarize the current state of our understanding of neurogenesis in the adult diseased brain as a basis for novel treatment strategies. Dr. Kuhn's presentation will show the role of neurotrophic factors in neurogenesis and recovery after stroke. Dr. Nilsson will talk about physical exercise and multimodal stimulation and their importance for both prevention and neurorehabilitation. Finally, Dr. Dinse will present dancing as a powerful motorical, sensory and cognitive stimulant and will discuss its potential for the prevention of motorical and cognitive decline in the elderly and for stroke rehabilitation.

Part 2 is scheduled for Thursday, January 29, 8:30–10:00 PM.

Panel • Thursday 4:30–6:30 PM • Ptarmigan B

65. Membrane Protein Trafficking within in Distinct Neuronal Compartments

Michael Tamkun, Jeffrey Martens, Don Arnold, José Esteban

Tremendous advances in ion channel and neurotransmitter receptor structure and function have been made over the past 20 years. The next frontier in this area of neuroscience is to understand how living cells process these membrane

proteins in real time. Rapid modulation of channel surface expression and localization is likely to represent a central mechanism in the regulation of neuronal electrical excitability in both synaptic and extra-synaptic regions. This session will examine the dynamic trafficking mechanisms involved in localizing various channels and receptors to specialized neuronal compartments. Emphasis will be placed on single molecule tracking approaches in addition to live cell fluorescent protein imaging. Michael Tamkun (Colorado State Univ.) will discuss the mechanisms underlying delayed rectifier K+ channel trafficking, localization and function on the soma of hippocampal neurons. Jeff Martens (Univ. of Michigan Medical School) will present data that define the mechanisms regulating protein transport to cilia of olfactory sensory neurons and the associated human pathologies. Don Arnold (Univ. of Southern California) will focus on the molecular mechanisms underlying trafficking of ion channels to specific axonal and dendritic compartments. José Esteban (Centro de Biología Molecular, Universidad Autónoma de Madrid (UAM)) will end the session with a discussion of the dynamic movement of AMPA receptors into synaptic regions during the establishment of long term potentiation.

Panel • Thursday 4:30–6:30 PM • Ptarmigan C

66. Mechanisms of Neuron-Glia Interaction in Myelination

Timothy Kennedy, Elior Peles, Jonah Chan, Matthew Rasband

Neurons and myelinating glia establish functional relationships during development that are controlled by the integration of complex molecular signals and pathways. Myelin formation is an exquisite example of an extensive cell-cell interaction between the myelin-forming cell and the neuron. Ultimately, myelination partitions axons into a series of functionally specialized segments: nodes of Ranvier, paranodes, juxtaparanodes, and internodes. These specializations organize and cluster ion channels that underlie axonal function. In this session, Dr. Elior Peles will discuss molecular mechanisms that direct node of Ranvier formation in the PNS; Dr. Jonah Chan will address mechanisms that initiate cell polarity and Schwann cell myelination; Dr. Matthew Rasband will discuss mechanisms that regulate node of Ranvier formation in the CNS; and Dr. Timothy Kennedy will address mechanisms that underlie the maintenance of paranodal junctions in the CNS.

67. Making Better Scientists through Chemistry: Norepinephrine, Psychostimulants, and Cognitive Enhancement

Barry Waterhouse, Kong Fatt Wong-Lin, Jill McGaughy, Kara Agster, Craig Berridge

"One in five *Nature* readers—mostly scientists—say they up their mental performance with drugs such as Ritalin", WebMD, April 28, 2008. While the survey cited in the above article was not scientific, the headline emphasizes the growing non-medicinal use of psychostimulant drugs to promote wakefulness, increase concentration, and enhance cognitive performance in normal individuals. Amphetamine-like psychostimulants share in common the ability to increase catecholamine neurotransmission in the brain. For example, methylphenidate (Ritalin) blocks reuptake of synaptically released norepinphrine (NE) and dopamine. This agent is used effectively in low dose, long-term regimens to treat ADHD and is gaining popularity among normal individuals for its cognitive enhancing effects. While there is general agreement regarding the primary biochemical action of methylphenidate, the conceptual framework for understanding the physiological basis for its efficacy in treating ADHD patients and enhancing cognition in normal subjects is lacking. This panel will review recent evidence suggesting a role for the noradrenergic system in optimizing neural circuit functions and mediating the cognitive enhancing actions of methylphenidate. First, KongFatt Wong-Lin (Princeton Univ) will discuss how operation of a biologically-based model of neural circuitry can be optimized by simulating localized cellular actions of NE. Next, Jill McGaughy (Univ. New Hampshire) will present results from behavioral studies in rodents that link the noradrenergic system and sub-regions of prefrontal cortex to specific dimensions of cognitive function. Kara Agster (Drexel Univ) will present electrophysiological data illustrating methylphenidate-induced facilitation of signal transmission through sensory networks in waking rats. Finally, Craig Berridge (Univ. Wisconsin - Madison) will describe relationships between cognitive task performance, NE release, and methylphenidate actions.

Panel • Thursday 8:30–10:00 PM • Bighorn C2/C3

68. Neurodevelopment of Cognitive Systems: Toward a Specification of Risk Trajectories for Child and Adolescent Mental Disorders

Kathleen Anderson, Beatriz Luna, Bradley Schlaggar, Bruce McCandliss, Silvia Bunge

Impaired cognitive functions (attention, executive control, response inhibition, working memory) are core features of many psychiatric disorders and the level of cognitive impairment often predicts the degree of functional recovery following treatment. Psychiatric disorders are increasingly recognized as having their origins in early childhood and adolescence. However, very little is known about how the neural networks that support these cognitive functions develop postnatally and even less about how disruptions in their development confer increased risk for psychopathology. This panel will highlight recent neuroimaging findings from the emerging field of developmental cognitive neuroscience. Speakers will explore how the brain networks that support different cognitive functions develop and how these findings can be used to elucidate the pathophysiological mechanisms leading to the early onset of mental disorders. Beatriz Luna will focus on the development of inhibitory control and associated neural circuits in adolescents. Bradley Schlaggar will present new observations on the emergence of functional connectivity across development and how deviations in these patterns contribute to psychopathology. Bruce McCandliss will discuss new insights into the neurodevelopment of white matter tracts associated with attentional processes and implications for understanding functional disruptions. Finally, Silvia Bunge will present research on the neurodevelopment of cognitive control systems and the relationship between dysfunctional cognitive control and Tourette syndrome. The findings highlighted in this panel will illustrate how a better understanding of the developmental trajectories of the circuits that support cognition can inform when and how to intervene to alter the onset and course of severe psychiatric disorders.

Panel • Thursday 8:30–10:00 PM • Hasty's

69. Descending Pathways and the Modulation of Pain and Body Functions by Mental States

Juan Carlos Marvizon, Hayley Foo, Donna Hammond

Mental states like stress, fear and arousal have a profound influence in pain sensitivity and other body functions. This relationship is controlled by descending pathways projecting from the brainstem to the spinal cord. However, extensive

focus has been placed on how brainstem neurons modulate cardiovascular and sensory function, to the detriment of a broader understanding of their other physiological roles. Similarly, much attention has been paid to midline structures (i.e., the periaqueductal gray and nucleus raphe magnus) whereas complementary pathways in lateral structures have received less attention. Dr. Foo will present an overview of the role of midline and lateral nuclei in physiological regulation, providing evidence that medullary ON and OFF cells play key roles beyond pain modulation. The predominant focus on brainstem regulation of the spinal cord has led to a top-down view of the neuroaxis. Yet, the spinal cord sends ascending projections to the brainstem, creating a spinal-bulbospinal network. Thus, sustained afferent input during persistent pain can alter the pharmacology and physiology of brainstem neurons, which in turn alters spinal cord function. Dr. Hammond will elaborate on the pharmacological and physiological mechanisms by which persistent pain states alter the ability of bulbospinal pathways to modulate nociception. She will discuss the implications of these changes for an organisms ability to respond to stress and pain. Finally, Dr. Marvizon will discuss how pain and stress activate different descending pathways that trigger the release of opioids, noradrenalin and dopamine in the spinal cord, and how these neurotransmitters modulate pain.

Panel • Thursday 8:30–10:00 PM • Ptarmigan A

70. "Rac"ing up Dendritic Spines

Thomas Soderling, Takeo Saneyoshi, Peter Penzes, Scott Soderling, Gary Wayman

Dendritic spines, the locus of glutamatergic excitatory synaptic input, are essential for neuronal circuitry. Abnormal development of spines is characteristic of several forms of mental retardation, and plasticity of spine morphology is essential to stable synaptic plasticity. Both the development and plasticity of spines are dictated by F actin dynamics regulated largely by Rac, a member of the Rho family of GTPases. The activation state of Rac is determined by its GTP-loading that is enhanced by GEFs and suppressed by GAPs. This panel will present recent results on neuronal signaling pathways that modulate Rac GEFs and GAPs to regulate spine morphology and density. Takeo Saneyoshi (Tokyo Japan) will describe an activity-dependent pathway whereby NMDA receptors activate CaM-kinase 1 to phosphorylate and activate betaPIX, a RacGEF, thereby promoting formation of spines and synapses. CaM-kinase 1 and betaPIX are part of a multiprotein signaling complex also containing Pak and GIT1 that is localized in spines. Peter Penzes (Northwestern Univ.) will present evidence for a parallel pathway in which CaM-kinase 2 regulates spine density through the RacGEF kalirin7. Levels of kalirin7 and spine density are coordinately modulated in schizophrenia and Alzheimers. Scott Soderling (Duke) will focus on the involvement in spine development of the RacGAP

WRP (WAVE Associated RacGAP), which is involved in 3p-syndrome mental retardation, and its spatial localization to spines via an FBAR domain. Lastly, Gary Wayman (Washington State University) will discuss how neuronal activity coordinates CREB-dependent transcription of microRNA132 and kalirin7. Elevated kalirin7 activates Rac whereas miR132, by suppressing translation of the RacGAP p250GAP, blocks inactivation of Rac. The coordinated convergence of these two signaling pathways stimulate dendritic morphogenesis and spine formation. These presentation will illustrate the diverse signaling mechanisms by which the actin cytoskeleton can modulate spine density and morphology and give insights to possible deficits in neuropathologies.

Minicourse • Thursday 8:30–10:00 PM • Ptarmigan A

71. Novel Strategies for CNS Regeneration and Modern Rehabilitation—Part 2

Milos Pekny, Pablo Celnik, Klas Blomgren, Maurice Curtis, George Kuhn

The brain is the most complex organ. It regulates a wide range of biological processes and controls most of the physical, emotional and cognitive functions. The ability to store information and to learn, as well as to adapt to a continuously changing environment, is critical for proper function of the central nervous system. Indeed, the human brain continuously undergoes structural and functional remodeling, which is the basis for brain plasticity. Plasticity is also the underlying mechanism for functional recovery following brain injury. This minicourse focuses on some novel strategies for CNS regeneration and modern neurorehabilitation. Dr. Blomgren will focus on the effect of tumor irradiation on the cognitive abilities of children and animal experimental subjects and on the ways this irradiation-induced cognitive deficit can be restored. Dr. Pekny will present the role of reactive astrocytes in CNS regeneration and will show data suggesting that some reactive astrocytes in adult human brain behave as neural stem cells. Dr. Curtis's talk will summarize the current state of our understanding of neurogenesis in the adult diseased brain as a basis for novel treatment strategies. Dr. Kuhn's presentation will show the role of neurotrophic factors in neurogenesis and recovery after stroke. Dr. Nilsson will talk about physical exercise and multimodal stimulation and their importance for both prevention and neurorehabilitation. Finally, Dr. Dinse will present dancing as a powerful motorical, sensory and cognitive stimulant and will discuss its potential for the prevention of motorical and cognitive decline in the elderly and for stroke rehabilitation.

Part 1 is scheduled for Thursday, January 29, 4:30–6:30 PM.

Workshop • Thursday 8:30–10:00 PM • Ptarmigan C

72. Rural and Global Health: Does Intellectual Property Reduce or Increase the Disparity?

Phuong Pham, Carol Stratford, Joseph Belanoff

Protection for intellectual property rights (IPRs) involves finding a balance between the need to provide incentives for innovation and the social benefits of disseminating the results of innovative activity, i.e., new and better drugs, as widely as possible. The recent decisions by Thailand and Brazil to issue compulsory licenses for AIDS drugs triggered strong responses from around the world - fury from drug companies but support from many non-profit organizations. Novartis' pursuit of patent rights for its cancer drug Gleevec in India as well as Abbott's announcement that it will not register any new drugs in Thailand, are a few steps the drug industry took in response to the latest IPR controversy. When the cost of bringing a new drug to the market exceeds $1 Billion, it's impossible for pharmaceutical companies to invest in new drugs that benefit developing countries. So, how important are the middle-income countries as a source of profits for multinational drug companies? What is a "fair share" for them to pay and for which drugs? In addition to Advance Market Commitments, are there other mechanisms that could be developed to stimulate research into diseases that affect primarily developing countries? Besides industry, many universities and their researchers also benefit from licensing fees of new technology/products. The aim of this Workshop is to discuss these issues to better understand all points of view, as well as entertaining potential solutions to find a balance between creativity for real market development and global health/charitable social responsibility for less developed countries.

Panel • Friday 7:30–9:30 AM • Bighorn C1

73. Too Much Excitement? Role of Glutamate Signaling in Relapse to Drug Seeking

Taco De Vries, Peter Kalivas, Chris Pierce, Marina Wolf, Sabine Spijker

This panel provides a set of talks on new and exciting data on drug-induced neuroplasticity, with a particular focus on glutamate signaling in corticostriatal pathways and its role in relapse to drug seeking following prolonged abstinence. Peter Kalivas will talk about cocaine-induced metaplasticity in the nucleus accumbens, including changes in dendritic spine morphology, proteins regulating actin cycling and field potentials evoked from the prefrontal cortex. It will be shown that preventing relapse in the reinstatement model of cocaine seeking by stimulating extrasynaptic mGluRs also prevents the expression of cocaine-induced metaplasticity. Chris Pierce will discuss results indicating differential

influences of AMPA receptor subunit trafficking in the nucleus accumbens shell on the reinstatement of cocaine seeking. Thus, increased insertion of GluR1 subunits into synapses and endocytosis of GluR2 subunits promote the reinstatement of cocaine seeking. Marina Wolf will describe results showing that GluR2-lacking AMPA receptors are added to excitatory synapses in the nucleus accumbens after prolonged withdrawal from cocaine self-administration and mediate the "incubated" cocaine craving observed after prolonged withdrawal. Data will be presented from experiments underway to evaluate the hypothesis that GluR2-lacking AMPA receptors form as a homeostatic response to decreased excitatory transmission after cocaine withdrawal. Sabine Spijker focuses on heroin relapse and will discuss how the synaptic proteome of the medial prefrontal cortex (mPFC) is acutely changed upon re-exposure to heroin-associated stimuli. The resulting synaptic depression at glutamatergic synapses of pyramidal neurons in the ventral part of the mPFC appears critical for cue-induced relapse to heroin.

Panel • Friday 7:30–9:30 AM • Bighorn C2/C3

74. Cannabinoids and the Brain: Behavioral Functions of Endocannabinoids in Motivation and Cognition

Tommy Pattij, Ken Mackie, Larry Parsons, Kornelia Kamprath

The endocannabinoid system, comprised of receptors, endogenous cannabinoids (endocannabinoids), and enzymes responsible for the synthesis and degradation of endocannabinoids is emerging as playing a role in a variety of behaviors. This panel will focus on endocannabinoid transmission in motivation and cognition. In the first talk Ken Mackie will briefly introduce the endocannabinoid system, present recent results highlighting the interplay of THC with this system, and will finish with some speculation on the novel directions the field may take. Larry Parsons will then present data demonstrating that volitional drug self-administration leads to site- and drug-specific alterations in extracellular endocannabinoid levels and he will present results from pharmacologic experiments evaluating the neural substrates that may be important in the endocannabinoid modulation of drug intake. In addition, Larry will present recent evidence that chronic drug exposure can lead to alterations in endocannabinoid function/signaling that may be involved in the maintenance of drug dependence. Next, Tommy Pattij will present data illustrating the involvement of the endocannabinoid system in higher-order cognitive functions, and in particular impulse control processes. Finally, Kornelia Kampraths' focus will be on endocannabinoid signalling in mnemonic functions and she will review evidence showing that endocannabinoids are critically involved in the extinction of

aversive memories. Recent experiments with different mutant mouse lines indicate that endocannabinoids mediate such fear adaptation processes primarily via cortical glutamatergic projections.

Panel • Friday 7:30–9:30 AM • Hasty's

75. Trials and Tribulations on the Translational Research Trail

James Fawcett, John Steeves, Andrew Blight, Dan Lammertse

You have developed a new treatment for your target disease, and you are convinced that it will be beneficial to human patients. What happens next? The path through the preclinical validation, safety testing, design of a clinical study, and then the various trial phases is tortuous and demanding. Moreover, in CNS disorders it has frequently been unsuccessful. There are probably good treatments that have been consigned to the trash can because the clinical trial was poorly designed and therefore unlikely to show efficacy. To undertake a clinical development program takes several years of preparation, so it is important to start planning when you are first convinced you have an effective treatment, rather than wait until all the basic science is finished. The panel will discuss the many issues and processes that need to be considered and how this thought process may need to shape the way you conduct basic science research. The panelists all have experience in the translational process from the perspective of spinal cord injury. James Fawcett will talk about patterns of spontaneous recovery of function, and how they affect the timing of a trial, selection of patients and the number of subjects that need to be recruited. John Steeves will discuss the development of appropriate outcome measures with which to assess efficacy, and the need to match a valid outcome measure with the clinical target and the type of subject recruited. Andrew Blight will describe the preclinical validation process and his experiences with phase 2 and phase 3 trials for potassium channel blockers in spinal cord injury and multiple sclerosis. Finally, Dan Lammertse will talk about the practical problems of running clinical trials from the perspective of the clinician involved in patient care and hospital management.

Panel • Friday 7:30–9:30 AM • Ptarmigan A

76. A Look into Long-Term Potentiation of GABAergic Synapses

Arianna Maffei, Melanie Woodin, Freshteh Nugent, Michela Fagiolini

Long-term modification of synaptic strength was until very recently considered a specific property of excitatory synapses. Inhibitory synapses were

thought to keep circuit excitability in check by preventing runaway excitation and promoting network synchronization to produce oscillatory patterns. New experimental evidence showed that GABAergic synapses can modify their strength in an activity dependent manner. In particular long term potentiation of inhibitory synapses has been observed in several cortical and sub-cortical neuronal microcircuits. Although the functional role of this novel and exciting form of plasticity has not been thoroughly explored, several pieces of evidence are now being gathered. The ability of GABAergic synapses to modify their strength might confer them a more complex function than previously thought. This session will focus on discussing the most recent findings about cellular mechanisms of inhibitory plasticity and its functional role in shaping neuronal circuits, their rewiring in response to drug addiction and experience and in neuropathology. Melanie Woodin will discuss her recent findings demonstrating that inhibitory synaptic plasticity is sufficient for the expression of pathway specific LTP in area CA1. Freshteh Nugent will present her exciting work on the mechanisms of inhibitory plasticity onto dopaminergic neurons in the VTA and its role in opioid addiction. Arianna Maffei will discuss her data on GABAergic LTP mediated experience dependent circuit rewiring in primary visual cortex during development. Michela Fagiolini's presentation will propose a role for GABAergic plasticity in regulating the duration of critical periods and in circuit malfunction in animal models for autism spectrum disorders.

Panel • Friday 7:30–9:30 AM • Ptarmigan B

77. OPRM1 Variation and Reward Sensitivity: Translation across Species and Situation

Christina Barr, William Copeland, Lara Ray, Annika Thorsell

The endogenous opioids mediate natural rewards and are involved in social attachment, aggression, and reproductive behavior. As such, genetic variation that influences endogenous opioid response may impact fitness. Because alcohol mediates some of it's rewarding effects through this system, genetic variants that confer increased sensitivity to natural rewards may also increase alcohol reward, thereby increasing its abuse potential. This panel will discuss how variation at the OPRM1 gene influences sensitivity to both natural rewards and alcohol across multiple species. Dr. Christina Barr (NIH/NIAAA) will show that a common variant in the rhesus macaque mu-opioid receptor gene (OPRM1 C77G) increases reward sensitivity, as reflected in increased infant attachment and alcohol response. She will also discuss how the 77G allele influences novelty seeking and alcohol-induced aggression. Dr. William Copeland

(Duke University) will show that a functionally similar polymorphism in humans (A118G, or Asn40Asp) predicts various aspects of parent-child interactions during childhood and adolescence, suggesting the118G allele to influence development of social attachment in humans. The OPRM1 118G allele is associated with alcohol response under laboratory conditions. Dr. Lara Ray (UCLA) will show that OPRM1 A118G also predicts alcohol response in the natural environment, as assessed by ecological monetary assessment (EMA). She will also present functional neuroimaging data that corroborate these findings. Dr. Annika Thorsell (NIH/NIAAA) is examining whether the A118G polymorphism affects alcohol response and other reward-based behaviors in a rodent model. She will present data from mice expressing a chimeric mu-opioid receptor that includes the human A118G SNP.

Panel • Friday 7:30–9:30 AM • Ptarmigan C

78. Molecular Regulators of Presynaptic Vesicle Cycling and Behavior

Maria Bykhovskaia, Kathrin Engisch, Gyorgy Lonart, Craig Powell

It is now established that synaptic plasticity and fine-tuning of synaptic activity underlies complex cognitive functions, including learning and memory. Although tremendous progress has been made in the investigation of postsynaptic mechanisms, less is known about the presynaptic plasticity and its significance for the behavioral learning. This panel will focus on presynaptic mechanisms and their implications in behavior. Dynamic regulation of the presynaptic vesicle cycle underlies presynaptic plasticity and fine-tuning of synaptic transmission. We will discuss recent advances in understanding the role of the major molecular players in regulating the release of neurotransmitters from nerve terminals, specifically, vesicle proteins synapsins and Rab3a, and an active zone protein RIM1. Although molecular interactions of these proteins have been extensively studied, the physiological role of this pathway is not well understood. We will discuss the function of the synapsin/Rab3a/RIM pathway at the molecular, cellular, and behavioral levels. Maria Bykhovskaia will discuss the role of synapsin, Rab3a, and their interaction in regulating the distribution and cycling of synaptic vesicles and calcium sensitivity of neurotransmitter release. Kathrin Engisch will discuss multiple ways by which Rab3a participates in activity-dependent modulation of release. Gyorgy Lonart will discuss the role of a Rab3 interacting molecule, RIM1, in the regulation of norepinephrine release and working memory. Craig Powell will focus on the role of these presynaptic proteins in behavioral studies.

Panel • Friday 4:30–6:30 PM • Bighorn C1

79. NMDA Receptor Modulation in Health and Disease

Robert Zaczek, Joseph Coyle, Robert Schwarcz, Richard Bergeron, Robert Greene

NMDA receptors are subject to multiple forms of modulation. For example, the NR1 subunit has a binding site for glycine/D-serine that must be occupied for glutamate to trigger channel opening. Mounting evidence suggests that reduced occupancy of the glycine site due to lower availability of D-serine could account for NMDA receptor hypofunction in schizophrenia. Coyle will review recent findings obtained in mice with null mutations of serine racemase (SR). SR-/- mice have >85% reduction of D-serine in the cerebral cortex. They exhibit a down regulation of GAD67, parvalbumin and GAT1 cartridges but no change in calretinin in cortex, similar to schizophrenia. Schwarcz will review his studies on the effects of altered levels of kynurenic acid (KA), an endogenous antagonist of both the NMDA receptor and the alpha-7 nicotinic receptor. He has demonstrated elevated KA in the cortex and caudate in post-mortem studies in schizophrenia. Bergeron utilizes the acute hippocampal slice preparation with whole cell clamp of CA1 pyramidal neurons to study glutamatergic neurotransmission at the Schaffer collateral synapse. He has found a significant reduction in NMDA receptor currents and >80% loss of LTP in SR-/- mice that can be reversed by perfusion of the slice with D-serine. He will contrast these findings to those in the GlyT1+/- mice, which have increased glycine site occupancy. Greene utilizes the same acute hippocampal slice preparation to characterize the effects of D1/5 dopamine receptors on NMDA receptor currents. He will describe how D1/5 receptor activation elicits bi-directional long-term plasticity (i.e., both LTP and LTD) of NMDA receptor mediated synaptic currents in CA1 pyramidal neurons and how the polarity is determined by subunit composition. Zaczek will chair the session and moderate the discussion.

Panel • Friday 4:30–6:30 PM • Bighorn C2/C3

80. Clinical Models of Drug Reward and Craving: Tools to Identify Therapeutic Potential in the Treatment of Addiction

Malcolm Reid, Thomas Newton, John Mendelson, Charles O'Brien

Understanding the neurobiological processes responsible for the motivation to use alcohol and other drugs remains an important challenge in addiction research. Clinical studies modeling the subjective, biochemical and

physiological correlates of withdrawal, craving and reinforcement have been a key element in this endeavor and have reached a stage where such tests can be employed to identify patient populations, and screen potential medications, for the treatment of addiction. This panel will present research from human laboratory studies with cocaine, methamphetamine, MDMA, and alcohol dependent patients. Malcolm Reid will explore the conditioned and unconditioned stimulus properties of cocaine cue and dosing procedures, and demonstrate distinct quantitative EEG activation profiles in prefrontal cortex associated with cocaine craving and reward. Tom Newton will present recent developments in the use of virtual reality to elicit craving for methamphetamine and demonstrate the use of computer based choice tasks to evaluate methamphetamine reinforcement levels. John Mendelson will describe pharmacokinetic and pharmacodynamic studies of acute MDMA, with a focus on neuroendocrine and emotional response profiles, and present data on the interactions of MDMA with adrenergic medications. Charles O'Brien's work examines the involvement of the endogenous opioid system with alcoholism. He will present recent genetic findings on a SNP that is associated with increased rewarding properties of acute alcohol, increased risk for alcohol or opioid dependence, and a marked therapeutic response to naltrexone treatment for alcoholism. A discussion of these human laboratory measures, and whether they may predict or identify therapeutic potential in drug or alcohol dependent patients, will follow.

Panel • Friday 4:30–6:30 PM • Hasty's

81. How Would We Perceive the World without Endocannabinoids?

Kuei-Yuan Tseng, Cecilia Hillard, Thanos Tzounopoulos, David Lovinger

Understanding how endocannabinoid (EC)/cannabinoid receptor signaling system influences synaptic transmission in neural networks from brainstem to cortico-subcortical structures is an important step to uncover the role of ECs in brain functioning. First, Cecilia Hillard will summarize data demonstrating that one very important function of the ECs is to regulate the response of the brain to stress. Chronic stress exposure to rodents results in dysregulation of EC signaling; in particular, chronic unpredictable stress decreases EC signaling in the hippocampus and causes a loss of CB1 receptor regulation of GABA release in the prefrontal cortex. Using in vitro patch clamp recordings, Thanos Tzounopoulos will show how EC signaling is critical in determining synaptic learning rules in the auditory cochlear nucleus following Hebbian and anti-Hebbian patterns in a cell-specific manner. Next, David Lovinger will present evidence for involvement of EC retrograde signaling in several forms of synaptic plasticity at GABAergic and glutamatergic synapses in the striatum, and discuss

the possibility that EC-dependent LTD produces a frequency-dependent shift in net output from striatal projection neurons. Finally, Kuei Tseng will provide data in favor of a role EC signaling in determining the balance of pre- and post-synaptic events underlying the developmental regulation of synaptic plasticity in the adolescent prefrontal cortex. We will conclude by proposing a common cellular mechanism that couples the role of EC-dependent plasticity in the regulation of cortico-subcortical functioning and its link to different forms neuroadaptations and behavioral outcomes.

Panel • Friday 4:30–6:30 PM • Ptarmigan A

82. Rolling, Sleeping, and Breathing: Serotonin Connection?

George Ricaurte, James Leiter, George Richerson, Dietrich Richter, Una McCann

The popular recreational drug 3, 4-methylenedioxymethamphetamine (MDMA, "Ecstasy") has the potential to damage brain serotonin neurons. Functional consequences of MDMA-induced toxicity to brain serotonin neurons remain largely unknown but recent work has implicated serotonin in sleep-disordered breathing (sleep apnea). Although sleep apnea is most commonly seen in older overweight individuals, recent preliminary findings suggest that MDMA-induced damage of brain serotonin neurons could put young and otherwise healthy recreational MDMA users at risk for sleep disorder breathing. This panel will address the mechanism by which this might occur. Dr. Leiter (Dartmouth University) will begin by discussing our present understanding of the role of medullary 5-HT neurons in the respiratory control. Dr. Richerson (Yale University) will follow and present data from a series of studies demonstrating that brain serotonin neurons have all of the properties of central respiratory chemoreceptors. Dr. Richter (August-Universität Göttingen) will then discuss current concepts regarding the role of brain serotonin systems and respiratory rhythm generation. Dr. McCann (Johns Hopkins) will conclude by presenting data from healthy young adults who have been exposed to the serotonin neurotoxin, MDMA, and who have been found to have dose-related increases in sleep disordered breathing. Collectively, these presentations are intended to highlight the vital role of brain serotonin in respiratory control, in general, and in sleep disordered breathing, in particular.

Panel • Friday 4:30–6:30 PM • Ptarmigan B

83. Stem Cell-Based Clinical Strategies

Hans Keirstead, Alan Lewis, Jane Lebkowski, Chris Airriess, Donald Fink

This panel will present three stem-cell based clinical approaches from the viewpoint of industry leaders, with comment from academia and the FDA. Novocell Inc., Geron Corporation and California Stem Cell Inc. are pioneers in the translation of stem cell technologies to the clinic. Alan Lewis will present Novocell's pre-clinical application of human embryonic stem cell-derived insulin-secreting to diabetes. Jane Lebkowski will present Geron Corporation's pre-clinical application of human embryonic stem cell-derived oligodendrocyte progenitor cells to acute spinal cord injury. Chris Airriess will present California Stem Cell Inc.'s pre-clinical application of human embryonic stem cell-derived motor neuron progenitor cells to spinal muscular atrophy and amyotrophic lateral sclerosis. Dr. Donald Fink of the FDA will present regulatory considerations pertinent to these stem cell-based clinical strategies. The session will be moderated by stem cell researcher Hans Keirstead. This panel will provide a unique perspective on the state of stem cell-based clinical approaches, and underscore the risks and benefits of pioneering stem cell technology to the patient, the companies, and the field.

Panel • Friday 4:30–6:30 PM • Ptarmigan C

84. Nanoscale Protein Assembly and the Pathogenesis of Amyloid-Related Neurodegenerative Disease

William Bunney, Christopher Ross, Judith Frydman, Charles Glabe, Steven Potkin

There is increasing evidence that many neurodegenerative diseases can be conceptualized as protein misfolding disorders. The panel will critically review this evidence and discuss the diagnostic and treatment implications for human brain disorders including Huntington's Disease (HD), Alzheimer's Disease (AD) and Parkinson's Disease (PD). Chaperones play an important role in achieving the 3-D functional structure of many proteins. Failure of appropriate folding often leads to accumulation of misfolded polypeptides with the potential to aggregate. Normally, these misfolded proteins are removed by a variety of "Quality Control" mechanisms. Failure of the cellular protein "Quality Control" mechanisms may result in accumulation of misfolded proteins in a variety of aggregates and protein inclusions. Understanding the pathways of quality control, as well as those leading to formation of intracellular aggregates may illuminate the

preferential accumulation of amyloidogenic proteins linked to human disease. Amyloidogenic proteins aggregate into several structurally distinct classes that are common to many different proteins. The role of these different aggregates and oligomers in disease pathogenesis is a critical question that remains to be established. Conformation dependent antibodies specifically recognize the various aggregation states and can be used to identify pathological steps and targets for intervention. A variety of ex-vivo tissue models with measurable physiological function have been developed for these illnesses. The use of these models to develop therapeutic targets will be discussed.

Don't forget to visit the exhibits

Fifteenth Annual
Blood-Brain Barrier Consortium Meeting
in collaboration with the
International Brain Barriers Society

"Engaging Neuroscience to Advance Brain Barriers Translational Research"

March 20-21, 2009
Salishan Resort, Gleneden Beach, Oregon, USA

You are cordially invited to attend the meeting "Engaging Neuroscience to Advance Brain Barriers Translational Research", March 20-21, 2009. This meeting is a collaborative effort with the International Brain Barriers Society. The purpose of the meeting is to explore concepts and technology used in neuroscience research, for their potential application to advancing brain barriers research. Topics include molecular physiology, transport biology, neurodevelopment, intercellular communication, and imaging, of the brain and brain barriers.

The Fifteenth Annual Blood-Brain Barrier Consortium meeting titled "Assessing Tumor Response and Toxicity as They Relate to CNS Vascular Targeted Therapy" will be held March 19, 2009. The meeting is partially funded by an R13 meeting grant from the NCI, NINDS and NIDCD. Both meetings will be held at Salishan Resort, Gleneden Beach, on the Oregon Coast.

The scientific program, registration, and travel information are available at www.ohsu.edu/bbb/meeting2009/

For further information, please contact:
Emily Hochhalter @ 503-494-5626 hochhalt@ohsu.edu

Poster Abstracts

P1. Understanding Resting Neurotransmitter Levels in the CNS: Second-by-Second Measurements using Microelectrode Arrays

Peter Huettl, Erin R. Hascup, Kevin N. Hascup, Martin Lundblad, Michelle Stephens, George Quintero, Francois Pomerleau, Greg A. Gerhardt

An understanding of how resting glutamate and dopamine (DA) levels are regulated in the central nervous system is central to understanding correlates between neurotransmitter function and behavior. Our unique coated (enzyme-based for glutamate) microelectrode arrays (MEA) are designed to selectively measure resting glutamate and DA levels in the CNS of awake animals. These MEAs used in conjunction with amperometry have sub-second (600 msec) time resolution with high selectivity over major electroactive CNS interferents such as DOPAC and ascorbate. Average measured glutamate resting 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) when one considers typical microdialysis probe recoveries (10-20% in vitro) and that the MEA placement is much closer to glutamate release in synapses than microdialysis probes. Less dilution and loss of signal to diffusion is occurring and thus the MEA signals should be larger than those observed with microdialysis studies. Using site-specific mPD coated MEAs we can now accurately measure resting DA levels in the intact rat striatum (20 nM) or 6-OHDA lesioned striatum (3 nM) by subtracting the signal recorded in brain areas shown to lack DA content from signals recorded in the striatum. The advantages of using MEAs instead of microdialysis probes are the high temporal resolution allowing for more rapid measurements as well as the close spatial orientation. Studies show that we can measure the effects of psychomotor stimulants and assess behavioral events.

P2. Pharmacological Characterization of Plasma Membrane-Expressed Human Trace Amine-Associated Receptor 1 (TAAR1) by a Novel Bioluminescence Resonance Energy Transfer (BRET) cAMP Biosensor

R. R. Gainetdinov L. S. Barak, A. Salahpour, X. Zhang, B. Masri, T. D. Sotnikova, A. J. Ramsey, J. D. Violin, R. J. Lefkowitz, M. G. Caron

Trace amines are recognized neurotransmitters in regulating invertebrate physiology. Recent studies indicate that trace amines may also play a role in mammalian physiology by binding to a novel family of G protein-coupled receptors (GPCRs). A major obstacle impeding the careful pharmacological characterization of trace amine associated receptors (TAARs) is their extremely poor membrane expression in model cell systems, and a molecular basis for this phenomenon has not been determined. In the present study, we show that the addition of an asparagine-linked glycosylation site to the N terminus of the human trace amine associated receptor 1 (TAAR1) is sufficient to enable its plasma membrane expression, and thus its pharmacological characterization with a novel cAMP EPAC (exchange protein directly activated by cAMP) protein based bioluminescence resonance energy transfer (BRET) biosensor. We applied this novel cAMP BRET biosensor to evaluate the activity of putative TAAR1 ligands at human TAAR1. This strategy to express TAARs and to identify their ligands using a cAMP BRET assay could provide a foundation for characterizing the functional role of trace amines in vivo and suggests a strategy to apply to groups of poorly expressing GPCRs that have remained difficult to investigate in model systems.

P3. Antisocial, Substance-Dependent Boys: Hypofunction in a Neural Network for Processing Risky Decisions

Thomas Crowley, Manish Dalwani, Carl Lejuez, Yiping Du, Marie Banich

Brain function in antisocial youths, who repeatedly take dangerous risks. may be influenced by frequently associated drug use, as well as by genes contributing to both the drug and the antisocial problems. HYPOTHESIS: Antisocial boys' brains process risky decisions differently than others' brains. METHOD: We studied 20 adolescent boys in treatment for severe conduct and substance problems, and 20 normal control boys. In each of 90 "Decision trials" subjects chose between doing a cautious behavior (always earning 1 cent), or a risky behavior (sometimes earning 5 cents, sometimes losing 10 cents). The probability of losing increased as the game progressed. For comparison, 90 "Directed trials" required no decision-making, but had visual-auditory stimuli and motor responses almost identical to the Decision Trials. With fMRI we examined

the 4-sec pre-response decision period. Our main contrast was (Decision Trial Activation)—(Directed Trial Activation). RESULTS: As controls decided between doing the risky or the cautious behavior, they activated an extensive neural network, including thalamus, nucleus accumbens, midbrain, insula, anterior cingulate, medial and superior frontal gyri, dorsolateral prefrontal cortex, and vermis. Currently substance-free antisocial boys, despite performing the task like controls, had widespread hypofunction in that network, including insula, anterior cingulate, dorsolateral prefrontal cortex, orbitofrontal cortex, and vermis. CONCLUSION: Hypoactivity of a risk-decision network may contribute to antisocial boys' dangerous, excessive, and sustained risk-taking. (Support: NIDA grants DA-009842 and DA-011015, and a donation from the Kane Family Foundation)

P4. Role of NADPH Oxidase in the Pathobiology of Traumatic Brain Injury

Alan Faden, David Loane, Kimberly Byrnes, Mian Xie, Bogdan Stoica

Microglial associated inflammatory responses have been implicated in acute neurodegeneration. We have shown that p22phox—a subunit of the NADPH oxidase complex—is up-regulated after spinal cord injury and its expression highly correlated with that of a number of microglial associated inflammatory factors. Activation of primary microglia or a microglial cell line with LPS up-regulates expression of p22phox and the catalytic subunit gp91, increasing NADPH oxidase activity and the release of reactive oxygen species (ROS). These activated microglia are toxic to neurons in culture; inhibiting NADPH oxidase activity- using siRNA's directed at p22phox or gp91, or pharmacological inhibitors like apocynin—markedly reduces such neurotoxicity. Gp91 knockout mice show reduced NADPH oxidase activity after controlled cortical impact (CCI) induced traumatic brain injury (TBI), as well as smaller lesion volumes and better behavioral recovery, than wild type litter-mates. Similarly, treatment with the structurally different NADPH oxidase inhibitors apocynin or DPI significantly reduce lesion volume, microglial activation and ROS release, while improving neurological outcomes after CCI as compared to vehicle treated controls. Together, these observations indicate that microglial activation after TBI increases NADPH oxidase activity and ROS release, thereby contributing to secondary tissue injury and related neurological deficits. NADPH oxidase appears to be a potentially important therapeutic target for the treatment of TBI.

P5. Dopamine D1 and D2 Modulation of Glutamatergic Transmission in Adult Rat Nucleus Accumbens Recorded *In Vitro*

Frederic Huppe-Gourgues, Patricio O'Donnell

Dopamine (DA) in the nucleus accumbens (NA) is essential for reward processing. We have recently shown that D2 receptor activation can enhance the amplitude of cortico-accumbens depolarizing post-synaptic potentials in slices from adult, but not juvenile, rats by recruiting a GABA component (Benoit-Marand and O'Donnell, *Eur. J. Neurosci*, 2008). As this depolarization would be the result of increased Cl^- conductance, it should not be accompanied by an increase in medium spiny neuron (MSN) excitability. Here, we tested this with whole-cell recordings in slices containing the NA from adult rats (PD >60), assessing the modulation of cell excitability by the D2 agonist quinpirole, and whether quinpirole potentiates the effects of AMPA on cell excitability. Perfusion of AMPA (0.2 μM) in the recoding bath increased the MSN excitability. The D2 agonist quinpirole (2 μM) increased the number of evoked spikes without significantly depolarizing the neurons. The GABA-A antagonist picrotoxin (50 μM) did not affect MSN excitability. AMPA had a similar effect in presence of picrotoxin (n=7, p=0.95) or quinpirole (n=9, p=0.16). Thus, D2 receptors do not modulate AMPA responses in slices from adult rats, suggesting that interactions with other glutamatergic receptor could explain the *in vivo* glutamate modulation by DA.

P6. Does the H5N1 Influenza Virus Induce Neurodegeneration and the Development of Post-encephalitic Parkinsonism?

Richard Smeyne, Haeman Jang, David Boltz, Robert Webster

Following the great influenza pandemic of 1918, an unusual worldwide epidemic of neurological diseases was observed. Circumstantial and epidemiological evidence linked several movement disorders, including post-encephalitic Parkinsonism (PEP) to this virus. This finding is of great concern considering the current global spread of the highly pathogenic H5N1 virus, an avian influenza strain with considerable pandemic potential. If H5N1 were to cause the next human influenza pandemic, it is possible that another epidemic of PEP could ensue. We are investigating if infection with H5N1 influenza viruses can either directly or indirectly lead to neurodegeneration in the brain, including the substantia nigra, the main structure that is lost in Parkinsonon's disease. In H5N1 infected mice, approximately 50% show neurological symptoms that

include hindleg paralysis and tremor. In these animals, H5N1 was observed- by immunohistochemistry- in numerous sites within the CNS including the substantia nigra, CA3 of the hippocampus, locus coeruleus, red nucleus, solitary nucleus, reticular nucleus and vagal nucleus infecting both neurons and microglia. Activated caspase-3, but not Fluorjade B, co-localised to these same areas, suggesting that the presence of the virus could induce neuronal cell death via an apoptotic mechanism. In the infected regions, we also observed a marked microgliosis without astogliosis.These results suggest that the H5N1 virus can affect motor systems in the CNS and if pandemic flu would strike, be a possible etiological agent for PEP. (Supported by the National Parkinson's Foundation and the American Lebanese Syrian Associated Charities.)

P7. Mapping and Identification of GABAergic Neurons That Project to Cardiac Vagal Neurons in the Nucleus Ambiguus Using Photo-Uncaging

David Mendelowitz, Julie G. Frank

The neural control of heart rate is determined primarily by the activity of parasympathetic cardiac vagal neurons (CVNs) originating in the nucleus ambiguus (NA). GABAergic inputs to CVNs play an essential role in determining the activity of these neurons including a robust inhibition during each inspiratory burst, however, the origin of GABAergic innervation has yet to be determined. To identify the populations of GABAergic neurons that project to CVNs, caged glutamate was used to identify both 1) clusters and 2) individual GABAergic neurons that evoke inhibitory GABAergic synaptic responses in CVNs in transgenic mice in which GABAergic neurons are identified with expression of eGFP under the control of the mouse Gad1 gene promoter. CVNs were patch-clamped in the whole cell configuration and the transverse slice was divided into approximately 90 quadrants, each 200 microns by 200 microns that were sequentially photostimulated. Inhibitory post synaptic currents (IPSCs) were recorded in CVNs following a 5msec photostimulation of 50 microM caged glutamate. The areas that contained GABAergic cells projecting to CVNs were 200 microns medial, 400 microns medial, 200 microns ventral, and 1200 microns dorsal and 1000 microns medial to patched CVNs. Once foci of GABAergic cells that project to CVNs were determined, photostimulation of individual GABAergic neurons was conducted. The results from this study indicate GABAergic neurons located in 4 specific areas project to CVNs, and that these neurons can be individually identified and stimulated using photouncaging to recruit a GABAergic neurotransmission to CVNs.

P8. Adolescent Seizures and Loss of Dentate Granule Neurons: Neuroinflammation and Neurogenic Capability

Gaylia Jean Harry, Christopher McPherson, Jennifer Collins, Andrew Kraft

In the adolescent brain, seizure activity results in damage to hippocampal dentate granule (DG) neurons. These neurons continue to be generated from the subgranular zone (SGZ), but the extent of repair capability has not been determined. We induced seizures and apoptotic death of DG neurons in 21-day-old CD1-mice with the hippocampal neurotoxicant, trimethyltin (2.0 mg/kg, ip). 24-hrs post-injection, neuronal death was accompanied by a resident microglia response and induction of CCL2, TNFa, TNF receptors, and TLR2 mRNA. A robust induction of hippocampal neurogenesis occurred during this localized immune response. At the inner portion of the dentate blades, new cells contact Iba-1+ microglia. BrdU+ cells migrate into the dentate and mature into NeuN+ neurons sufficient to fully replace the 40% neuronal loss. STAT3 staining suggested a contribution of cytokine signaling in induction and migration. To identify the molecular profile of the "neurogenic niche" we captured the SGZ by laser capture microdissection and isolated RNA for Affymetric microarray analysis. Genes were clustered into functional groups using David Bioinformatic Resources database or overlaid on canonical pathways using Pathway Architect using KEGG, DIP, and BIND databases. With regards to cytokines, these data analyses suggested a differential expression of key molecules in the IL-1a signaling pathway, confirmed by qPCR. It has been implied that inflammation down-regulates neurogenesis. Our data suggests that the local immune response of microglia does not inhibit the hippocampal neurogenesis in the adolescent brain but rather may contribute to the significant level of repair.

P9. Oxidative Stress and Synaptic Decline in Mild Cognitive Impairment

Stephen W. Scheff, Mubeen A. Ansari

Oxidative stress and synaptic loss have been associated with progressive neuropathology in Alzheimer's disease (AD). We have previously shown that synaptic numbers are significantly lower in frontal cortex (FC) of AD subjects. The aim of this study was to investigate the relationship between antioxidant capacity, localized oxidative stress, and synaptic protein makers in postmortem FC from non-cognitive impairment (NCI, control) subjects, patients with mild cognitive impairment (MCI), mild/moderate-AD (mAD), and end stage AD. Groups were matched for age, sex, and postmortem time. Brain samples were processed for mitochondrial and synaptosomal fractions. The samples were analyzed for several antioxidants [glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), superoxide dismutase

(SOD), catalase (CAT)]. In addition, several markers of lipid peroxidation [thiobarbituric acid reactive species (TBARS), 4-hydroxynonenal (HNE), acrolein] were analyzed along with protein carbonyl and 3-nitrotyrosine (3-NT) levels. Quantitative changes in the levels of synaptic protein (Synapsin-I, PSD-95, and SAP-97, GAP-43) were analyzed by Western blot. The results showed significant oxidative stress in frontal cortex of MCI, mAD and AD brain that correlated significantly with changes in synaptic markers. All analyzed antioxidants and oxidants were significantly altered in the synaptosomal fraction in MCI, mAD, and AD compared to NCI. Oxidative stress, which is more localized to the synapses, might underlie AD-related synaptic loss. These results suggest a need to initiate anti-oxidative therapy early in the disease process, perhaps with the starting of MCI or even at an earlier time point (pre-MCI) for precautionary protection. (NIH/NIA AG27219)

P10. Posiphen and Analogs: Experimental Alzheimer Agents That Reduce Amyloid-beta Peptide by Lowering Amyloid Precursor Protein Levels in Culture and *In Vivo*

Harold Holloway, Donald Ingram, Maria Maccecchini, Nigel Greig

Major hallmarks of Alzheimer's disease (AD) are synaptic loss and abnormal protein deposition, particularly of toxic amyloid-β (Aβ) peptide that is derived from amyloid-β precursor protein (APP). Current AD therapeutic strategies include improving cognitive processes and reducing brain Aβ levels. Cholinesterases inhibitors (ChE-Is) and memantine are the only FDA approved drugs for AD, but primarily provide symptomatic relief. Our ChEI, phenserine, lowers APP and Aβ in neurons via non-cholinergic post-transcriptional regulation of APP synthesis. Whereas phenserine improves cognition and regional cerebral glucose utilization in AD subjects (*Ann Neurol* 63:621-31, 2008), like other ChEIs, it is ultimately dose-limited by cholinergically mediated nausea and vomiting. A new series of AD drug candidates were hence designed to optimally match ChEI activity with APP/Aβ lowering action to generate agents that substantially lower brain amyloid-β and yet provide immediate sympomatic improvement: posiphen and analogs. These agents lower APP and Aβ levels in culture and animals, and possess ChEI activities less potent than phenserine to allow administration of greater doses to thereby generate greater Aβ inhibition in brain. Ongoing studies are elucidating the mode of action of these compounds on the APP processing pathway. Posiphen has proven well tolerated in initial phase 1 clinical trials at doses substantially greater than tolerated with phenserine, and achieves concentrations associated with substantial inhibition of Aβ in animal models. These results suggest that posiphen and analogs are promising experimental drugs for diseases where a lowered brain APP or Aβ is valued. (Supported in part by the Intramural Research Program, NIA/NIH)

P11. Distinct AMPA-type Glutamatergic Synapses in Developing Rat CA1 Hippocampus

Elizabeth A. Stubblefield, Tim A. Benke

We assessed α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPAR) properties during synaptogenesis in order to describe the functional development of individual glutamatergic synapses onto principal neurons in the CA1 region of the rat hippocampus. Following pharmacological isolation of AMPAR-mediated glutamatergic synaptic currents (evoked by stimulation of the Schaffer Collateral pathway, sEPSCs), we substituted extracellular strontium for calcium to take advantage of the properties of asynchronous EPSCs (aEPSCs) in order to analyze populations of individual synapses. During early postnatal development (P5-P22) at CA1 synapses, we found that for AMPAR-mediated aEPSCs, quantal amplitudes increased while single-channel conductances were relatively consistent across development. aEPSC amplitudes were directly modulated by the number of activated receptors and showed the highest coefficient of variation (CV) at P5-7. AMPAR kinetics (aEPSC τdecay) were variable from P5-P7 but became slower from P8 until P18. As with quantal amplitude, aEPSC τdecay exhibited the greatest CV at P5-7. Further analysis demonstrated that in many neurons at P5-7, two functionally distinct populations of synapses were activated. One population was characterized by fast kinetics, while the other was characterized by slower kinetics similar to those found at P8-18. AMPAR-mediated sEPSCs had greater inward-rectification at ages P5-P7 compared to P8-22, suggesting an age-dependent mechanism of calcium regulation with implications for synaptic plasticity and neurodevelopmental disorders. Synapses that contain faster kinetics may selectively cluster inward-rectifying and likely calcium-permeable AMPARs. These findings support a mechanism of tightly controlled developmental regulation of AMPAR expression: at P5-7 two different types of AMPAR synapses are present, whereas at P8-22 synapses are more similar.

P12. Contributions of Hindbrain GLP-1 Receptor Activation to the Control of Food Intake: Role of the Endogenous Ligand and Mediation by Several Intracellular Pathways

Matthew R. Hayes, Harvey J. Grill

WITHDRAWN

P13. An Essential Role for Dopamine in Fear Conditioning

Jonathan P. Fadok, Tavis M. K. Dickerson, Richard D. Palmiter

Although the role of dopamine (DA) in reward is well established, its role during aversive events is less well understood. To examine the role of DA in fear-related learning, dopamine-deficient (DD) mice were tested in a fear-potentiated startle (FPS) paradigm. DD mice display normal responses to a range of sound intensities and footshock; however, when tested 24 hours after 30 conditioning trials where a light predicted a foot shock, DD mice do not manifest long-term memory for FPS. Interestingly, FPS can be established in DD mice by administering L-dopa (to restore DA) immediately after training, but not 1 or 3 hours later. These results clearly indicate that DA is necessary for learning a Pavlovian fear conditioning task. Mice lacking the dopamine D1 receptor (D1R KO) also have impaired FPS, whereas FPS is intact in mice lacking the dopamine D2 receptor (D2R KO). Administration of the D2R-like antagonist eticlopride before training blocks learning in D2R KO mice, indicating a need for multiple DA receptor subtypes. Short-term memory (STM) and shock sensitization, assessed 10 minutes after training, also depend on DA. STM is intact, yet shock sensitization is impaired in D2R KO mice, whereas D1R KO mice had intact shock sensitization but impaired STM. Using pharmacological and genetic methods, we are currently investigating in which brain regions DA is mediating its effects during FPS.

P14. Tetanus Toxoid Vaccination Induces Acute Spinal Cord Neuroinflammation and Accelerates Onset of ALS-like Disease in hmSOD1 Transgenic Rat Model

Brent Harris, D. Graber, K. Merkens, C. Cogbill, A. Hernan, D. Elwood, E. Stommel

Amyotrophic lateral sclerosis (ALS) is a fatal, rapidly progressive adult-onset neurodegenerative disease in which the upper and lower motor neurons (MN) gradually die. Sporadic ALS, which accounts for about 90% of cases, has no known etiologies and is thought to occur to due to some combination of genetic predisposition and environmental exposures. Epidemiologic studies have shown an increased incidence of ALS in military personnel. We hypothesize that more frequent vaccinations with tetanus toxoid (TT) in military personnel may induce MN degeneration. TT is formulated by formaldehyde inactivation of tetanus toxin and linked to aluminum to improve immunogenicity. MN can directly uptake TT and retrogradely transport it. The toxoid, aluminum conjugate, and/or formaldehyde could have cytotoxic effect in MN. To test a link between TT vaccination and ALS we have employed a rat hmSOD1(G93A)

transgenic model that develops ALS-like paralysis due to motor neuron degeneration over 4-5 months. For acute studies, WT and pre-clinical hmSOD1 animals are injected in the right hamstring with vaccine or saline, sacrificed 3 days post injection, and lumbar spinal cord tissues harvested for examination of astrocyte and microglial activation. Preliminary findings show an ipsilateral increase in gliosis acutely in the lumbar spinal cord of TT injected animals. For long-term studies, wild type and hmSOD1 animals are injected with saline or TT vaccine at one and three months of age prior to onset of paralysis. Initial trials suggest an earlier onset of ALS-like disease in TT injected hmSOD1 animals compared to saline injected and no clinical effect in WT animals. We conclude that some component of TT may induce localized neuroinflammation that in genetically susceptible animals can accelerate ALS. This may also be a useful model to induce neuroinflammation and ALS initiation to study new susceptibility genes in ALS.

P15. Serotonin Receptors of the Nucleus Accumbens Shell Differentially Affect Feeding in the Rat

Wayne E. Pratt, Megan Connolly, Mary Jane Skelly

The nucleus accumbens is known for its role in directing goal-seeking behavior. Although there has been recent interest in understanding how serotonin may be involved in modulating the reinforcing impact of drugs of abuse, few experiments have examined the role of serotonin receptors within the nucleus accumbens shell on feeding behavior. These experiments tested whether stimulation or blockade of serotonin (5-HT) 6 or 1/7 receptors of the nucleus accumbens would impact feeding on a high fat/sucrose palatable diet in non-deprived animals. Male Sprague-Dawley rats were implanted with bilateral guide cannulas aimed at the nucleus accumbens shell and were presented with a high fat/sucrose diet for daily 2-hr feeding sessions. Food intake and locomotion were monitored throughout each session. On experimental days, individual groups of rats (N= 6/group) received intra-accumbens infusions of the following serotonergic agents prior to placement in the feeding chambers: the 5HT6 agonist EMD 386088 (at 0, 1.0, and 4.0 microg/side); the 5HT6 antagonist SB252585 (at 0, 1.0, 2.0, and 4.0 microg/side); the 5HT1/7 receptor agonist 5-CT (at 0, 0.5, 1.0, and 4.0 microg/side); or the 5HT7 receptor antagonist SB 269970 (at 0, 1.0, 2.0, and 4.0 microgr/side). 5-HT6 receptor stimulation of the nucleus accumbens shell significantly increased food consumption compared to vehicle infusion, while 5-HT(1/7) receptor stimulation dose-dependently decreased food intake across the 2-hr. Neither antagonist affected food intake. These experiments indicate that different serotonin receptors within the nucleus accumbens shell serve unique roles in modulating feeding behavior.

P16. Integrated Neurochemical and EEG Measurements in Freely Moving Rodents

Daniel Aillon, Erik Naylor, David Johnson, Hans Harmon, George Wilson

Second by second measurement of neurochemicals such as glutamate, glucose and lactate in the brain using electrochemical biosensors is a powerful tool that has been used to profile concentration changes due to pharmacological and behavioral interactions. Now this ability to measure metabolic changes in targeted regions of the brain has been integrated with a very low-noise, turn-key electroencephalograph (EEG) recording system. As an example of this system's strength, male C57 mice were simultaneously implanted with an intracerebral guide cannula targeting the prefrontal cortex and electrodes to measure cortical EEG. Real-time, second by second measurements of glucose levels and EEG activity were recorded over a 24 hour period. Results showed that glucose levels in mice transitioning from waking to slow-wave sleep rose an average of 116 ± 27.0 uM (n =57 episodes). Conversely, glucose levels in mice transitioning from sleep to wakefulness resulted in an average decrease of 121 ± 27.0 uM glucose. (n=54 episodes). Additional data will be presented demonstrating the system being used to monitor changes of neurotransmitters during normal sleep and periods of sleep deprivation. This ability to continuously monitor neurochemical regulation along with cortical activity will allow researchers to more thoroughly investigate the mechanisms regulating brain function. Furthermore, because of its robust design, this new, integrated biosensor and EEG measurement system can be easily integrated into complicated behavioral experiments where animals are subjected to experimental challenges such as extended sleep deprivation or during seizure episodes.

P17. Polyinosinic:Polycytidylic Acid Elicits NF-kappa B Activation and IL-6 Production in CNS-derived Cells

Frederick Franken, Aaron Janowsky

Polyinosinic:polycytidylic acid (poly I:C) is a synthetic double-stranded RNA capable of eliciting an immune response via recognition by Toll-like 3 receptors (TLR3) and the double-stranded RNA dependent kinase (PKR). Poly I:C has recently been employed in a wide range of experimental models of central nervous system (CNS) infection, including developmental models of schizophrenia. Therefore, we sought to determine whether poly I:C could elicit an immune response in immortalized cell lines of macrophage, microglial, and astrocytic origins. Exposure to poly I:C in all three cell lines caused activation

of nuclear factor-kappa B (NF-kappa B) as indicated by Western blot analysis of the transient degradation of inhibitory protein I-kappa B-alpha. Furthermore, the presence of Interlukin-6 (IL-6), a proinflammatory cytokine released during an immune response, was measured by ELISA following 24 hours of exposure to a range of poly I:C concentrations. A robust dose-dependent increase in IL-6 production following poly I:C exposure was observed in macrophage and astrocytic cell lines. These results indicate that immortalized cell lines of microglial and astrocytic origin could provide useful tools for the study of immune responses within the central nervous system following viral infection or poly I:C exposure in experimental models.

P18. Organization and Reorganization of Forepaw Barrelettes in Cuneate Nucleus in Juvenile Rats

Robert Waters, Qiuhong Yang, Cheng-Xiang Li

Large-scale cortical reorganization in rodent forepaw barrel subfield (FBS) cortex, which follows forelimb amputation, likely depends on changes in subcortical input. Here, we describe the detailed organization of forepaw cuneate nucleus (CN), a first order somatosensory relay nucleus, followed by a description of changes that occur in CN following forelimb amputation. Cytochrome oxidase staining of CN reveals the presence of clusters of cells, called barrelettes, which are likely associated with the representation of the forepaw. Knowledge of the relationship of these cell clusters to the forepaw skin surface will serve as an ideal template to study potential changes in representation that may occur following forelimb amputation. In rats anesthetized with Ketamine/Xylazine (100 mg/kg), multiunit recordings were used to map the forelimb representation in CN in relationship to the underlying barrelettes. Once the relationship was established, the studies were repeated in deafferented juvenile rats. Our results support the notion that barrelettes are composed of four medial-lateral running bands associated with the representation of digits 2 (D2) through D5. Immediately adjacent to the digit representation are clusters associated with the representation of the three digit pads, and lying most medial are two clusters associated with the thenar (TH) and hypothenar (HT) pads. D1 representation lies immediately ventral to the pads. Following forelimb amputation, cells within the barrelettes become responsive to new input from the shoulder, trunk, and face. The present study is an important step towards identifying subcortical structures that may provide a substrate for large-scale cortical reorganization that follows forelimb amputation.

P19. Loss of Peptidergic and Nonpeptidergic Intradepidermal Nerve Fibers in an STZ-induced Mouse Model of Insensate Neuropathy

Douglas Wright, Janelle Ryals, Megan Johnson

Peptidergic and nonpeptidergic nociceptive neurons represent parallel yet distinct pathways of pain transmission, but the functional consequences of such specificity are not fully understood. We quantified the progression of peptidergic and nonpeptidergic axon loss within the epidermis in the setting of a dying-back neuropathy induced by diabetes. STZ-induced diabetic MrgD mice heterozygous for GFP in nonpeptidergic DRG neurons were evaluated for sensitivity to mechanical and noxious thermal and chemogenic stimuli 4 or 8 weeks post-STZ. Using GFP expression in conjunction with PGP9.5 staining, nonpeptidergic (PGP+/GFP+) and peptidergic (PGP+/GFP) intraepidermal nerve fibers (IENFs) were quantified at each time point. At 4 weeks post-STZ, nonpeptidergic epidermal innervation remained unchanged while peptidergic innervation was reduced by 40.6% in diabetic mice. By 8 weeks post-STZ, both nonpeptidergic innervation and peptidergic innervation were reduced in diabetic mice by 34.1% and 43.8%, respectively, resulting in a 36.5% reduction in total epidermal IENFs. Behavioral deficits in mechanical, thermal, and chemogenic sensitivity were present 4 weeks post-STZ, concomitant with the reduction in peptidergic IENFs, but did not worsen over the next 4 weeks as nonpeptidergic nerve fibers were lost, suggesting that the early reduction in peptidergic nerve fibers may be an important driving force in the loss of cutaneous sensitivity. Furthermore, behavioral responses were correlated at the 4-week time point with peptidergic, but not nonpeptidergic, innervation. These results reveal that peptidergic and nonpeptidergic nociceptive neurons are differentially damaged by diabetes, and behavioral symptoms are more closely related to the losses in peptidergic epidermal nerve fibers.

P20. Elevated Potassium Associated with Ischemia Produces Neuronal Damage Independent of Calcium Influx into Hippocampal CA1 Cells

M. Bruce MacIver, Lisa Rotenstein, Rona G. Giffard

We investigated the short-term physiological effects of traditional oxygen glucose deprivation (OGD), and compared this to more physiologically relevant ODG solutions with altered ionic compositions that reflect changes seen in vivo during ischemia (ODG + low sodium, high potassium and low pH; OGD+HiK), or high potassium alone (90 mM; HiK); either in the presence or absence of calcium (low Ca + high Mg; CaMg). A five minute exposure

to ODG solution produced a complete depression of synaptic transmission, measured using Schaffer-collateral to CA1 neuron evoked population spike (PS) amplitudes. Full recovery from this depression occurred within 10 min following reperfusion with normal solution. OGD+HiK solution exposure also completely depressed PS amplitudes, and only partial recover of response amplitudes were seen on reperfusion. HiK solution completely mimicked the OGD+HiK effect, indicating that the elevated potassium alone was sufficient to produce irreversible damage. Removing Ca from the reperfusion solution improved the speed of recovery from HiK exposure, but did not improve the degree of recovery. These results indicate that increased potassium concentrations during ischemia appear to be the major contributing factor to neuronal damage. The lack of a protective effect of CaMg solution during reperfusion suggests that the flow of calcium into cells during ischemia do not contribute substantially to neuronal damage—this is consistent with the lack of protection seen in clinical trails of NMDA and calcium antagonists, but opposite to the protective effect demonstrated in focal ischemic models with a variety of glutamate receptor blockers. (Supported by NIH DA017884 and NS053898)

P21. The Food Intake Inhibition of Leptin: Amplification of the Satiating Effects of Gastrointestinal Signals in NTS Neurons with AMP-Kinase Activity as a Putative Common Signal

Harvey J. Grill

WITHDRAWN

P22. PKC Regulation of Intraneuronal Zinc Mediates Neuronal Survival during Preconditioning

Mandar Aras, Elias Aizenman

Sub-lethal activation of cell death processes initiate pro-survival signaling cascades in neurons. As Zn2+ liberation from intracellular stores acts as a common mediator in many neuronal cell death pathways, we tested whether a sub-lethal increase in intracellular Zn2+ is required for neuroprotection in an in vitro model of excitotoxic tolerance. Neuronal free Zn2+ transiently increased following preconditioning with chemical ischemia and, importantly, this Zn2+ rise was both necessary and sufficient for conferring neurons excitotoxic tolerance. Lethal exposure to NMDA in non-preconditioned neurons led to a delayed increase in Zn2+ that contributed significantly to excitotoxicity.

This excitotoxic increase in Zn2+ was not present in preconditioned neurons, but could be restored by chelating preconditioning-induced free Zn2+. This suggests that preconditioning-induced Zn2+ triggers the expression of Zn2+-regulating processes, which, in turn, prevent subsequent Zn2+-mediated toxicity. Indeed, preconditioning increased metal response element (MRE)-driven Zn2+-regulated gene expression in neurons. Protein kinase C (PKC) activity was required not only for MRE activation, but also for the preconditioning-induced increase in Zn2+ fluorescence, suggesting that PKC may act directly on the intracellular source of neuronal Zn2+. As such, we identified a putative PKC phosphorylation site at serine-32 (S32) of metallothionein that was important in modulating Zn2+-regulated gene expression and in conferring excitotoxic tolerance, strongly suggesting that PKC can alter the release of Zn2+ from the Zn2+-binding protein. These results indicate that neuronal Zn2+ serves as an important, highly regulated signaling component responsible for the initiation of a neuroprotective pathway critical for excitotoxic tolerance.

P23. Ultrastructural Investigation of Synaptic Vesicle Pools in *Drosophila melanogaster*

Annette Denker, Silvio O. Rizzoli

The Drosophila neuromuscular junction (NMJ) is a widely used model system for the investigation of the mechanism of synaptic transmission and synaptic vesicle recycling. In this system, two functionally distinct vesicle pools have been proposed: the exo/endo cycling pool, which is released upon mild stimulation and is thought to be located at the bouton periphery, and the reserve pool, which is only released upon stronger stimulation and is believed to be located in the bouton center (Kuromi and Kidokoro, *Neuron*, 1998; see also review by Kuromi and Kidokoro, *J. Neurocytol.*, 2003). The physical separation of these two pools, deduced from light microscopy experiments, is however contradictory to the known ultrastructure of the Drosophila NMJ boutons, as their centers appear devoid of vesicles in electron microscopy. To elucidate the localizations of the different vesicle pools, we employed photoconversion, a technique combining labeling of recycled vesicles with a fluorescent styryl dye (FM 1-43) and visualization of localization by electron microscopy. The technique is based on the dye's property to produce reactive oxygen species upon illumination. These compounds oxidize diaminobenzidine, in which the preparation is incubated, to produce an electron-dense precipitate, which can be detected within the labeled vesicles in the electron microscope. The vesicles from both pools appear to be scattered throughout the boutons. Moreover, the bouton centers generally appear to be devoid of labeled vesicles (or of other labeled organelles). We conclude that the functionally distinct vesicle pools are fully intermixed at the ultrastructural level.

P24. MR Imaging of Beta-Amyloid Plaques and Histological Analysis in Both Human Alzheimer's Disease and APP/PS1 Transgenic Mice

Qing X. Yang, Mark Meadowcroft, James Connor

WITHDRAWN

P25. Ephrin-A2 Localization in Primary Somatosensory Cortex during the Early Postnatal Period

Cynthia L. Kenmuir, Nicolas L. Chiaia, Richard D. Lane, Richard D. Mooney

Ephrin ligands and Eph receptors play a variety of signaling roles in cortical development extending from neurogenesis and process outgrowth to cellular migration, axon pathfinding, and topographic innervation of targets. Previous work has established that ephrins and Ephs are expressed in rodent primary somatosensory cortex (S-I) during late embryonic and early postnatal periods. Here, we focus on identifying the intracortical location and cellular source of ephrin-A2 in postnatal rats. Immunohistochemistry (IHC) and Western blot revealed ephrin-A2 protein expression within the posterior medial barrel subfield (PMBSF) of S-I at postnatal day 8 (P8), which is the age of peak protein expression within layer IV for several other ephrins and Ephs (Mooney et al, 2007). Double immunofluorescent labeling with neuron-specific Hu RNA-binding protein demonstrated that the ephrin-A2 cortical expression was confined to neurons. Moreover, in situ hybridization (ISH) of ephrin-A2 mRNA at P7 revealed discrete cellular staining within barrel septa and abundant cellular staining in dysgranular cortex adjacent to the PMBSF, indicating a cortical source for the ephrin-A2 protein expression seen in S-I. Finally, ISH at P2 revealed cellular staining of ephrin-A2 in the developing cortical plate as well as in the ventroposteromedial (VPM) thalamus. These results indicate that ephrin-A2 may have a continuous or multiphasic postnatal expression profile in both VPM and in cortex, with an especially strong hybridization boundary in dysgranular cortex at the PMBSF perimeter. These findings are consistent with involvement of ephrin-A2 in axon terminal refinement, pattern maintenance, and boundary formation in rat barrel cortex. (Supported by NIH P01-NS049048)

P26. Angiogenesis and Exercise-Induced Neuroprotection in the Substantia Nigra of MPTP-treated Mice

Michelle Smeyne, Richard Jay Smeyne

Exercise promotes neurological, cognitive, and cardiovascular health. Epidemiological studies provide evidence that aerobic exercise or lifetime exercise habits decrease the risk of stroke, Alzheimer's and Parkinson's disease (PD). In rodent models of ischemia, treadmill exercise reduces infarct size as well as increasing capillary volume, expression of vascular endothelial growth factor (VEGF) and angiopoietins. Angiogenesis, increased capillary density, and heightened blood flow in the brain have been documented in animals living in exercise conditions compared to inactive controls. Remodeling of the brain microvasculature is of interest in the study of PD for several reasons. First, there is an increase in the number of endothelial cells in the vasculature of the SNpc of PD patients. Second, monkeys treated chronically with MPTP show changes in the SN that include increased vessel number, SN volume occupied by vessels, and number of VEGF expressing neurons. Previously, we have shown that exercise protects dopaminergic (DA) neurons in the SN from MPTP toxicity. The amount of DA neuron protection is dependent upon the duration and the intensity of voluntary running wheel exercise. Three months of exercise promotes increased capillary length in the SN. Molecules involved in angiogenesis signaling, VEGF and VEGFR1 (Flt-1) are present in DA neurons, while HIF1 alpha and HIF2 alpha are localized in different cell populations in the SN. HIF1 alpha is present in dopaminergic neurons, while HIF2 alpha is present in astrocytes. We are currently investigating exercise-induced angiogenesis as one mechanism that provides protection from oxidative stress in the SN.

P27. The Development of Excitatory and Inhibitory Intracortical Circuits in the Reorganized Somatatosensory Cortex of Neonatally Amputated Rats

Richard D. Lane, Cynthia L. Kenmuir, Nicolas O. Chiaia, Richard D. Mooney

Previous work has shown that the reorganization of the forelimb-stump representation in the primary somatosensory cortex (SI) of neonatally amputated rats includes the expression of significant hindlimb input mediated via an intracortical pathway from the SI hindlimb representation (*J. Neurophysiol.* 85:407-413, 2001). However, the hindlimb receptive fields in the SI stump representation are extensively suppressed by GABAergic synapses within the

stump representation of adult animals (*J. Neurophysiol.* 92:372-379, 2004). These findings raise several questions regarding the development of excitatory and inhibitory intracortical circuit between the hindlimb and forelimb-stump representations: 1. When is the intracortical circuit underlying the anomalous hindlimb projection established?, and 2. Is the development of GABAergic suppressive circuitry coincident with that of the aberrant excitatory pathway? To address these questions, the forelimb-stump representations of normal and neonatally amputated rats were mapped between the ages of postnatal day (P) 10 and 28 utilizing multi-unit electrophysiological recording procedures to map receptive fields within the stump-forelimb representation prior to and during GABA receptor blockade. The results suggest that the inter-representational intracortical circuit initially develops as an excitatory circuit by P14 and is subsequently suppressed by GABAergic synapses by P21.

P28. Reinstatement of Drug-Seeking Behavior in Adolescent and Adult Male Rats

James Doherty, Chen Li, Yvonne Ogbonmwan, Bonnie Williams, Kyle Frantz

Adolescence is a developmental stage known for heightened novelty-seeking and risk-taking across multiple species. Teenagers are often labeled as "vulnerable" to drug abuse, and early-onset drug use increases chances of later drug addiction. A key characteristic of addiction is relapse after abstinence. In lab animals, drug intake and relapse are modeled with self-administration and reinstatement after extinction, neither of which has been studied extensively in adolescence. We tested cocaine and morphine self-administration in adolescent and adult rats, followed by extinction and reinstatement. After recovery from catheterization, adolescent (35 days old) and adult (74-78 days old) male rats acquired lever-pressing maintained by cocaine (0.36 mg/kg/infusion) or morphine (0.38 mg/kg/infusion) on an FR1 schedule, in 2 hr daily sessions over 14 days (cocaine) or 1 hr sessions 6 days/week for 4 weeks (morphine). Cocaine intake was nearly identical across ages. In contrast, adolescents took less morphine than adults. Following recess (1, 14, 30 or 60 days for cocaine; or 15 days for morphine), both cocaine and morphine groups displayed similar rates of extinction across ages. On the other hand, rats that self-administered cocaine as adolescents displayed less cue-induced reinstatement after 30 or 60 days of recess, compared with adults. Reinstatement was similarly attenuated in rats that took morphine as adolescents, compared with adults. Thus, younger rats may be less sensitive than adults to some long-term effects of drug exposure. If so, it may be possible to identify ontological neuroprotective factors, and capitalize upon them to design relapse prevention strategies for humans.

P29. Effect of Sleep on Working and Long-Term Memory

Katya Potkin, William E. Bunney

Sleep plays an important role in the consolidation of memory. This has not been previously studied in adolescents. Forty male and female adolescents (ages 10-14) were randomly assigned to sleep and no sleep conditions. Subjects were trained on a paired-associate declarative memory task and a control task at 9am, and tested at night (12 hours later) without sleep. The same number of subjects was trained at 9pm and tested 9am following sleep. An increase of 27% in long-term memory, as measured by the number correct in a paired-associate test, following sleep was observed compared to the group who was tested at the same time interval without sleep ($p<0.005$). The control working memory task was not affected by sleep. This was the first study to specifically look at the effects of sleep on declarative memory in an adolescent sample. Adolescent memory is important in school performance and consequent social functioning, and is affected by sleep.

P30. Clinical and Neurocognitive Correlates of Suicidal Behavior in Bipolar I Disorder

Raphael J. Braga, Jessica Garno, Nisha Chitkara, Yaniv Shaya, Nisali Gunawardane, Katherine E. Burdick

Background: Suicide is the 11th leading cause of death in the USA and bipolar disorder (BPD) patients have the highest risk of suicidal behavior among all psychiatric illnesses. However, there is a paucity of data focusing on correlates of suicide in BPD. Methods: We assessed 37 BPD patients to identify the factors that contribute to suicide attempts. Mood ratings were completed at the time of the neurocognitive assessment, which included measures of IQ, attention, memory and executive functioning. History of suicidal behavior (e.g. method, lethality) was characterized using a structured interview. Additional measures of impulsivity, aggression, hopelessness, and childhood trauma were also completed by patient self-report. Results: Nineteen patients had no history of suicide attempts and did not differ demographically (mean age 41+/–13 years, 21% female), from eighteen patients with a significant suicide attempt history (mean age 39+/–12 years, 47% female, all p-values>0.05). In general, cognitive functioning was also comparable between groups, with only verbal memory differentiating the non-attempters (HVLT delayed mean = 5.4+/–2.3) from the attempters (HVLT delayed mean = 7.7+/–2.0). Among the attempters, higher lethality was associated with executive dysfunction, [Trails B ($r=0.52$; $p=0.04$), Wisconsin Card Sorting Perseverative errors ($r=0.64$; $p=0.02$)] and with lower levels of impulsivity [Barrett Impulsivity Rating Scale ($r=0.67$; $p=0.01$)]. Conclusions: Our results suggest that BPD patients with a history of suicide attempt perform better on tests of verbal memory than non-attempters. Further,

for those who have attempted suicide, increased severity of attempt is associated with more impairment in executive functioning and lower ratings of impulsivity.

P31. Fluorescence Activated Cell Sorting: A Novel Method to Study Neurons Selectively Activated during Context-Specific Cocaine Sensitization

Danielle H. Guez, Brandon K. Harvey, Marina R. Picciotto, Bruce T. Hope

We hypothesize that learned associations between specific stimuli are encoded within a pattern of sparsely distributed neurons called "neuronal ensembles". In context-specific locomotor sensitization, rats learn to associate cocaine stimuli with stimuli in the drug administration environment. When cocaine-activated neuronal ensembles in nucleus accumbens are specifically lesioned, rats no longer express the learned response to cocaine. Therefore, the cells that make up these neuronal ensembles are important for behavior. We are developing a method for identifying neuroadaptations in neuronal ensembles responsible for context-dependent cocaine sensitization. This is a unique approach; until now, scientists have studied changes in homogenates of the relevant brain areas. Homogenates do not differentiate between activated and non-activated cells, and are therefore likely to obscure the changes seen only in activated cells. We use c-fos-lacZ transgenic rats to identify the neurons that make up these ensembles. Electrophysiological activation of neurons activates the c-fos promoter to transcribe the lacZ gene, which encodes beta-galactosidase. Beta-gal expression is used to identify the small number of electrophysiologically activated cells amongst the majority of minimally activated cells that do not express beta-gal. These cells are labeled with antibodies and separated using Fluorescence Activated Cell Sorting (FACS). We have separated beta-gal-positive from -negative neurons and extracted mRNA from sorted cells. We are currently using real time 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 the unique molecular neuroadaptations in selectively activated neuronal ensembles that mediate learned associations.

P32. Probing Afferent-Specific Synaptic Strength and Transmission in the Nucleus Accumbens

Garret Stuber, Dennis Sparta, Antonello Bonci

Rapid changes in synaptic function are hypothesized to aid in the storage of new information about the environment and contribute to subsequent behavioral output. While many brain structures are involved in different learning

processes, neurotransmission in the nucleus accumbens (NAc) is thought to integrate limbic and motor information in order to facilitate behavior, especially in response to rewards or to stimuli that predict them. The NAc receives glutamatergic inputs from areas such as the medial prefrontal cortex, the basolateral amygdala (BLA), and the hippocampus, as well as rich dopaminergic innervation from the midbrain. However, because dopamine and glutamate afferents to the NAc are heterogeneous is has been particularly difficult to study afferent specific synaptic transmission or strength. Here, we describe techniques to selectively perturb neurotransmission in brain slices using optical stimulation of afferent terminals in the NAc expressing channel rhodopsin-2 (ChR2). The BLA of adult mice were injected with an adeno-associated virus coding for ChR2-YFP under control of the CaMKIIα promoter, to predominantly transfect glutamatergic projection neurons. Following 10-12 days post transfection YFP positive fibers were observed millimeters away from the injection site, including the NAc. Patch-clamp electrophysiological experiments in medium spiny neurons of the NAc revealed that terminal stimulation of BLA afferents via activation of ChR2 resulted to detectable EPSCs at -70 mV that were blocked by bath application of the AMPAR antagonist, CNQX (10 μM). Ongoing studies will address whether there are afferent specific changes in synaptic strength following goal-directed learning.

P33. Medial Amygdalar Nucleus: A Novel Limbic Hypoglycemia-Sensing Region in the Rodent That Communicates Directly with the Glucose-Sensing Ventromedial Hypothalamic Nucleus

Ligang Zhou, Dina Podolsky, Zhen Sang, Barry Levin, Rory McCrimmon

It is well established that the hypothalamus and hindbrain contribute to the regulation of glucose homeostasis through specialized glucose-sensing neurons. Whether other brain regions have glucose-sensing capability is unknown. In the current study, we identify a novel limbic glucose-sensing region, the medial amygdalar nucleus (MAN). We show that the MAN contains glucokinase-expressing neurons, and responds directly to manipulation of glucose both in vitro and in vivo. In vitro, we demonstrate using fura-2 calcium imaging, that the MAN contains glucose-excited neurons (GE) and glucose-inhibited neurons (GI). Subsequently, using single-cell rt-PCR we found that 54% of GE neurons and 42% GI neurons express glucokinase, a critical regulator of neuronal glucosensing. In vivo, we show in rodent studies that infusion of 2-deoxyglucose (to create local glucopenia) to the MAN amplifies the counterregulatory glucagon and epinephrine responses during systemic hypoglycemic. Finally, we demonstrate that the MAN is linked reciprocally with the ventromedial nucleus (VMN), an established glucose-sensor during hypoglycemia, via a neural pathway involving urocortin 3 and steroidogenic factor 1 (SF1) neurons.

In conclusion, we demonstrate the presence of a novel glucose-sensing region in the MAN, and show that it is reciprocally linked with the VMN. This suggests that glucose-sensing in different brain regions may be integrated, resulting in a tightly regulated, counterregulatory hormonal response to hypoglycemic stress.

P34. Mapping of Active Inputs on Thalamorecipient Neurons in the Auditory Cortex Revealed a Novel Mechanism of Effectiveness of Thalamocortical Pathways

Robert J. Richardson, Jay A. Blundon, Ildar T. Bayazitov, Stanislav S. Zakharenko

Despite being substantially outnumbered by intracortical inputs on thalamorecipient neurons, thalamocortical projections efficiently deliver acoustic information to the auditory cortex. This disconnect between functional and morphological data suggests that to outperform intracortical inputs, thalamocortical inputs must exploit additional mechanisms such as synchronization/amplification of thalamic inputs or making thalamocortical synapses stronger. We hypothesized that to increase their effectiveness, thalamic projections may also form synapses at optimal locations on dendritic trees of cortical neurons. Performing calcium imaging of individual dendritic spines, we constructed maps of active thalamic and intracortical inputs on dendritic trees of thalamorecipient cortical neurons. These maps revealed that thalamic projections synapse on stubby dendritic spines within 100 microns of the soma, whereas intracortical projections are less selective and synapse at various locations on different types of spines. Two-photon glutamate uncaging at stubby dendritic spines in the perisomatic area elicited the strongest postsynaptic potentials in the soma of thalamorecipient cortical neurons. These results suggest a novel mechanism of effectiveness of thalamocortical synaptic transmission in the sensory cortices—the positioning of crucial afferent inputs at optimal synaptic locations.

P35. DaunO2 Lesions Neuronal Ensembles That Encode Learned Associations between Cocaine and Its Administration Environment

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Learned associations between cocaine and its administration environment modulate cocaine-induced locomotor sensitization, also called context-specific sensitization. We hypothesize that a small fraction of sparsely distributed nucleus accumbens neurons called "neuronal ensembles" encode this learned association and are selectively altered during repeated drug exposures to

mediate context-specific sensitization. We tested this hypothesis by specifically lesioning these ensembles, utilizing the prodrug Daun02 that undergoes cytotoxic conversion to daunorubicin by bacterial beta-galactosidase (beta-gal) expressed in activated neurons of c-fos-lacZ transgenic rats. We injected rats with cocaine outside their home cages in a locomotor activity chamber once daily for seven days. Seven days later on "induction day," we injected rats in the same (paired) or different (unpaired) environment with cocaine, to induce accumbens beta-gal, or with saline as a control that does not induce beta-gal. Ninety minutes later we injected Daun02 or vehicle into the accumbens. Three days later on "test day", we injected cocaine or saline to all rats in the paired environment and assessed sensitized locomotor activity and accumbens neuronal activity using beta-gal histochemistry. Daun02 injections in the paired environment after cocaine, but not saline injections attenuated cocaine-induced locomotor activity and accumbens beta-gal. Saline-induced locomotor activity and accumbens beta-gal were unaffected. Daun02 injections in the unpaired environment or in rats injected with acute cocaine on induction day did not affect cocaine-induced locomotion. These findings suggest that Daun02 attenuates context-specific sensitization by lesioning specific neuronal ensembles that encode the learned association between cocaine and the drug administration environment.

P36. Phasic Dopamine Deficiency Impairs Cue-Dependent Learning

Larry S. Zweifel, Jones G. Parker, Paul E. M. Phillips, Richard D. Palmiter

Dopamine (DA) neurons fire in two characteristic modes, tonic and phasic, which are thought to have distinct roles in DA signaling and behavior. DA neurons respond to a variety of environmentally salient stimuli and phasic DA neuron activity shifts from unpredicted rewards to predictive stimuli during reinforcement learning. Although considerable evidence supports the role of phasic DA in learning about salient events, observations that hyper- and hypodopaminergic signaling modulate incentive motivation, or "wanting", but not learning has led to the suggestion that DA acts downstream of reward learning to provide an incentive salience signal to engage in goal-oriented tasks. The interdependence of incentive motivation and learning, the role of DA in motor and cognitive function, and the inability to selectively disrupt patterns of DA neuron activity has encumbered the ability to provide a comprehensive analysis of the role of phasic DA in behavior. N -methyl-D-aspartate-type glutamate receptors (NMDARs) potently modulate burst firing by midbrain DA neurons, suggesting that selective inactivation of NMDAR signaling in DA neurons could provide the means to assess the behavioral function of DA neuron burst firing. We found that selective genetic inactivation NMDARs in DA neurons

attenuated DA neuron burst firing and subsequent DA release, without altering tonic neural activity. Disruption of phasic DA neuron activity impaired the acquisition of numerous conditioned behavioral responses and dramatically attenuated learning about discrete cues that predicted rewarding events while leaving motivation and other DA-dependent behaviors unaffected.

P37. Orbitofrontal Cortex Inactivation Impairs Reversal of Pavlovian Learning by Interfering with Disinhibition of Responding for Previously Unrewarded Cues

Kathryn Burke, Yuji Takahashi, Jessica Correll, P. Leon Brown, Geoffrey Schoenbaum

Orbitofrontal cortex (OFC) is critical for reversal learning, as demonstrated across several species. Reversal deficits have typically been demonstrated in complex settings, such as ones that combine both Pavlovian and instrumental learning components. Yet recent behavioral and recording work has implicated OFC specifically in behaviors guided by Pavlovian associations, between cues and the specific outcomes that they predict. To test whether OFC is important for reversing such Pavlovian associations in the absence of potentially confounding instrumental requirements, we trained rats on a simple Pavlovian task in which two auditory cues were presented, one paired with reward and the other paired with no reward. After learning, we reversed the cue-outcome associations. Prior to each reversal session, rats received bilateral infusions of either saline or a cocktail of muscimol and baclofen. Consistent with previous data in discrimination tasks, inactivation of OFC impaired the ability of these rats to reverse their behavior. However, this deficit occurred because inactivated rats were unable to develop normal responding for the previously unrewarded cue. Inactivation of OFC had no impact on the ability of the rats to inhibit responding to the previously rewarded cue. These data demonstrate that OFC is critical to reversal of Pavlovian responding. Additionally, these data show that the role of the OFC in this behavior cannot be explained as a deficit in response inhibition.

P38. Risky Decision Making Following Adolescent Alcohol Exposure

N. A. Nasrallah, T. W. H. Yang, I. L. Bernstein

Although it has been demonstrated that individuals who abused alcohol at an early age show deficits in decision-making, the question of whether maladaptive choice constitutes a predisposing factor to, or a consequence resulting from,

alcohol remains open. In order to better understand the relationship between adolescent alcohol use and decision-making, the present study assessed the effects of voluntary alcohol consumption on choice behavior in a rodent model. Because most strains of rats do not freely consume significant amounts of alcohol in solution, these studies employed an ethanol gelatin preparation that has been shown to yield high levels of intake. The present study utilized a probability-discounting operant task to assess the effects of sustained alcohol exposure during adolescence on risk-based choice in a drug-free state during adulthood. Male Sprague Dawley (SD) rats were exposed to a 10% EtOH or virgin gelatin from PND 30-50. Animals began testing 20 days after treatment (PND70) in adulthood after weeks of alcohol abstinence. They were tested on an operant task consisting of a choice between a lever associated with the certain delivery of a small reward (one sucrose pellet) or one associated with a large reward (four sucrose pellets) delivered probabilistically (75, 50, 25%). The discounting task consisted of a sequence of forced and then choice trials each day with the probability of reinforcement for the large reward lever kept static during a daily session and altered between sessions. Analysis of responses during choice trials generated typical discounting curves with decreasing probability of large reward delivery leading to increases in choice of the certain but small reward lever. While control animals perform this task near optimally, rats that consumed high levels of alcohol during adolescence demonstrate increases in risk preference and sub-optimal decisions. This research demonstrates a causal link between adolescent ethanol exposure and adult decision-making and provides a model for investigating the neurobiological underpinnings of this link.

P39. Evidence for the Role of Dopamine D3 Receptors in Mediating Methamphetamine Addiction

Amanda E. Higley, Eliot L. Gardner

Methamphetamine (METH) is a potent psychomotor stimulant and a major drug of abuse in many parts of the USA. There are no effective medications available for the treatment of METH addiction. Like other drugs of abuse, METH produces strong rewarding effects by elevating extracellular dopamine in the brain reward-circuit. Previous research indicates that acute administration of selective dopamine D3 receptor antagonists significantly inhibits cocaine self-administration and reinstatement to cocaine-seeking behavior. While D3 antagonist efficacy against cocaines addictive potential seems well established, there is no published data on D3 antagonist efficacy against the more potent and addictive METH. The present investigation examined the effects of two D3 receptor antagonists SB-277011A and PG-01037 on METH self-administration under a PR reinforcement schedule and on reinstatement to drug seeking

behavior. Acute administration of both SB-277011A (12, 24 mg/kg i.p.,) and PG-01037 (10, 30 mg/kg i.p.,) dose-dependently lowered the break-point for METH self-administration but had no effect on sucrose self-administration under PR reinforcement conditions. These findings suggest D3 antagonism may be effective in attenuating the rewarding effects of drugs of abuse such as METH without affecting natural rewards. Furthermore, both SB-277011A and PG-01037 significantly inhibited METH- and Cue- triggered reinstatement of drug-seeking behavior in rats extinguished from daily METH self-administration. Our laboratory has previously shown that D3 receptor antagonists have broad efficacy against cocaine, morphine, heroin, and nicotine in a wide array of preclinical animal models of addiction. The present data extend those findings to METH, arguably the most powerfully addictive and problematic illicit drug. The present data add powerfully to an emerging body of evidence suggesting that D3 receptor antagonism may be a useful and safe anti-addiction, anti-relapse treatment at the human level without affecting normal and biologically essential reward driven functions.

P40. Prior Cocaine Exposure Occludes Potentiation of Basolateral Amygdala-Evoked Responses in Medial Prefrontal and Orbitofrontal Cortices but Not Nucleus Accumbens

Clinton B. McCracken, Anthony A. Grace

Repeated exposure to cocaine is known to produce cognitive deficits in humans and animals, particularly with respect to behavioral flexibility. Recent evidence suggests these deficits are mediated in part by a circuit involving the medial prefrontal and orbitofrontal cortices (mPFC and OFC), nucleus accumbens (NAC) and basolateral amygdala (BLA). To examine how cocaine may alter synaptic plasticity in these regions, rats were treated with cocaine (30 mg/kg, i.p.) or saline for 14 days. At least one month later, the rats were anesthetized and spontaneous LFP activity was recorded simultaneously from BLA, NAC, mPFC and OFC. In addition, the effects of cocaine exposure on theta burst stimulation (TBS)-induced potentiation of BLA evoked responses were examined in each of these afferent regions. Compared to saline controls, cocaine-treated rats showed less oscillatory activity in the beta and gamma bands in all regions. BLA TBS potentiated BLA-evoked responses in all regions in saline-treated animals; in contrast, potentiation was occluded in the mPFC and OFC (but not NAC) of cocaine-treated rats. These data suggest that cocaine treatment can induce persistent and specific changes in neuronal synchronization and limbic-cortical plasticity, and these changes may contribute to the prolonged cognitive deficits observed with extended cocaine exposure.

P41. Effects of Differential Rearing on Amphetamine-Induced c-fos Expression in the Basolateral Amygdala and Nucleus Accumbens

Margaret Gill, M.E. Cain

While previous research has shown that environmental enrichment decreases psychostimulant use, the effects of enrichment on the mesocorticolimbic dopamine pathway are unclear. *C-fos* expression has been observed following exposure to novel environments and psychostimulants. The current study determined the effects of acute amphetamine exposure on *c-fos* expression in the basolateral amygdala (BLA) and nucleus accumbens (NAcc), following rearing in either an enriched (EC), impoverished (IC), or social condition (SC). Male Sprague-Dawley rats were reared in EC, IC, or SC environments for 30 days, after which an acute amphetamine (1.0 mg/kg; s.c.) or saline injection was administered, and locomotor activity was measured. Immediately following the 1-hr locomotor test, rats were perfused and immunohisotchemistry was used to measure *c-fos* expression in the BLA and NAcc. Analysis of locomotor data revealed main effects for environment and treatment. SC amphetamine rats showed significantly greater amphetamine-induced hyperactivity than EC or IC amphetamine rats. Analysis of *c-fos* expression in the BLA revealed that enrichment altered c-fos expression. Regardless of treatment, IC rats had significantly greater *c-fos* expression compared to EC rats. Following treatment with amphetamine, SC rats showed significantly greater *c-fos* expression than EC rats. Amphetamine treatment, when compared to saline treatment, resulted in a marginally significant reduction in *c-fos* expression in EC amphetamine rats. Analysis of *c-fos* expression in the NAcc revealed that regardless of treatment, IC rats had significantly greater levels of *c-fos* expression than EC or SC rats. IC rats that received amphetamine showed significantly greater levels of *c-fos* expression compared to EC rats that received amphetamine. These results suggest that environmental enrichment alters amphetamine-induced *c-fos* expression in the BLA and NAcc and suggests enrichment-induced changes within the mesocorticolimbic dopamine pathway may contribute to the ability of enrichment to decrease psychostimulant use. (Supported by USPHS DA021359 and Kansas State University)

P42. Methamphetamine Neurotoxicity and the Ubiquitin Proteasome System

Anna Moszczynska, Bryan K. Yamamoto

High-dose methamphetamine (METH) produces loss of striatal dopamine (DA) terminals. One of the factors involved in METH neurotoxicity is an oxidative stress, which can lead to damage of proteins. Damaged proteins are

degraded by the ubiquitin proteasome system (UPS). METH decreases UPS activity and causes accumulation of damaged proteins in vitro. Parkin, a UPS component, is present in protein aggregates after METH and is selectively vulnerable to DA-mediated oxidative stress. There is no direct in vivo evidence that METH affects the UPS. Proteasome and parkin functions were measured 1, 24 and 48 h after the last dose of METH in the striatum, frontal cortex and cerebellum of male Sprague Dawley rats. In striatal synaptosomes, METH produced a decrease in parkin levels at all time points and a decrease in the levels of the proteasome at 24 h and 48 h. In frontal cortex synaptosomes, METH produced a decrease in parkin levels at 1 h and 24 h, followed by an increase at 48 h. In contrast, when homogenates were examined that presumably contain cell bodies and glial cells, METH produced an initial upregulation of parkin at 1 h after METH. These data suggest that METH neurotoxicity might be mediated by an increase in the levels of damaged proteins in striatal terminals. It also suggests that frontal cortex terminals and striatal cells may be less vulnerable to protein accumulation as evidenced by an upregulation of the UPS.

P43. Role of Phasic Nucleus Accumbens Dopamine in Effort-Related Decision Making

Jeremy Day, Joshua Jones, R. Mark Wightman, Regina Carelli

Optimal reward seeking and decision making requires that organisms correctly evaluate both the costs and benefits of multiple potential choices. One such cost is the amount of effort required to obtain rewards, which can be increased through a number of environmental and economic constraints. Dopamine transmission within the nucleus accumbens (NAc) has been heavily implicated theories of reward learning and cost-based decision making, and is required for organisms to overcome high response costs to obtain rewards. Here, we monitored dopamine concentration within the NAc core on a rapid timescale using fast-scan cyclic voltammetry during an effort-related decision task. Rats were trained to associate different visual cues with rewards that were available at low cost (FR1), high cost (FR16), or choice (FR1 or FR16) effort levels. Behavioral data indicate that animals successfully discriminated between visual cues to guide behavior during the task, that behavioral output increased when required to obtain reinforcement on high cost trials, and that choice allocation was sensitive to cost requirements. Electrochemical data are preliminary, but indicate that cues predicting low-cost effort requirements evoked significantly greater increases in dopamine concentration than cues which predicted high-cost effort requirements. On choice trials, cue-evoked dopamine concentration was similar to low-cost cues presented alone. There were no differences in dopamine concentration during the response period or upon reward delivery. These findings are consistent with previous reports that implicate NAc dopamine function in reward prediction and the allocation of response effort during reward-seeking

behavior, and indicate that dopamine may influence decision making by reflecting the effort requirements associated with available rewards.

P44. Neurons in the vSub Are Activated by Noxious Stimuli and Are Modulated by NE Afferents

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. Nonetheless, the effects of noxious stimuli and locus coeruleus (LC) inputs 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 and local field potentials (LFPs) in the vSub of urethane anesthetized rats. Application of footshock was found to activate 45% of vSub neurons (five fold firing rate increase relative to baseline, N = 18/38), and inhibit the firing of 10% of neurons tested (60% firing rate decrease relative to baseline, N = 5/38). The remaining vSub neurons exhibited no significant change in firing rate (N = 15/38) during footshock. Likewise, electrical train stimulation of the LC was found to activate 38% of neurons in the vSub (5 fold firing rate increase 60 s following LC train, N = 12/32), and decrease the firing in 16% of neurons tested (60% firing rate decrease relative to baseline, N = 5/32). Moreover, there was a strong correlation between responses to footshock and LC stimulation in neurons tested with both stimuli. Single neuron responses to footshock and LC stimulation were also accompanied by high frequency LFP oscillations, indicating the presence of synchronized network activity. Systemic application of the beta NE antagonist propranolol blocked the response to LC stimulation in a subset of LC-responsive neurons that were also activated by footshock (N = 3). In addition, iontophoretically applied NE produced both inhibitory and excitatory responses in singe vSub neurons, suggesting that the responses to LC stimulation and to aversive stimuli may be mediated via adrenoreceptors in the vSub. The vSub expresses high levels of adrenoreceptors, and its response to aversive stimuli dictates the way the brain modulates stress states. These experiments demonstrate that the NE signal of LC projections to vSub is likely to be critical in mediating the response to stress and, based on vSub functional studies, this system likely provides a contextual component to stressful events.

P45. Changes in Reward-Related Signaling in the Basolateral Amygdala—Attention or Error Signaling?

Donna Calu, Matthew Roesch, Geoffrey Schoenbaum

Neurons often fire differently to unexpected reward. In the dopamine system, such activity has been reported to signal errors in reward prediction. However, such firing might also reflect other variables that change in response to unexpected reward, such as attention, surprise, or arousal. Single neurons in basolateral amygdala (ABL), like dopamine (DA) neurons in the midbrain, respond to unexpected reward delivery. However, few studies have recorded from both areas using the same behavioral paradigm, making it difficult to dissociate the respective roles of these two areas in reinforcement learning. Here we use the same behavioral task to demonstrate that a significant number of reward-responsive neurons in ABL, like midbrain dopamine neurons, fire more strongly when reward is delivered unexpectedly. However, this signal does not reflect errors in reward prediction. Instead these changes are more closely correlated with surprise generally, or changes in arousal or attention.

P46. Expression Genetics of Neurocognitive Genes

Audrey Papp, Wolfgang Sadee

Hundreds of genes have been proposed to be involved in a spectrum of neurocognitive syndromes including schizophrenia, depression, autism, and drug addiction. Linkage and genome wide association studies have produced statistical information, suggesting candidate genes and gene regions. Regulatory promoter polymorphisms (rSNPs) and variants that alter mRNA processing (termed here structural RNA SNPs, or srSNPs) have been a largely ignored, but potentially vast reservoir of functional genetic variants. Allelic variations in DNA sequence can lead to differences in mRNA expression levels, causing allelic expression imbalance (AEI). Using allelic mRNA expression as a proximate phenotype, we have identified both rSNPs and srSNPs, discovering diverse mechanisms by which mRNA expression, splicing, and turnover are affected. We observed significant AEI in 30-50% of ~100 genes analyzed to date. In general, we have found large differences in AEI between gene classes. Germ line tumor suppressor genes have shown the least allelic expression imbalance, while >50% of the central nervous system candidate genes exhibit AEI. For mu 1 opioid receptor, tryptophan hydroxylase II, multidrug resistance 1, and dopamine receptor D2, we have linked the AEI ratios to srSNPs in the transcribed region of the gene, involved in mRNA processing, turnover, and splicing. A critical innovation for the present study is the use of high-throughput, massively parallel sequencing of transcript fragments as a "next generation" AEI assay. This

functional approach directly links gene sequence variations to mRNA expression variation as a trait, and is likely to reveal novel functional polymorphisms in key candidate genes.

P47. Tumorigenicity, Allodynia, Biodistribution, and Toxicity Study of Human Embryonic Stem Cell (hESC) Derived-Motor Neuron Progenitors Following Transplantation into the Spinal Cord in NOD/SCID Mice

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

Type I infantile spinal muscular atrophy (SMA) is a pediatric genetic disorder characterized by progressive motor neuron death due to mutations in the gene encoding the motor neuron survival protein SMN. This deficit leads to total paralysis and death. We have developed methodologies for scaled manufacture of high purity motor neuron progenitors (MNPs) from human embryonic stem cells (hESCs) with the intent to develop a combination cell replacement and neuroprotective therapy for SMA. In this six-month study, we evaluated tumorigenicity, allodynia, biodistribution, and toxicity following transplantation of hESC-derived MNPs in the spinal cord of NOD/SCID mice. In addition, we examined the threshold for undifferentiated hESC contaminants added to the hESC-derived MNP population that may lead to tumor formation. At multiple time points our analyses indicated that hESC-derived MNP transplantation did not result in tumors, allodynia, distribution of cells to other organs, or toxicity. Additionally, hESC-derived MNPs contaminated with 6% and 20% undifferentiated hESCs did not form tumors, while 100% undifferentiated hESCs did result in tumor formation. These data from a comprehensive safety study support the use of hESC-derived MNPs for the treatment of SMA.

P48. Dichotomous Dopaminergic Control of Striatal Synaptic Plasticity

Weixing Shen, Marc Flajolet, Paul Greengard, D. James Surmeier

At synapses between cortical pyramidal neurons and principal striatal medium spiny neurons (MSNs), postsynaptic D1 and D2 dopamine (DA) receptors are postulated to be necessary for the induction of long-term potentiation and depression, respectively, forms of plasticity thought to underlie associative learning. Because these receptors are restricted to two distinct MSN populations, this postulate demands that synaptic plasticity be unidirectional in each cell type. Using brain slices from DA receptor transgenic mice, we show that this is

not the case. Rather, DA plays complementary roles in these two types of MSN to ensure that synaptic plasticity is bidirectional and Hebbian. In models of Parkinson's disease, this system is thrown out of balance, leading to unidirectional changes in plasticity that could underlie network pathology and symptoms.

P49. Tumor Characteristics of Neural Stem Cells

Olle Lindberg, Axel Jansson, Christiana Cooper-Kuhn, H. Georg Kuhn

All forms of cancer arise from disturbances of critical cellular functions such as proliferation, apoptosis, and tissue invasion. It has become increasingly apparent that the postnatal mammalian brain harbors highly proliferative stem cells. These cells are critically important for the final stages of brain development in the juvenile brain, but they are also discussed as a potential source for primary brain tumors. In this project, we study very early steps in oncogenic transformation of neural stem cells *in vivo*. We demonstrate that EGF receptor stimulation of neural stem cells in the lateral ventricle wall of rodents leads to three distinct features: ***hyperproliferation with neoplastic growth*** protruding into the ventricle, specific ***neovascularization of hyperplasias*** and change of stem cell ***migration pattern with infiltration*** into the brain parenchyma. In order to identify the underlying cellular mechanisms, we have characterized the cellular and molecular composition of EGF-induced neoplasms and found an increasing number of GFAP-nestin-Sox2 positive cells. On the contrary, the number of neuronally committed progenitor cells as determined by DCX labeling was drastically reduced. Endothelial cell response was induced by EGF only in the vicinity of the stem cell niche. Since FGF-2, a known angiogenic factor, was not able to induce this response, we conclude that an EGF-dependent signal is released from stem cells to stimulate neoangiogenesis. We have begun analyzing the angiogenesis-inducing activity mediated by EGF receptor signaling. The comparative analysis of EGF signaling in neural stem cells and tumor cells could improve our understanding of stem cell transformation and oncogenesis and possibly provide novel targets for intervention in brain tumor therapy.

P50. Learning Deficits, Impaired LTP, and Altered Synaptic Excitation-Inhibition Ratio in Mice Over-Expressing Neuroligin 1

Regina Dahlhaus, Rochelle Hines, Brennan Eadie, Timal Kannangara, Dustin Hines

Trans-synaptic cell adhesion molecules have been implicated in regulating CNS synaptogenesis. Among these, the Neuroligin (NL) family (NL's 1-4) of post-synaptic adhesion proteins have been shown to promote the development and specification of excitatory versus inhibitory synapses. NLs form a heterophilic complex with the presynaptic transmembrane protein Neurexin (NRX). A

differential association of NLs with postsynaptic scaffolding proteins and NRX isoforms has been suggested to regulate the ratio of excitatory to inhibitory synapses. Using transgenic mice, we have tested this hypothesis by overexpressing NL1 in vivo to determine whether the relative levels of these cell adhesion molecules impacts synapse maturation and specificity, long-term potentiation (LTP), and learning behaviors. We found that NL1-overexpressing mice show significant deficits in memory acquisition, but not in memory retrieval. Golgi and electron microscopy analysis revealed changes in synapse morphology indicative of increased maturation of excitatory synapses. In parallel, electrophysiological examination indicated a shift in the synaptic activity towards increased excitation, as well as impairment in LTP induction. Our results demonstrate that altered balance in the expression of molecules necessary for synapse specification and development (such as NL1), can lead to defects in memory formation and synaptic plasticity, and outline the importance of rigidly controlled synaptic maturation processes.

P51. NG2 Glial Cells Are Targets for Neurovirulent Murine Retroviruses: Implications for Differentiation and Spongiform Neuropathogenesis

Ying Li, Rochelle Cutrone, Wendy Macklin, William Lynch

Certain murine leukemia viruses (MLVs) are capable of inducing progressive non-inflammatory spongiform neurodegeneration resembling that observed in prion diseases. Interestingly, vacuolar changes are observed in motor neurons and macroglial elements, however, microglia are the major infected cells associated with neurodegeneration. Surprisingly, the microglia are not detectably altered by neurovirulent MLV infection, raising the possibility that disease is mediated by infection of another cell type. Recent work has begun to define a 4th glial element, the NG2 cell, which raises the question of whether this cell type might constitute a target for neurovirulent MLVs. And, if NG2 cells are targets, are they involved in neurodegeneration? To address these questions we explored two approaches. In the first approach we directly examined NG2 cells for virus in brains of mice infected with the highly neurovirulent MLV, FrCasE. In the second approach, we engineered neural stem cells (NSCs) with the neurotoxic component of the MLV, the env gene, followed by CNS transplantation to assess their fate. The results showed that around thirty percent of virus infected cells were indeed NG2 cells. Remarkably, FrCasE infected NG2 cells were found associated with vacuolar changes. Interestingly, transplanted NSCs expressing neurovirulent env engrafted and expressed NG2, but did not express Olig2, a marker for cellular differentiation. These data indicate that NG2

cells are a target for neurovirulent MLVs, which could interfere with the normal differentiation and function of these cells. The implications for spongiform neuropathogenesis will be discussed. (This work was supported by NIH grant NS37614 to WPL.)

P52. Evidence for a Neuromodulatory Role of the Dopamine Metabolite 3-methoxytyramine

Tatyana D. Sotnikova, Jean-Martin Beaulieu, Xiaodong Zhang, Ali Salahpour, Larry S. Barak, Marc G. Caron, Raul R. Gainetdinov

Trace amines are endogenous amines of unknown function that are structurally related to dopamine and other monoamines and normally found at low concentrations in the brain. The best characterized trace amine associated receptor 1 (TAAR1), can be activated in in vitro cAMP assay by a variety of endogenous and exogenous compounds including trace amines, amphetamines and monoamine metabolites such as 3-methoxytyramine (3-MT), the major extracellular metabolite of dopamine. Using a mouse model of acute dopamine deficiency, we performed screening of putative trace amine receptor ligands for potential effects on movement control and observed that 3-MT is able to induce abnormal movements in dopamine-deficient mice (dopamine depleted dopamine transporter knockout mice, DDD mice). Furthermore, we investigated motor and signaling responses to 3-MT (administered i.c.v.) in normal mice and mice lacking TAAR1 (TAAR1-KO mice). 3-MT dose-dependently induced hyperactivity and abnormal movements in normal mice. Furthermore, 3-MT administration induced cAMP-related in vivo signaling events in striatal cells as evidenced by increased ERK and CREB phosphorylation. These results are consistent with the demonstrated ability of 3-MT to activate TAAR1 receptors in in vitro cellular cAMP assays. In contrast, in TAAR1-KO mice both the behavioral and signaling effects of 3-MT were significantly attenuated. In conclusion, 3-MT can induce behavioral and signaling changes in dopamine-independent manner, and these effects are partially mediated by TAAR1. Thus, 3-MT may be not just inactive metabolite of DA, but a novel neuromodulator in its own right that potentially can be involved in movement control.

P53. Hypoxia-Ischemia Induces an Endogenous Reparative Response by Local Oligodendrocyte Progenitors in Postnatal Mice

Maria Dizon, Jill Toms, Francis Szele, John Kessler

Hypoxia-ischemia (HI) is a dominant mechanism in neonatal brain injury especially white matter injury. HI causes accumulation of oligodendrocyte

progenitors (OLPs) resulting from the combination of blocked differentiation to mature oligodendrocytes and delayed death of OLPs. It is not known whether HI also changes fate commitment of neural progenitor cells in vivo as suggested by in vitro experiments. To explore this question, we first tested whether HI causes emigration of OLPs from SVZ using multiphoton microscopy and an Olig1-GFP reporter mouse. We did not find any changes. Next we examined regional changes in cells expressing GFP and found a decrease within corpus callosum. Unexpectedly, we found an increase within striatum. We performed immunohistochemistry to assess for cells expressing Olig1 and observed decreases within both corpus callosum and striatum. We also assessed for cells expressing Olig2. We found no change within SVZ, however we did observe increases within corpus callosum, striatum, internal capsule and supracallosal radiations. In pulse chase experiments, we did not observe a change in Olig2+/CldU+ cells within SVZ but observed a increase within striatum and internal capsule. Thus, we conclude that SVZ does not contribute progenitors to a regenerative oligodendroglial response. Increased GFP within striatum could be explained by an initial transcriptional response followed by translation failure, implying regulation at the level of mRNA processing. CldU uptake suggests proliferation of OLPs in internal capsule and striatum. One possible explanation for the increase in Olig2+ cells following HI is an increased commitment of bipotential progenitors to the oligodendroglial lineage.

P54. A Zn^{2+}-Dependent Dual Phosphorylation Checkpoint in Kv2.1 Regulates the Apoptotic Surge of K^+ Currents

Patrick T. Redman, Karen A. Hartnett, Edwin S. Levitan, Elias Aizenman

Oxidant-liberated intracellular Zn^{2+} regulates neuronal apoptosis via an exocytotic membrane insertion of Kv2.1-encoded ion channels, resulting in a requisite enhancement of voltage-gated K^+ currents. In the present study, we show that an N-terminal tyrosine of Kv2.1 (Y124), which is targeted by src, is critical for the apoptotic current surge. Moreover, Y124 works in concert with a C-terminal serine (S800) target of p38 MAPK to regulate Kv2.1-mediated current enhancement. While Zn^{2+} was previously shown to activate p38, we demonstrate here that this metal inhibits cytoplasmic protein tyrosine phosphatase ε (Cyt-PTPε), which specifically targets Y124 and antagonizes the actions of src. Importantly, disruption of Y124 phosphorylation by a point mutation or by Cyt-PTPε over-expression protects cells from injury. Therefore, a dual tyrosine-serine phosphorylation checkpoint on Kv2.1 regulates neuronal survival by providing a converging input for two Zn^{2+}-dependent signal transduction cascades.

P55. Accelerating Spongiform Neurodegeneration: Pushing the Limits Using Neural Stem Cell-Based Brain Chimeras

Sandra M. Cardona, William P. Lynch

Vacuolar changes in the mammalian CNS are most commonly associated with diseases of abnormal protein accumulation. Such pathology is typically associated with prion diseases but is also notable in retroviral, genetic and sporadic diseases as well. These diseases are generally characterized by extended preclinical periods, presumably due to the extended time it takes for the build-up of abnormal or "toxic" proteins within the brain. To explore this question more directly, we have been investigating a model of spongiform neurodegeneration induced by neurovirulent murine retroviruses. To date these studies have demonstrated that spongiosis is limited by 1) virus entry and accumulation within the brain, and 2) by the developmental maturity of susceptible neural elements. Herein, we investigate a strategy to bypass these limitations to assess the inherent capacity of the toxic viral element, Env, to cause spongiform neurodegeneration. This was accomplished by transplanting engineered neural stem cells (NSCs) to acutely saturate susceptible brain regions with neurovirulent Env, followed by a kinetic analysis of spongiosis. The results indicate that spongiform changes could be accelerated up to within one week of NSC transplant. Because this delay period cannot be accounted by the retrovirus life cycle alone, these findings suggest that spongiform changes require Env-mediated events beyond viral entry, spread, or protein expression. Such events could include formation of a pathogenic oligomer, production of a cellular toxin, or accumulation of incremental Env-mediated cellular damage. Reconciling the delay between NSC-mediated Env expression and vacuolation should provide critical clues regarding the cellular mechanisms of neural spongiosis.

P56. Genetic Variation in GRM7 Predicts Amygdala and Hippocampal Response to Emotional Stimuli

Kristin L. Bigos, Francis J. McMahon, Roberta Rasetti, Venkata S. Mattay, Daniel R. Weinberger

GRM7, the gene that codes for the metabotropic glutamate receptor mGlur7, has been previously identified as a possible risk gene in studies of association with schizophrenia and bipolar disorder. In this study, we evaluated the impact of a single nucleotide polymorphism (rs13071462) in the GRM7 gene on amygdala and hippocampal activity in response to emotional stimuli as measured by functional MRI. For the first task, we genotyped 132 healthy volunteers for this SNP (38 C/C, 67 C/T, and 27 T/T) and evaluated their neuronal response to emotional faces. Homozygotes for the rare allele (T/T)

had significantly greater activity in the amygdala, hippocampus, and parahippocampus compared to common allele carriers (C/C and C/T). In a second task, we genotyped 119 healthy volunteers for this SNP (34 C/C, 62 C/T, and 23 T/T) and evaluated their response during the encoding and retrieval of aversive images. During the encoding of aversive images, subjects with T/T genotype had significantly greater activity in the amygdala and hippocampus than those with C/C or C/T, and rare allele carriers (C/T and T/T) had greater activity in the parahippocampus than those with C/C genotype. During the retrieval of aversive images, subjects with T/T genotype had greater activity in the hippocampus and parahippocampus than those with C/C and C/T genotype. These data provide evidence that the GRM7 gene may play a role in modulating the response of the limbic circuit in the encoding and retrieval of emotional information.

P57. Mild Cognitive Impairment Gene Expression Profile Is Unique from Normal Aging and Alzheimer's Disease

Nicole Berchtold, Paul Coleman, Joseph Rogers, Carl Cotman

Nicole Berchtold* Mild cognitive impairment (MCI) is a clinical diagnosis for individuals who are not cognitively normal for age and yet do not have overt dementia. It has been alternatively argued that MCI represents accelerated aging, or that it is prodromal Alzheimer's disease (AD). Microarray analysis was used to identify the signature associated with MCI, normal aging, and in AD. MCI diagnosis was based on the Petersen criteria, with a clinical dementia rating (CDR) ? 0.5. The regions assessed were the hippocampus (HC), entorhinal cortex (EC), superior frontal gyrus (SFG) and post-central sensory gyrus (PCG). In MCI, the HC is the primary region to show functional changes, as evidenced by HC-dependent cognitive tests and fMRI. Tissue was obtained from 11 MCI (age 83-90 yrs, mean age 87.5), 26 AD (age 83-90 yrs, mean age 87.5) and 16 normal controls (age 82-91, mean age 86), all groups sex-balanced, from Alzheimer's disease research center (ADRC) brain banks (UC Irvine, Sun Health Research Institute, Johns Hopkins, USC, U Rochester, Mayo Clinic). RNA was individually hybridized to Affymetrix Hg-U133A chips, and only probe sets flagged significant ($p<0.01$) by both GC-RMA and PLIER analyses were included in the interpretation. The gene profile in MCI was distinct from both normal aging and AD, and was striking in a robust gene upregulation of many gene classes, in particular related to synaptic function, energy metabolism and RNA/protein processing. The gene changes are likely representing compensatory gene mobilization to counter declining brain function. These gene changes are markedly different from those observed in aging, or AD.

P58. Methylene-Tetrahydrofolate Reductase A1298C Polymorphism Modulates Brain Function

Fabio Sambataro, Venkata S. Mattay, Jeffrey Reed, Bhaskar Kolachana, Joseph H. Callicott, Daniel R. Weinberger

Methylene-tetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism. Two functional single nucleotide polymorphisms of *MTHFR* have been associated with risk for Schizophrenia: C677T (rs1801133) and A1298C (rs1801131). The risk alleles in these two variants, namely 677T and the 1298C ('C') code for a thermo-labile enzyme with decreased activity. Although these variants have been associated with the risk for schizophrenia, the neurobiology underlying their effects remains relatively unexplored. We examined the effects of these two *MTHFR* polymorphisms on the physiology of brain regions known to be implicated in the pathophysiology of schizophrenia, namely hippocampal formation and the dorsolateral-prefrontal cortex. 293 Caucasian healthy subjects matched for gender, age, IQ and years of education were included in the study. Participants underwent fMRI while performing a working memory (WM) task and a simple declarative memory task. Neither *MTHFR* variant showed any effect on task performance. Image analyses showed a significant effect of the A1298C variant with 'C' carriers (risk) showing greater left posterior parahippocampal activation (N=127; p=0.001) during the encoding (q-FDR=0.06) as well as during the recognition phase (q-FDR=0.03) of the declarative memory task relative to AA subjects. In addition, the 'C' carriers also showed greater dorsolateral-prefrontal activation during the WM task (N=293; p<0.0001; p-FWE=0.036). There was no significant effect of the C677T variant on brain activations. These data suggest that the A1298C variant of *MTHFR* modulates the neurophysiological response underlying working memory and declarative memory and may help us to better understand the effect of these variants on risk for schizophrenia.

P59. Polymorphism in the Fibroblast Growth Factor-20 Gene Modulates Grey Matter Volume in the Medial Temporal Lobe

Herve Lemaitre, Vankata Mattay, Fabio Sambataro, Beth Verchinsky, Richard Straub, Joseph Callicott, Ron McKay, Daniel Weinberger

Fibroblast Growth Factor 20 (FGF20) is a neurotrophic factor that preferentially enhances the survival of midbrain dopaminergic neurons and has been implicated in normal developmental and physiological processes. Three Single Nucleotide Polymorphisms (SNP) lying within the FGF20 gene have been associated with increased risk for Parkinson's Disease: rs12720208 T, rs1721100 C and rs11203822 C alleles. In this study, we explored the effect of these polymorphisms on brain structures in 195 healthy normal adults using voxel-based

morphometry (VBM). Subjects underwent a structural T1-weighted MRI and were genotyped for these three SNPs. MRI scans were analyzed with SPM2 using an optimized VBM procedure. The effect of each SNP was examined on the smoothed, modulated and normalized gray matter (GM) images. Statistical thresholds were set to $p < 0.001$ uncorrected for multiple comparisons at the voxel level and to $p < 0.05$ FWE corrected at the cluster size level. For rs12720208, the voxel-based comparison of the GM maps showed a selective increase in GM within the hippocampal region bilaterally and within the right middle temporal gyrus in T carriers as compared to C/C homozygotes. There were no significant regional GM differences across genotype groups for rs1721100 and rs11203822. In vitro, rs12720208 T allele has been shown to increase FGF20 expression by disrupting a binding site for microRNA. The greater hippocampal volume in individuals with T allele may be due to the neurotrophic activity of FGF20 through activation of FGF receptor 1 which has been shown to be abundantly expressed in the hippocampus.

P60. A Link between the Systems: Functional Differentiation and Integration within the Human Insula Revealed by Meta-analysis

Florian Kurth, Angela R. Laird, Peter T. Fox, Katrin Amunts, Karl Zilles, Simon B. Eickhoff

The human insula cortex is involved in a wide variety of sensorimotor, cognitive, and limbic processes and has hence been ascribed an integrative role. However, several reports indicate not only integration but also a segregation of functions in this region, although this differentiation remains largely elusive. Here we present a new map of the human insula based on large-scale coordinate-based meta-analysis of published functional neuroimaging studies. We examined the co-activation patterns of studies with known insular activation that are listed in the BrainMap database under twelve different functional categories (e.g., "emotion", "pain" or "memory"). DTI tractography in 40 probands was subsequently applied to the resulting activation foci. Spatial comparison of the resulting patterns of activation foci and DTI tractography revealed three distinct functional domains on the insula. Co-activation patterns for these three insular sub-regions, defined by functional and anatomical connectivity results, represent differential networks for limbic, cognitive and sensorimotor processing. Conjunction analysis of these co-activation patterns revealed the anterior dorsal insula and the thalamus as brain regions involved in all three systems. The present results thus implicate an insular differentiation by three distinct functional systems, with the anterior dorsal portion acting as a putative link between them.

P61. Why Do So Many Parkinson's Disease Medications Fail?

Peter LeWitt

Over the 4 decades since introduction of the dopamine precursor levodopa, several dozen medications for Parkinson's disease (PD) have undergone clinical trials. Unlike levodopa, the gold standard of PD therapeutics, most haven't succeeded. Despite the wealth of information about PD pathophysiology, the translation of pharmacological principles to effective therapy has been surprisingly limited. Most of the currently available PD medications offer the typical patient relatively minor gains. Several recent drugs duplicate each other (e.g., three dopaminergic agonists, four monoamine oxidase-B inhibitors, and two catechol-O-methyltransferase inhibitors). Furthermore, these levodopa-enhancing drugs offer their benefits that are generally modest. The remarkable improvements achievable with high-frequency electrical stimulation of the subthalamic nucleus have highlighted other therapeutic options for PD besides stimulating dopamine receptors. Several neurotransmitter and neuromodulator systems are active in the motor pathways "downstream" from dopaminergic projections to striatum. Despite the new opportunities these non-dopaminergic targets offer, innovative PD treatments have had an unmet challenge to deliver clinically meaningful results. This presentation, by PD specialist LeWitt (Wayne State University School of Medicine) will summarize experience in unsuccessful clinical trials for PD with dopaminergic agonists (27 tested in man since 1974), glutamate antagonists (remacemide, E2007, MK-0657), an adenosine A2a antagonist (istradefylline), a serotonin 5-HT1A antagonist (sarizotan), a neurotrophic factor (GDNF), and injection of levodopa-generating retinal pigment epithelial cells (Spheramine). A dozen unsuccessful neuroprotection clinical trials will be summarized, along with a discussion of the methodological challenges inherent in studying PD (such as its prominent placebo effect and limits of clinical and biomarker rating options).

P62. Endothelin-1 Receptor A Antagonists Improve Neurologic and Cognitive Outcome Following TBI

Christian Kreipke, Patrick Schafer, Steven Schafer, Paula Dore-Duffy, Jose Rafols

Among multiple sequelae, traumatic brain injury (TBI) results in three major pathologies: 1) cerebral edema which leads to a critical rise in intracranial pressure, 2) diffuse axonal injury which brings about disruption of neural circuits underlying cognitive and motoric behaviors, and 3) alterations in the brain's microcirculation that cause a persistent state of hypoperfusion and improper delivery of vital metabolites to neural tissue. Over 25 clinical trials aimed at the

first two pathologies have been developed, none of which have been effective in the treatment for TBI. Therefore, novel studies leading to new clinical trials are necessary. To date no one has initiated a clinical trial addressing the third pathology, dysfunctional vascular reactivity following TBI. Furthermore, how improved blood flow to the brain ultimately improves cognitive outcome has not bee investigated. Our laboratory and others have previously shown that endothelin-1, a powerful vasoconstrictor, and its receptors, A (ETrA) and B (ETrB), are upregulated following TBI, this upregulation being temporally associated with decreased cerebral blood flow (CBF) following injury. Further evidence suggests that vasoconstriction is mediated through ETrA. Therefore in the present study we sought to test the effects of ETrA antagonists on CBF and neurologic and cognitive outcomes following TBI. Using an acceleration impact model of TBI modified from Marmarou and colleagues (450 g weight dropped onto a steel helmet affixed to the skull of 400-450 g rats) brain injury was induced. One hour following injury animals were given IV injection of either the ETrA antagonist BQ-123 or Clazosentan, an ETrA antagonist undergoing clinical trial for ameliorating vasospasm after stroke, and tested for CBF using Arterial Spin Labeling-MRI (ASL-MRI), neurologic outcome using FluoroJade staining, and cognitive outcome using a radial arm maze. Our results indicate that not only are ETrA antagonists effective at ameliorating hypoperfusion after trauma, but also reduced the extent of nerve cell damage and improved performance in a spatial learning task. This suggests that improved CBF after trauma leads to cognitive sparing. Taken together, these results indicate that ETrA antagonists may be effective in treating the deleterious effects of TBI.

P63. Surface Accumulation of NR2B-containing NMDA Receptors during Status Epilepticus Increases Both Phasic and Tonic Excitatory Currents

David E. Naylor, Claude G. Wasterlain

The balance between excitation and inhibition affects seizure onset and evolution to status epilepticus (SE). Previously, a reduction of synaptic GABA-A receptors during SE was described, and this study addresses excitatory NMDA receptor changes. After 1 hour of lithium-pilocarpine induced status epilepticus (SE), NMDA miniature EPSCs (mEPSCs) show an increase peak amplitude from –16.2 +/– 0.4 for controls to –19.5 +/– 2.4 pA for SE and increase AUC (-662.52 +/– 267.92 for control vs. -896.84 +/– 280.95 pA·ms for SE; $p<.001$). With antagonism of NR2B containing receptors (ifenprodil; 3 uM), SE NMDA-mEPSCs have a decrease in amplitude of 17.1% as AUC decreases to –760.98 +/– 264.80 pA·ms ($p < .01$). After ifenprodil, no significant difference between SE-mEPSCs and controls exists, suggesting that NR2B-containing receptors primarily account for the SE-related increase in synaptic NMDA currents.

Mean-variance analysis of NMDA-mEPSCs before and after ifenprodil suggests an increase from 5.2 +/– 1.2 NMDA receptors per synaptic event with controls to 7.8 +/– 1.2 receptors with SE (50% increase; p<.001), with 1.9 +/– 1.6 of receptors being ifenprodil sensitive for SE vs. 0.7 +/– 1.6 for controls. Ifenprodil caused a -20.5 +/– 10.6 pA (p<.001)greater NMDA tonic current baseline shift for SE compared to controls with no tonic current difference between SE and controls with addition of APV (~50 uM) after ifenprodil (27.8 +/– 19.3 pA for control vs, -24.9 +/– 24.4 pA for SE). This suggests surface accumulation of NR2B-containing NMDA receptors contribute to tonic current as well as phasic current increases with SE.

P64. Distributed Representation of Single Touches in Somatosensory and Visual Cortex

Michael S. Beauchamp, Steven LaConte, Hualou Liang, Nafi Yasar

Multi-voxel pattern analysis (MVPA) was used to analyze blood-oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) data, which were acquired as human subjects received brief vibrotactile stimulation of their hands and feet. Support vector machines trained and tested on the whole brain fMRI data were able to accurately decode the body site of single touches, with mean performance of 92% in a two-way discrimination task (chance performance 50%) and 70% in a four-way discrimination task (chance performance 25%). Primary and secondary somatosensory areas (S1 and S2) alone decoded the touched body site with high accuracy. S1 was more accurate at decoding touches closely spaced on the body surface (different fingers of the same hand) while S2 was more accurate at decoding widely spaced touches (hand vs. foot). The hand and foot regions of S1 (S1hand and S1foot) were separately examined in a two-way classification task. S1hand was better able to decode the hand of stimulation (left vs. right), and S1foot was better able to decode the foot of stimulation. In addition to S1 and S2, vibrotactile responses were observed in a region of visual cortex, area MST and associated areas (MST+) in lateral occipito-temporal lobe. MST+ was able to accurately decode the hand but not the foot of stimulation, supporting the idea of a role for MST+ in eye-hand coordination.

P65. Cerebral Neuronal Calcium Sensor 1 Is Altered after Methylphenidate Exposure in Young and Adult Brain Rats

Renan Souza, Eliane Soares, Daniela Rosa, Joao Quevedo, Marco Romano-Silva

Methylphenidate has been used as an effective treatment for Attention Deficit Hyperactivity Disorder. Methylphenidate blocks dopamine and norepinephrine

transporters causing an increase in extracellular levels. Psychostimulants use continues to rise due to both the treatment of Attention Deficit Hyperactivity Disorder and illicit abuse. Methylphenidate sensitization mechanism has still poor knowledge. Neuronal calcium sensor 1 was identified as a dopaminergic receptor interacting protein. When expressed in mammalian cells, neuronal calcium sensor 1 attenuates dopamine-induced D2 receptor internalization by a mechanism that involves a reduction in D2 receptor phosphorylation. Neuronal calcium sensor 1 appears to play a pivotal role in regulating D2 receptor function, it will be important to determine if there are alterations in neuronal calcium sensor 1 in neuropathologies associated with deregulation in dopaminergic signaling. Then, we investigated if methylphenidate could alter neuronal calcium sensor 1 expression in five brain regions (striatum, hippocampus, prefrontal cortex, cortex and cerebellum) in young and adult rats. These regions were chosen because some are located in brain circuits related with attention deficit hyperactivity disorder. Our results showed changes in neuronal calcium sensor 1 expression in hippocampus, prefrontal cortex and cerebellum mainly in adult rats. The demonstration that methylphenidate induces changes in neuronal calcium sensor 1 levels in rat brain may help to understand sensitization mechanisms as well as methylphenidate therapeutic effects to improve attention deficit hyperactivity disorder symptoms.

P66. Multiple Treatment Protocols: Optimizing Functional Outcomes for Traumatic Brain-Injured Patients

Jacob VanLandingham, Nicholas Rich, Sheree Porter, Cathy Levenson, Donald Stein

In the United States today there are over 5 million people living with a disability secondary to a traumatic brain injury (TBI). Unfortunately, there is no pharmacological treatment that has proved successful for improving not only survivability but acquisition of daily functions. Following a TBI there is a multitude of molecular events that lead to increased neuronal cell death. These events include; increased cell permeability and subsequent edema, cellular release of inflammatory mediators and the buildup of intracellular free radicals. Behavioral changes are many following TBI where patients present with such findings as impaired memory, sensory neglect and emotional distress. This poster presentation will discuss the current animal research as it relates to the treatment of TBI as well as the current technological and pharmacological trends in treatment of patients in both the hospital and inpatient rehabilitation setting. In this poster we will present data on the use of natural progesterone (PROG) as a pharmacological treatment for TBI and how this work has been used to develop the clinical trial, PROtect. New data on the combinatorial effects of thyrotropin releasing hormone, vitamin D and PROG following TBI will be discussed. We

will also present data showing the beneficial effects of caloric restriction on histological and behavioral outcomes following TBI. In final, this poster presentation will discuss the current acute and sub-acute pharmacological treatments utilized for TBI patients and the recent technological advances in the treatment of TBI in the rehabilitation setting.

P67. AMPA Receptor Potentiators Differentially Modulate Glutamate Binding Affinity

Hong Yu, Bruce Gitter, Jeffrey Horn, David Bredt

AMPA receptors are the major excitatory neurotransmitter receptor in the brain. AMPA receptors potentiators enhance ion flow through the channel. These AMPA receptors potentiators have therapeutic potential in several neurological and psychiatric diseases but have differential efficacy in animal models. This differential efficacy of AMPA receptors potentiators does not correlate with their maximal efficacy for enhancing ion flux in vitro. Using FLIPR technology and stable cell lines expressing AMPA receptors, we found that AMPA potentiators dramatically and differentially increase receptor affinity for glutamate. To determine if this differential increase in receptor affinity was expressed in brain, we used a labeled AMPA selective agonist, [3H] 5-fluorowillardiine, to examine the effects of AMPA potentiators on ligand binding to membrane preparations and to frozen tissue sections by quantitative receptor autoradiography. These experiments showed that AMPA potentiators augment agonist binding in a brain region specific manner. This regional specificity may be related to the differential efficacy of AMPA potentiators in animal models of diseases.

P68. Virus-Induced Spongiosis Is Associated with Spontaneous Firing in Specific Neuronal Cell Types

William P. Lynch, Shobhana Sivaramakrishnan, Ying Li, Ying Xiao, Sandra Cardona, Joseph Shivers

Certain retroviruses are capable of inducing progressive spongiform encephalopathy ("holes" in the brain), similar to that caused by prions. These viruses specifically affect the motor system resulting in clinical neurological disease analogous to amyotrophic lateral sclerosis (ALS). While a great deal is known about the structure and cell biology of retroviruses and prions, very little is known about how these infectious agents mediate spongiform neuropathology and neuronal dysfunction. Toward this end, we have been investigating the molecular details of retrovirus-induced neurodegenerative disease in a murine leukemia virus (MLV) model referred to as CasBrE. Our results to date have

revealed that a single component of the CasBrE virus, the viral envelope protein (Env), mediates neuropathogenesis. It remains unknown what features and activities of CasBrE Env cause vacuolation, however, ultrastructural studies indicate that holes first arise at post-synaptic processes. These findings suggest that alterations in synaptic properties may play a role in neurodegeneration, however to date, no electrophysiological studies have been undertaken that could address such issues. Herein, we examined the inferior colliculus (IC), an auditory midbrain region containing multiple distinct neuronal subtypes, which undergoes spongiform neurodegeneration in response to CasBrE infection. Patch clamp analysis of IC slices was undertaken before during and after the initial onset spongiform neurodegeneration and compared with age-matched controls. These experiments revealed that rebound neurons uniquely exhibited bursts of spontaneous firing that were not observed in controls or other neuron-subtypes. Importantly, bursting behavior was temporally coincident with the first appearance of vacuolation. Implications for neuropathogenesis will be discussed. (This work was supported by NIH grant NS37614 to WPL.)

P69. Mesolimbic Dopamine and the Costs of Future Rewards

Jerylin Gan, Michael Lee, Sheena Barnes, Mark Walton

For many animals, the ability to make optimal decisions is a matter of life and death. To make these decisions, animals must weigh the benefits of an action versus the required costs. To do so, an animal must have neural mechanisms that utilize previous experiences to predict likely outcomes of different actions. One neural system with the ability represent predictions and modify behavior is the mesolimbic dopamine system. But though dopamine has been implicated, its role in the decision-making process is unclear. Thus, to determine the role of mesolimbic dopamine, we trained animals to perform operant decision-making tasks while recording electrochemical measurements of dopamine with fast-scan cyclic voltammetry. Each behavioral session entailed choosing between two levers assigned either differential amounts of food reward (benefit) or the same amount of reward but with different response requirement (i.e. cost). Within one experimental day, animals experienced two behavioral sessions. In the second behavioral session, contingencies were reassigned so that the previously high-benefit/cost lever became the low-benefit/cost option. Voltammetric data from sessions when the reward was varied suggests that dopamine release correlates with reward magnitude. However, effort costs are not so robustly encoded in the dopamine signal. In particular, data from experimental days where costs are varied reveal session effects that are not present in reward-modulated days.

P70. Environmental Modulation of Haloperidol-Induced Fos Expression in Rat Nucleus Accumbens Following Repeated Drug Administration in a Novel Environment

Sam A. Golden, Bella R. Shah, Bruce T. Hope

Haloperidol is a commonly prescribed antipsychotic drug, but the neuronal mechanisms underlying its clinical efficacy are not fully understood. We previously showed that drug administration context plays an important role in modulating neuronal activity in the nucleus accumbens following repeated cocaine injections. This finding raises the possibility that haloperidol's action on the brain is influenced by its administration context. Acute administration of haloperidol increases neuronal activity in the nucleus accumbens, dorsal striatum and prefrontal cortex of rats, as measured by the neuronal activity marker 'Fos'. The aim of this study is to investigate whether drug administration context modulates striatal and prefrontal Fos expression after repeated injections of haloperidol. We injected rats with haloperidol (0.0 or 0.1 mg/kg, i.p.) once-daily for 7 days in a locomotor activity chamber, and 7 days later gave test injections of haloperidol (0.0, 0.1 or 1.0 mg/kg, i.p.) in the same 'drug paired' context. Test injections of 1.0, but not 0.1 mg/kg haloperidol enhanced Fos expression in the nucleus accumbens core and shell, with more robust activation in the shell subregion. No significant changes were observed in the dorsal striatum, and a non-significant increasing trend was observed in the prefrontal cortex. We are currently investigating the effects of test injections of haloperidol following repeated haloperidol administration in a drug non-paired context on Fos expression. We speculate that specific information in the drug administration context alters haloperidol-induced neural activation in the nucleus accumbens, in a manner similar to that observed following repeated cocaine administration.

P71. The Effects of Selective Cannabinoid Receptor 1 Antagonist in Various Rodent Models of Cognition

Philip Iredale

The cannabinoid system has long been known to play a central role in learning and memory. Furthermore, antagonists of the 1 receptor subtype have shown some activity in a variety of different cognitive tasks (both alone and reversing the effects of an agonist). The goal of this present study was to examine the effects of a selective cannabinoid-1 receptor antagonist in two different rodent memory models (Radial Arm Maze and Novel Object Recognition). In addition, we measured changes in the levels of acetylcholine in pre-frontal cortex. In

the radial arm maze assay, rats were trained in a two-phase procedure, consisting of acquisition and retrieval tests, which were separated by an 18 h delay. The antagonist was administered 30 min before the acquisition phase, immediately after the acquisition phase, or 30 min before the retrieval test to assess its effects on acquisition and retrieval processes. Administration before and immediately after the acquisition phase significantly decreased the number of errors committed during the retrieval test. On the other hand, administration 30 min before the retrieval test had no effect on the number of errors committed. In the novel object recognition assay, scopolamine disruption of working memory was reversed in the presence of the antagonist, however, there was also an accompanying overall decrease in explorative behavior. Finally, administration of the selective antagonist induced a modest increase in pre-fontal acetylcholine levels. In summary these data suggest a potential role for cannabinoid signaling in cognitive processes which will be further discussed.

P72. Precise Dissection of Human Postmortem Brain Tissue and Nucleic Acid Quality

Ross Buerlein, Thomas Hyde, Barbara Lipska, Joel Kleinman

High quality RNA and DNA extracted from human postmortem brain tissue is critical for obtaining accurate and reliable results in gene expression and genotyping studies. The quality of RNA depends on many pre- and postmortem factors, including conditions surrounding death, the length of postmortem interval (PMI) and methods used for obtaining tissue samples. Similarly, DNA quality may be affected by prolonged PMI and handling of tissue during and after dissections. This study examined the effect of two dissection techniques on the quality of human brain specimens: 1) dissection using an electric dental drill that is anatomically precise but may possibly affect RNA and DNA quality because of the heat produced during dissection, 2) dissection with a small handsaw, which is less precise but releases less heat. RNA (using Lipid Tissue Midi Kit) and DNA (using Gentra Puregene Cell Kit) were extracted from frozen normal control cerebellar samples obtained from 10 post-mortem brains using either a drill or a handsaw. We used Nanodrop to measure concentration of RNA and DNA, Agilent2100 Bioanalyzer to measure quality of RNA (RIN) and SeaKem Gold Agarose gels to assess quality of DNA. We determined that dissection technique did not affect RNA or DNA quality or yield (p values >0.9 for all comparisons). Gels showed sharp clear bands, indicating high quality DNA obtained with both methods. Therefore, these results support the use of a high-speed hand-held electric dental drill as an efficient and anatomically precise means of human brain dissection without compromising tissue quality.

P73. Spatial Uncertainty Associated with Stereotaxic Coordinates of Neuroimaging Results

Simon B. Eickhoff, Angela R. Laird, Christian Grefkes, Karl Zilles, Peter T. Fox

Neuroimaging results are usually reported as stereotaxic coordinates for local maxima. While comparison across studies is therefore almost exclusively coordinate-based, the spatial uncertainty associated with these maxima is still unknown. Here empirical assessment of the spatial uncertainty associated with local maxima was performed based on fMRI data from 21 subjects imaging a simple motor task. Each subject was preprocessed and analysed 9 times, using different approaches for registration into MNI space. The maxima coordinates representing 16 functionally defined regions were identified in each individual analysis and the ensuing 9 group analyses. Between-subject and between-template variability was quantified by the mean Euclidean distance (ED) between corresponding maxima and parameterised by the full width of half maximum FWHM of a Gaussian variance model. Between-subject variability was comparable across normalisations (11.0–12.1mm), and ranged from 7.6mm (caudate nucleus) to 17.6mm (prefrontal cortex). The average ED (across areas and normalisations) was 11.6mm. Converting into a Gaussian displacement and scaling by sample size yields an uncertainty of 17.1/sqrt(Nsubjects)mm FWHM. The EDs between coordinates for a particular area as obtained from the 9 group analyses (differing only by normalisation) ranged from 4.3mm to 8.4mm with a mean of 5.7mm, corresponding to a Gaussian FWHM of 8.4mm. Combining these estimates indicates that the spatial uncertainty associated with local maxima is substantial with FWHMs between 10.8mm (8 subjects) and 9.0mm (30 subjects). We conclude that maxima coordinates represent valid point-estimators of an effect, but their associated uncertainty must be considered before statements about converging results are made.

P74. Serum Prolactin Gender Difference and Psychopathology in First Episode Non-medicated Schizophrenia

Amresh Shrivastava, Yves Bureau, Manoj Tamhane, Meghana Thakar, Nilesh Shah

The literature on serum prolactin in drug naïve first episode schizophrenia patients is inconsistent. This discrepancy prompted us to measure prolactin levels in 30 male and 30 female non-medicated first episode schizophrenia patients. We hypothesized that prolactin levels would be higher in patients compared to volunteers and that this difference would be greatest for females given that females have higher prolactin levels in general. Prolactin measurements took place at a tertiary psychiatric setting in Mumbai, India at the time of

the patients' admission (baseline). We also measured prolactin levels in 15 male and 11 female healthy volunteers. Patients were evaluated for psychopathology using the BPRS and the PANSS on the first day (baseline), three and six weeks of admission. Serum prolactin levels were elevated for 75% of patients. We conducted a 2-way analysis of variance for prolactin measures between gender and illness status. Females in general had higher prolactin levels ($p<.001$) as did all patients in the cohort ($p<.001$). We also observed a significant gender by illness status interaction ($p<.001$) indicating that females (18.0 vs. 60.5 ng/ml) have greater prolactin level differences between illness statuses compared to males (17.0 vs. 31.1 ng/ml). We also found a negative Pearson Product-Moment correlation between prolactin with BPRS and PANSS scores in females only at all time points indicating that higher prolactin levels predict lower psychopathology. Prolactin levels at baseline are greatest in female patients than any other category and that prolactin measures in females can predict psychopathology in drug naïve first episode schizophrenia patients.

P75. Neuroprotective Role of Lithium in Aluminum-Induced Behavioral and Functional Alterations in Rats

Punita Bhalla, Devinder Kumar Dhawan

In the present study, aluminium (Al) was administered at a dose of 100mg/kg b.wt./day whereas lithium was supplemented in diet (1.1 g/Kg diet, daily) for the period of two months. Significant decrease in the retention time (short-term memory) and muscular activity (rota rod and total locomotor tests) were observed in Al treated animals. Further, significant increase in the number of escaped trials (active avoidance test), anxiety levels (elevated plus maze) and depression time (behavior despair test) were also observed in animals exposed to Al. Lithium co-administration was able to regulate the behavioral changes and muscular activity of animals. Al treatment caused a decrease in the acetylcholinesterase activity as well as in the levels of serotonin and dopamine in brain (cerebrum and cerebellum), which were significantly increased upon lithium supplementation. A significant increase in the monoamine oxidase activity was observed following Al treatment in cerebrum only, which however was decreased following lithium treatment. Ca2+ ATPase activity was observed to be decreased in Al treated animals. Further, a significant increase in Ca2+ influx as well as in the levels of cAMP was also observed following Al treatment, which was reversed with lithium co-administration. Al treatment caused a significant increase in the levels of phopholipase C (PLCÝ1), which was normalized following lithium supplementation. The study demonstrates that lithium has the potential in containing or reversing the Al-induced behavioral and functional

changes as evidenced by behavioral disorders, altered neurotransmission and altered calcium homeostasis as well as disordered signal cascade in experimental animals.

P76. Neuroprotective Effect of Piperine on Dopaminergic System Modulation, Behavioral Changes, and Oxidative Stress after Intrastriatal Administration of 6-OHDA for Hemi-Parkinsonian Rat Model

Pallavi Shrivastava, Kumar Vaibhav, Fakhrul Islam

Background and aims: Parkinson's disease is characterized by a depletion of dopamine (DA) neurons in the nigrostriatal pathway. Stereotaxic injections of 6-hydroxydopamine(6-OHDA), results in a massive DA denervation of the nigrostriatal pathway. Piperine is an active principle of Black pepper (piper nigrum).The present study investigated oxidative damage and neuroprotective effect of Piperine for the antiparkinsonian effect in neuronal death produced by intrastriatal infusion of a potent free radical generator and mitochondrial inhibitor, 6-OHDA (6-Hydroxydopamine) in rats. Methods: Unilateral stereotaxic intrastriatal infusion of 6-OHDA caused significant decrease of striatal dopamine levels as measured employing oxidative stress parameters, D2 Receptor Binding, HPLC-electrochemistry,PARP binding and followed by, stereotypical contra lateral rotational behavior when challenged with DA agonists such as apomorphine. Results: The present study also shows the significant results in the elevated body swing test (EBST) as a measure of asymmetrical motor behavior of hemiparkinsonian animals in a drug-free state.6-OHDA-induced oxidative stress increases TBARS in rats which were attenuated by Piperine. Piperine (10 mg/kg bwt, oral for 15 days) treatment attenuated 6OHDA-induced reductions in glutathione (GSH) levels, Glutathione Peroxidase, Glutathione Reductase, Superoxide dismutase and catalase in the striatum. Piperine also significantly attenuated D2-receptors in striatum. The present study also proposes the behavioral parameter for balance and co-ordination of motor activities in parkinsonian rats. Narrow beam test analysis is a behavioral parameter for 6-OHDA induced Parkinson's rats. Piperine significantly reverses the alterations in the Parkinson's rats. Conclusions: Our findings suggest that unilateral intrastriatal infusion of 6OHDA reproduces neurochemical, neuropathological and behavioral features of PD in rats and Piperine can protect the dopaminergic neurons from 6OHDA-mediated neurodegeneration in brain. These results not only establish oxidative stress as one of the major causative factors underlying dopaminergic neurodegeneration as observed in Parkinson's disease, but also support the view that Piperine is a potent free radical scavenger and an antioxidant.

P77. MEG Response Reconstruction via Variational EM Algorithm

Jing Kan

Magnetoencephalography (MEG), is non-invasive complementary techniques used to measured the magnetic induction outside the head and the scalp electric potentials produced by the electrical activity in neural cell assemblies respectively, which is commonly used in both research and clinical settings, such as intractable epilepsy, Parkinson's diseases. MEG presents more accurate advantage in the temporal field compared with PET and fMRI. In this paper, we try to solve neuro-response source reconstruction of MEG (Magnetoencephalography) via Variational EM algorithm. As a ill-posed problem, the unknown response sources in brain has been looked as multiple currents with different orientation j that are spread in different location r in brain. We assumes the integration of unknown T(j, r) in every source located voxel as the parameter that we try to estimate using VEM. Firstly, with the Boit-Sarvart Law, we can build the mathematical model for magnetic field out side the scalp. With the measured data of magnetic field within particular time interval, we can give the distribution of independent observation data. Then, we build the smoothing prior model of unknown parameter based on Gaussian Random Field. So, the parameter estimation problem is actually the MAP estimate with the condition above. As the feature for non-stationary Gaussian prior distribution, VEM is best to apply to solve this problem, so that the information of response current can be found.

P78. Navigating Drug Development Moguls for Potential Biotechnology Moguls

Eric W. Harris

Academic and clinical scientists are increasingly involved in the development and commercialization of regulated medical products (drugs, biologics and devices, including diagnostics). Examples of such involvement include testing others' proprietary technologies, conducting clinical trials, serving on scientific advisory boards, or joining biotechnology companies. But, even in the hands of the most seasoned scientists, most technologies to reach marketing approval; this is particularly so for products targeting neurological or psychiatric diseases, for which there are few (e.g., ALS) or no (e.g., neuroprotection after stroke) successful precedents to follow. The more scientists understand the overall terrain (clinical development), the finish line (marketing applications), and the gatekeepers (e.g., FDA) the more likely they are to push off in an optimal direction and to avoid crashing their projects. This poster provides a representative

"trail map" (Integrated Development Plan) for new product approval by 1) organizing activities along four primary tracks (clinical, regulatory, nonclinical, and CMC (Chemistry, Manufacturing and Controls), and 2) aligning them on a timeline that illustrates their sequence and interdependence. Integrated Development Plans tailored to specific projects have proven useful to scientists and entrepreneurs who are new to the pharmaceutical industry, or who are experienced and want to proceed efficiently, or who need to communicate business plans to potential investors. The poster also includes a "Top Ten List" of ways to stay on track product development, a glossary of common drug development terms, and links to related government and industry web sites.

Don't forget to visit the exhibits

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