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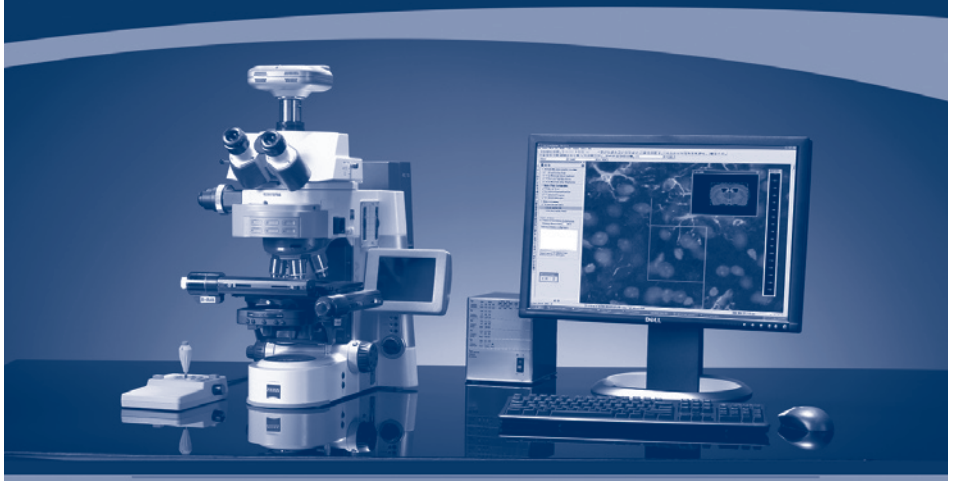

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41st Annual Winter Conference on Brain Research 2008

41st Annual

Winter Conference on Brain Research

January 26–February 1, 2008
Snowbird, Utah

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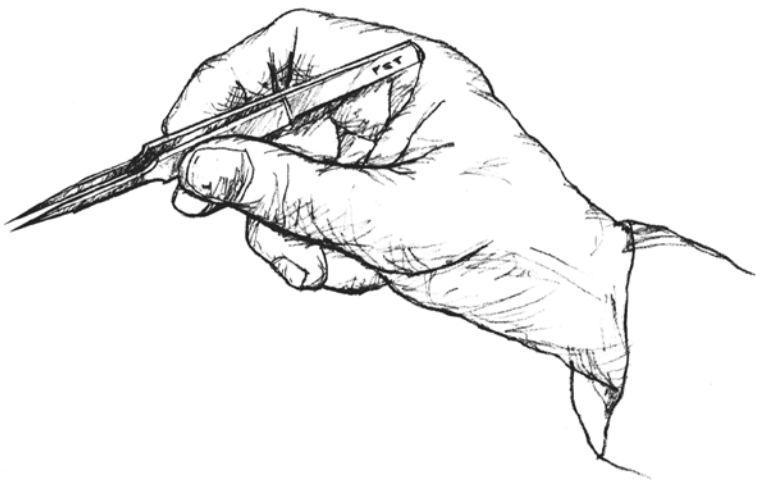

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Welcome to the 41st annual meeting of the Winter Conference on Brain Research

I extend a special welcome to all of you who are new to the meeting. I believe that you will find this to be one of the most diverse, high-quality, and content-heavy meetings in neuroscience that many of you will attend. Besides having the chance to hear neuroscientists from around the world present their work at formal sessions, this meeting offers the unique opportunity to socialize and ski with these same scientists in an informal setting. Those of you who are WCBR habitués know that the success of the meeting depends upon your individual contributions to each session, even if you are not a panel or workshop speaker or a poster presenter. Our biggest strength is the scientific interaction that occurs at these formal sessions, as well as the personal interactions that take place after the sessions have ended. For this reason, I urge you to welcome newcomers (blue badges) and Travel Fellows (badges with purple dots) into your discussions, and social and ski groups as often as possible to make sure that this will be the first of their many future WCBR meetings.

The week begins on Saturday night with the opening reception. The opening breakfast on Sunday will feature our keynote speaker, Dr. Samuel Weiss. A previous WCBR attendee known to many of you, Sam is also a Professor in the Department of Cell Biology & Anatomy/Pharmacology & Therapeutics, and a member of the Genes and Development Research Group Faculty of Medicine, University of Calgary. In addition to being a co-discoverer of the metabotropic glutamate receptor, he and his collaborators have made many seminal contributions to our understanding of how stem cells function in the brain. Sam's talk is entitled, "The Hope and Hype of Neural Stem Cells: What Does the Future Hold?"

Other special events during the rest of the week will include: 1) the **School Outreach** program, which will be run by Karen Greif with help from Frank Welsh. It includes ~12 WCBR participants who bring neuroscience to students in three local schools; 2) a **Town Meeting** for locals and hotel guests at Snowbird and Alta lodges, which is organized by Kristin Anstrom-Kelly with a talk by Jon Cohen entitled, "The Vulcanization of the Human Brain: Brain Imaging Studies of "Cognition-Emotion" Interactions in Decision Making"; 3) the **Smitty Stevens Memorial** (NASTAR) **Ski Race** organized by Dale Pelligrino and Tom Swanson and the **Mountain Lunch** will be held on Wednesday afternoon; 4) the **Business Meeting** will also be held on Wednesday at

6:30 PM, immediately following the afternoon sessions. Please attend to elect new board members and to provide your thoughts on the program, overall organization, and future meeting sites. Because board members play a vital role in the governance of WCBR, we ask all of you to consider nominating yourself (or a "friend") for open positions in the categories of cell/molecular, clinical or systems/behavioral neurosciences; 5) the **Annual Banquet** finishes the week on Friday night with live music, awards, and some wild and crazy neuroscientist dancers.

I want to remind you that this is an all-volunteer organization. We have an especially dedicated group of officers, board of directors, and committee chairs. Tom Swanson has done a wonderful job as Facilities chair working with the University of Illinois at Urbana-Champaign conference planners to make this a successful meeting. Program Chair Patricio O'Donnell and his committee have worked hard to increase the number of high-quality scientific proposals. The result is an exceptionally broad and interesting program this year. Jacqueline McGinty is now in her second year as Treasurer and has made sure we have remained in excellent fiscal health. We also all owe a considerable debt to the members of the Board of Directors for their valuable insights and continued input to the governance of this year's meeting.

Steve Levison, Exhibits Chair, is our liaison with the exhibitors who provide important financial support for the meeting. This year, he is being helped by Paul Dore-Duffy. Our exhibitors sponsor the afternoon breaks, and I urge you to visit their booths at these breaks. Gretchen Snyder and George Wilcox have taken over the Travel Fellow program this year and have worked hard to raise funds to underwrite these fellowships. They and their committee have chosen 14 pre- and postdoctoral students and junior faculty as Travel Fellows and have recruited an equal number of volunteers from our ranks to serve as mentors.

On a related point, I note with sadness the passing this year of our longtime friend, scientific colleague, and WCBR attendee, Ann Kelley. She will be sorely missed by all who knew her. Because of her importance to WCBR and its attendees, we have named one of the travel fellowships in her honor.

Finally, Kim Topp will take over as our new Conference Chair at the final banquet. She is an extremely capable and experienced leader, and I feel very comfortable leaving the conference in her able hands.

In conclusion, I hope that you will all enjoy the meeting, your colleagues, and the snow.

Barry Levin
Conference Chair

Contents

Don't forget to visit the exhibits

AMERICAN SOCIETY
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39th Annual Meeting

San Antonio, Texas

March 1—5, 2008

Join us for four days of symposia, colloquia and workshops designed to address the four major themes of our Society:

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For More Information & Meeting Updates Go To:

www.ASNeurochem.org

General Information

Headquarters is the Cliff Lodge Conference Center. All scientific activities will be held there.

WCBR Information Desk and Message Center are in the Registration area, Cliff Lodge, Level B.

The desk hours are as follows:

	Morning	*Afternoon*
Saturday 1/26	8:00–10:00 AM	3:30–9:00 PM
Sunday 1/27	6:30–10:00 AM	3:30–7:00 PM
Monday 1/28–Thursday 1/31	7:00–9:45 AM	3:30–7:00 PM
Friday 2/1	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. Attendance at this conference is strictly limited to **preregistered** participants. On-site registration is not available.

Posters will be available for viewing in three different sessions during the week in Ballroom 2 & 3: Poster Session 1, Sunday–Monday, Poster Session 2, Monday–Tuesday, and Poster Session 3, Tuesday–Thursday. Poster presenters will be by their posters for discussion from 3:30 to 4:30 PM according to the schedule listed on pages 23–28. Presenters may put up their posters after 8:30 PM on the day their session starts. Presenters should take down their posters by 8:30 PM on the final day of their session. Please see Poster Sessions section in program for titles and names of presenters.

Exhibits and Lounge are in Ballroom 2 & 3. Coffee is available there from 9:30–10:30 AM, Monday through Friday. Refreshments are provided 3:30–4:30 PM, Sunday through Thursday. Exhibits close after 10:30 AM on Friday. Friday's afternoon break will be in the Ballroom Lobby.

Breakfast is served to all registrants on Sunday, 7:30–8:30 AM, in the Ballroom, and on Monday through Friday, 6:00–10:00 AM, at the Aerie Restaurant (Cliff Lodge Level 10) or The Forklift (Snowbird Center Level 3). The tickets in your registration packet are required for admission.

Ski Lift Tickets will be available from the WCBR Information Desk. Daily tickets can be purchased or prepaid tickets can be picked up during desk hours.

Banquet table sign up sheets will be posted next to the Registration area, Monday–Friday. Attendees will have the opportunity to reserve a table at the Friday banquet. This will make it easier for you and your friends to sit together at the banquet without rushing to hold a table when the doors open. If you have any questions, inquire at the Registration area.

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We thank the individuals and organizations that have generously supported the Travel Fellowship program.

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Special Events

Saturday, January 26

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

Sunday, January 27

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

The plenary keynote speaker will be **Dr. Samuel Weiss**, Professor and Director, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada.

"The Hope and Hype of Neural Stem Cells: What Does the Future Hold?"

The identification and isolation of neural stem cells in the early 1990s invigorated the field of neuronal cell replacement. Subsequently, an enhanced understanding of endogenous neural cell genesis, spanning early development to adulthood, has complemented advances in the cell biology of rodent and human neural stem cells.

For many years, it has been suggested that these discoveries would dramatically impact neuronal transplantation and/or endogenous neuronal replacement for treating neurodegenerative diseases, such as Parkinson's disease, and neurological injuries, including stroke and spinal cord injury. In many cases, however, advances in neural stem cell biology have surpassed those that have advanced neuronal cell therapy, such that the two have yet to intersect effectively in the clinic.

The promise of neural stem cell therapeutics applications of the future, in fact, may have little to do with neuronal replacement. With respect to neurological injury, current findings suggest that neural stem cells may participate in recovery of neurological function indirectly, for example, through enhancement of intrinsic brain plasticity or myelination. Remarkably, compelling reports suggest that neural stem cell biology may have its most significant impact in the fields of neuropsychiatric/behavioral disorders and brain cancer. Supported by the Canadian Institutes of Health Research and the Canadian Stem Cell Network.

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

Monday, January 28

First Meeting of the Board of Directors • 6:30–8:30 AM, White Pine

Tuesday, January 29

Breakfast for Travel Fellows Meeting • 6:30–7:30 AM, Aerie Restaurant (Cliff Lodge Level 10)

Town Meeting • 7:00 PM, Summit Room (Cliff Lodge, Level 10) Attendance is open to all.

Wednesday, January 30

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 AM, Lower Wilbere Ridge, NASTAR registration cards to be completed no later than Monday, January 28, 8:00 AM at WCBR Information Desk.

Mountain Lunch • 11:30 AM–2:00 PM, Outdoor lunch at Gad Valley; required lunch ticket is in your registration packet. Non-skiers requiring transportation should sign up at the WCBR Information Desk by Monday, January 29.

Business Meeting • 6:30 PM, Ballroom 1

Election of Conference Chair-Elect and four members of the Board of Directors, presentation of budget, and discussion of future meeting sites.

Friday, February 1

Second Meeting of the Board of Directors • 6:30–7:30 AM, White Pine

Banquet and Dance • 7:30 PM, Ballroom

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

Preamble to the Program

The 2008 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 27

7:30 AM

Plenary Session • Ballroom

Dr. Samuel Weiss, Hotchkiss Brain Institute, University of Calgary

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30–6:30 PM

1. Panel • Ballroom 1

Encoding Value: The Neural Basis of Decision Making

Paul Phillips (chair), Geoffrey Schoenbaum, Joseph Paton, Shunsuke Kobayashi, Read Montague

2. Panel • Magpie

Assessing the Genetics of Neurocognitive Dysfunction in Schizophrenia and Bipolar Disorder: Diverse Approaches towards a Common Goal

Richard Keefe, **Katherine Burdick (chair)**, Anil Malhotra, David Goldstein

3. Panel • Maybird

Neurobiology of Aging Is Going to the Dogs

Donald Ingram (chair), N. W. Milgram, Carl Cotman, Patrick Sullivan, Elizabeth Head

4. Panel • Wasatch

Circadian Clocks and Non-Image Forming Retinal Physiology: from Mice to Men

Susan Doyle (chair), Michael Iuvone, Samer Hattar, Xudong Qiu, Steven Lockley

5. Panel • Superior A

The Brain Does Not Live by Glucose Alone: Alternate Fuels for Brain Metabolism

Sami Harik (chair), Joseph LaManna, Gerald Dienel, Pierre-Gilles Henry

6. Panel • Superior B

The Challenge of Modeling and Therapeutic Development for Mild TBI

Edward Hall (chair), David Hovda, Jonathan Lifshitz, Douglas Smith, Barclay Morrison

8:30–10:00 PM

7. Panel • Ballroom 1

Dissecting the Role of Reactive Astrocytes in Neurotrauma, Stroke and Neural Grafting in the CNS

Milos Pekny (chair), Ole Petter Ottersen, Yang Teng

8. Panel • Magpie

Where in the Brain Is Schizophrenia?

Sharon Eastwood (chair), Clare Beasley, Steven Arnold, Dwight Dickinson

9. Panel • Maybird

Sleep and Drug Dependence: Some Stimulating Data

Colleen McClung, Peter Morgan, **Una McCann (chair)**

10. Panel • Wasatch

Of Pain and Chocolate: Exploring the Opioid-Feeding Link across the Neural Axis

Wayne Pratt (chair), Kenny Simansky, Charles Billington, Kyle Smith, Robin Kanarek

11. Panel • Superior A

The Emerging Role of HDACs in Neuronal Function and Disease

Michael Ahlijanian (chair), William Renthal, Ghazaleh Sadri-Vakili, Andre Fischer

12. Panel • Superior B

Synaptic Signal Transduction and Striatal Neurodegeneration in Huntington's Disease

Edoardo Marcora, Ilya Bezprozvanny, Lynn Raymond, **Veronique André (chair)**

Monday, January 28

7:30–9:30 AM

13. Panel • Ballroom 1

Regulation of Excitatory Synapses

Katherine Roche (chair), David Bredt, A. Villu Maricq, Roger Nicoll

14. Panel • Magpie

Can't Stop Loving You: Role of Impulsivity in Drug Seeking Behavior

Taco De Vries (chair), Catharine Winstanley, Jeffrey Dalley, Tommy Pattij, Harriet de Wit

15. Panel • Maybird

Sorting Out Morphological and Electrophysiological Differences between Striatal D1 and D2 Receptor-Containing Striatal Neurons: Myths and FACS

Anton Reiner, **Carlos Cepeda (chair)**, Michelle Day, William Yang

16. Panel • Wasatch

Will Genome-Wide Association Studies Rewrite the Genetics of Bipolar Disorder and Schizoprhenia?

William Bunney (chair), Francis McMahon, Anil Malhotra, Steven Potkin, David Goldstein

17. Panel • Superior A

Neuroprotective Therapies for Parkinson's Disease: How Much Help Can We Get from Animal Models?

Yoland Smith (chair), Erwan Bezard, Joel Perlmutter, Warren Olanow

18. Panel • Superior B

Synaptic Mechanisms in the Outer Retina

Ron Gregg, Teresa Nicolson, Stephen Massey, **Catherine Morgans (chair)**

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30–6:30 PM

19. Panel • Ballroom 1

The Adolescent Reward System: Too Much of a Good Thing?

Susan Andersen, **Patricio O'Donnell (chair)**, Adriana Galvan, Monique Ernst

20. Panel • Magpie

To Be or Not To Be: Hanging in the Balance

Joseph LaManna, **Paula Dore-Duffy (chair)**, Gregory del Zoppo, Denson Fujikawa, Dale Pelligrino

21. Panel • Maybird

Using Biomarkers To Guide Drug Activity in Psychiatric Indications

Menelas Pangalos (chair), Ann Olincy, Mitchel King, Eve Johnstone, Mark Day

22. Panel • Wasatch

New Insights into Glial-Neuronal Interactions

Ken McCarthy, **Stephen Traynelis (chair)**, Michael Robinson, Aude Panatier

23. Panel • Superior A

Voxel-Based Meta-Analysis: Neural System Models Emerge from Data Mining

Peter Fox (chair), Angela Laird, Tomas Paus, Simon Eickoff, Jane Neumann

24. Minicourse • Superior B

Homeostasis in the Visual System

Arianna Maffei, Michael Crair, Hey-Kyoung Lee, **Ronald Meyer (chair)**

8:30–10:00 PM

25. Panel • Ballroom 1

Exactly How Does "Ecstasy" Produce Long-Term Effects?

George Ricaurte (chair), Glen Hanson, Terry Monks, Bryan Yamamoto

26. Panel • Magpie

Imaging of Pain

Richard Gracely, Bruce Naliboff, Pamela Paulson, **Thomas Morrow (chair)**

27. Panel • Maybird

Novel Views of Myelin

George Bartzokis, Michael Georgieff, **James Connor (chair)**

28. Panel • Wasatch

Using Transport to Map the Brain: Live Imaging of Neuronal Connections with MRI

Elaine Bearer (chair), Russell Jacobs, Arthur Toga

29. Panel • Superior A

Novel Functions of Intracellular Loops in Ligand-Gated Channels

Tim Hales, David Weiss, **Sheryl Smith (chair)**

30. Workshop • Superior B

All for One and One for All: Emerging Ideas of Population Coding in the Brain

Vivien Casagrande (chair), Kristina Nielsen, Walter Jermakowicz, Andrew Schwartz

Tuesday, January 29

7:30–9:30 AM

31. Panel • Ballroom 1

The Role of the Medial Prefrontal Cortex in Fear and Drug Memories

Jacqueline F. McGinty (chair), Suzanne Haber, Ronald See, Jamie Peters, Douglas Bremner

32. Panel • Magpie

No Gene Is an Island: COMT and Its Interactions Contribute to Complex Brain Phenotypes

Paul Harrison (chair), Daniel Weinberger, Yoshi Sei, Elizabeth Tunbridge, Joshua Roffman

33. Panel • Maybird

Neuroinflammation: Is There an Alternative?

Carol Colton (chair), Fredrik Kamme, David Wink, Michael Vitek

34. Panel • Wasatch

Connexins in Physiology and Pathology of CNS

David Spray, **Vladimir Parpura (chair)**, Christian Giaume, Christian Naus

35. Panel • Superior A

Seizures from Broken Channels: Regulation and Therapeutics of Acquired Channelopathies in Epilepsy

Anne Anderson, **Nicholas Poolos (chair)**, Shelley Russek, Amy Brooks-Kayal

36. Panel • Superior B

Sex Hormones—and Why the Lack of Them Makes You Fat

Thomas Lutz (chair), Debbie Clegg, Richard Simerly, Stephen Benoit

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30–6:30 PM

37. Panel • Ballroom 1

To Move, or Not, to the Rhythm: Physiological and Pathological Oscillations in Cortico-Basal Ganglia Networks

Peter Magill (chair), Andrew Sharott, Rui Costa, Nicolas Mallet, Thomas Boraud

38. Panel • Magpie

Diverse Mechanisms Underlying Brain Reward

Sarah Leibowitz (chair), Friedbert Weiss, Rainer Spanagel, Charles O'Brien

39. Panel • Maybird

Exploiting DISC1 to Understand the Biology of Schizophrenia and Develop New Preclinical Disease Model

Nick Brandon (chair), Mirian Hayashi, Kozo Kozo Kaibuchi, Steve Clapcote, Akira Sawa

40. Panel • Wasatch

Roles of Mitochondria in Synapse Formation and Dysfunction

Leonard Kaczmarek (chair), George Spirou, Elizabeth Jonas, Gordon Rintoul, Ella Bossy-Wetzel

41. Panel • Superior A

Cerebellar Plasticity: James McElligott Memorial Panel

Robert Baker, James Bloedel, Edward Keller, **Laurence Young (chair)**

42. Panel • Superior B

Chronic Pain New Mechanisms for Few Analgesics

Peter Reeh, **Michael Costigan (chair)**, William Lariviere, Simon Beggs

7:00 PM

Town Meeting • Summit Room (Cliff Lodge Level 10)

8:30–10:00 PM

43. Workshop • Ballroom 1

Hemichannels or Giant Ion Channels: The New World of Gap Junction Proteins

Brian MacVicar (chair), Michael Bennett, Bruce Ransom, Roger Thompson, David Spray

44. Panel • Magpie

Sequestosome 1/p62, Aggregation and Neurodegeneration

Marie Wooten (chair), Henry Paulson, Haning Zhu, Geir Bjorkoy, Ted Dawson

45. Panel • Maybird

Reeling Rats and Mice of Vice: Novel Rodent Models of Addiction

John Crabbe, Nick Gilpin, **Chris Olsen (chair)**, Andrew Holmes

46. Panel • Wasatch

Neurological Emergencies with Methamphetamine & MDMA (Rodent Models)

Jerry Frankenheim (chair), Daniel Rusyniak, Jon Sprague, Bryan Yamamoto, Gary Gudelsky

47. Panel • Superior A

Toll-like Receptors in CNS Injury and Infection

Tammy Kielian (chair), Trevor Owens, Phillip Popovich, Timothy Vartanian

48. Workshop • Superior B

Neonatal Programming of Neuroendocrine Function

Greti Aguilera (chair), Karen Bales, Stafford Lightman, Tallie Baram, Michael Meaney, Jonathan Seckl

Wednesday, January 30

7:30–9:30 AM

49. Panel • Ballroom 1

New Directions in Behavioral Neurogenetics: Genetic Dissection of Brain, Behavior, and Disease Pathways

Amanda Law (chair), Daniel Weinberger, Colin Hodgkinson, David Goldman

50. Panel • Magpie

CRF Effects on Midbrain Dopamine Neurons: Implications for Psychostimulant Action

Roy Wise, Matt Wanat, **Michael Beckstead (chair)**, Arthur Riegel

51. Panel • Maybird

Deep Brain Stimulation for Obsessive-Compulsive Disorder: From Clinical Perspectives to Basic Mechanisms

Benjamin Greenberg, Darin Dougherty, Suzanne Haber, **Clinton McCracken (chair)**

52. Panel • Wasatch

Sex Differences in the Brain: It's Not Just About Sex Anymore!

Margaret Altemus, Victoria Luine, **Jill Becker (chair)**, David Standaert

53. Panel • Superior A

New Insights into the Cellular Basis for Familial Epilepsies and Other Sodium Channelopathies

Todd Scheuer (chair), Massimo Mantegazza, Alan Goldin

54. Panel • Superior B

New Pistes for IGF Signaling in the Nervous System

Steve Levison, Cunming Duan, Kim Heidenreich, **Terri Wood (chair)**

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30–6:30 PM

55. Panel • Ballroom 1

Learning and Brain Plasticity, the Schizophrenics Dilemma

Henry Holcomb (chair), Robert Astur, Laura Rowland, Carol Tamminga

56. Panel • Magpie

Drug of Abuse: What Dopamine Neurons Do and Don't Do!

Christopher Ford, Christian Luscher, Michela Marinelli, **Francois Georges (chair)**

57. Panel • Maybird

Polyphenols and Polyunsaturated Fatty Acids: the Pollyannas of Brain Neurodegeneration

James Joseph, Marva Sweeney, Henriette van Praag, **Tom Kuhn (chair)**

58. Panel • Wasatch

Old Toxins and New Tricks: Modeling Parkinson's Disease in Rodents, Flies, and Worms

Michael Levine (chair), Marjorie Ariano, David Krantz, Bernd Meurers, Richard Nass

59. Workshop • Superior A

Give Haptics A Hand

Gerald Loeb (chair), Karen Moxon, Tansu Celikel, Gene Fridman, Francisco Valero-Cuevas

60. Panel • Superior B

The Role of the Serine/Threonine Phosphate PP2A in Neuronal Signaling

Johannes Hell (chair), Angus Nairn, Estelle Sontag, Mary Horne, Stefan Strack

6:30–7:30 PM

Business Meeting and Elections • Ballroom 1

Thursday, January 31

7:30–9:30 AM

61. Panel • Ballroom 1

Neurobiology of Dopamine Terminals: What Do Cannabinoid Receptors Have To Do with It?

Joseph Cheer (chair), David Lovinger, Alexander Hoffman, Anatol Kreitzer, Eliot Gardner

62. Panel • Magpie

Protein Misfolding—A Common Theme in Neurodegenerative Diseases

Menelas Pangalos (chair), Rakez Kayed, Daniel Otzen, Donald Lo, Peter Reinhart

63. Panel • Maybird

In Vivo Physiology in Genetic Models: Bridging the Gene/Behavior Gap

Joshua Gordon (chair), Patricio O'Donnell, Malcolm Nason, Rui Costa

64. Panel • Wasatch

Yin and Yang of Glial Cell Responses in Cerebrovascular Disorders

Jarowslaw Aronowski (chair), Mark Goldberg, Gregory Del Zoppo, Bruce Ransom

65. Panel • Superior A

Your Brain on (Neuro)Steroids: A Myriad of Beneficial Functions in Animals and Human Beings

Leslie Morrow, Michael Rogawski, Roberta Brinton, **Synthia Mellon (chair)**

Thursday, January 31, continued

66. Minicourse • Superior B

Generating Tools for the Study of Nervous System Function Using Adeno-Associated Viral Vectors: Design, Production and Applications

Corinna Burger (chair), Edgardo Rodriguez

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30-6:30 PM

67. Panel • Ballroom 1

Motivation, Learning, or Reward: What is Orexin's Role in Addiction?

Jim Fadel (chair), Stephanie Borgland, Rachel Smith, Brian Baldo

68. Panel • Magpie

Learning and Plasticity: What's Arc Got To Do with It?

John Guzowski, Kristen Keefe, David Rademacher, **Jacqueline F. McGinty (chair)**

69. Panel • Maybird

Neurodevelopmental Features of Schizophrenia: Genetic, Molecular, and Clinical Studies

Joel Kleinman (chair), Paul Harrison, Barbara Lipska, Thomas Hyde, Eve Johnstone

70. Panel • Wasatch

Neuromodulation of Synaptic Transmission and Neuronal Excitability in the Medial Prefrontal Cortex (mPFC)

Mark Yeckel, Donald Cooper, Evelyn Lambe, **LiLian Yuan (chair)**

71 Panel • Superior A

Shared Functional Genetic Loci and Neurobiologies of Pain/ Stress and Emotion

Jon-Kar Zubieta, Luda Diatchenko, Mitchell Max, **David Goldman (chair)**

72. Panel • Superior B

Bugs and Your Brain: Consequences and Cures

Jean Harry (chair), Fulton Crews, James Joseph, Nigel Greig, Susanna Rosi

8:30–10:00 PM

73. Workshop • Ballroom 1

U.S. Patent Reform: Is It Good/ Bad for Scientists/Companies/ Economy?

Phuong Pham (chair), James Fox, Joseph Belanoff

74. Panel • Magpie

Distinguishing the Immature from the Mature Brain: Response to Drugs and Injury

Christopher Turner (chair), Slobodan Todorovic, Vesna Jevtovic-Todorovic

75. Panel • Maybird

Your Aging Brain: The Monkey on Your Back

Mary Ann Ottinger (chair), Peter Rapp, Steven Kohama, Donald Ingram, Don Gash

76. Panel • Wasatch

Translational Research in Stimulant Dependence

Thomas Newton (chair), Ron See, Edythe London

77. Panel • Superior A

Human Embryonic Stem Cells, from Pluripotency to Neuroregeneration

Catherine Schwartz (chair), Martin Pera, Mahendra Rao, Xiamin Zeng

78. Panel • Superior B

Skin Biopsies for Diagnosis of Polyneuropathy; Beyond Neurite Counts

William Kennedy, Anne Louise Oaklander, Anne Bertelsen, **George Wilcox (chair)**

Friday, February 1

7:30–9:30 AM

79. Panel • Ballroom 1

Synaptic Plasticity: The Short and Long of It

William Catterall (chair), Ling-Gang Wu, Alexandra Few, Roger Nicoll, Rob Malenka

80. Panel • Magpie

Exercise Enhanced Neuroplasticity in Parkinson's Disesae and Its Animal Models

Michael Jakowec (chair), Giselle Petzinger, Charles Meshul, Richard Smeyne, Beth Fisher

81. Panel • Maybird

New Ideas about Synaptic Integration in the Retina

Stewart Bloomfield (chair), Joshua Singer, Jeffrey Diamond, Robert Miller

82. Panel • Wasatch

ADHD: Rare and Common Gene Variants in Risk and Treatment Response

Harriet de Wit, **Randy Blakely (chair)**, Aurelio Galli, Kwang-Soo Kim

83. Panel • Superior A

What Are the Roles of Trace Amine-Associated Receptor 1 in Primates?

Jerry Frankenheim (chair), Theresa Branchek, David Grandy, Thomas Scanlan, Gregory Miller

84. Panel • Superior B

Functional Organization of Axons

Bettina Winckler, **Matthew Rasband (chair)**, Edward Cooper, Elior Peles

3:30–4:30 PM

Exhibits & Posters • Ballroom 2 & 3

4:30-6:30 PM

85. Panel • Ballroom 1

Impact of the Serotonin Transporter Genotype on Cognition and Affect in Mice, Monkeys, and Humans

Charles Bradberry (chair), Andrew Holmes, Elizabeth Murray, Hank Jedema, David Goldman

86. Panel • Magpie

Beyond Reinforcement: Neurobehavioral "Systems" that Promote Addiction and Eating Disorders

Jeffrey Grimm (chair), Hans Crombag, Sara Ward, Mary Olmstead

87. Panel • Maybird

How Does the Adolescent Brain Become an Adult when Dr. Dopamine and Her Limbic Colleagues Are Not Around?

Janet Finlay, Gregorio Galiñanes, Andrew Chambers, **Kuei Yuan Tseng (chair)**

88. Panel • Wasatch

Factors Affecting Impact of Early Stage Brain Damage

Bill Greenough (chair), Donald Stein, Timothy Schallert, Michelle LaPlaca, David Hovda

89. Panel • Superior A

Kainate Receptors: New Vistas for Cortical Function

Graham Collingridge, Karen Wilcox, Roland Jones, **Mark Cunningham (chair)**

90. Panel • Superior B

Skiing the Bowl: Post-Structural Insights into Glutamate Transporter Mechanism

Christof Grewer, Peter Larsson, **Joseph Mindell (chair)**, Richard Bridges

Don't forget to visit the exhibits

Poster Session 1

Sunday–Monday • Ballroom 2 & 3

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

P1. CP-809,101: A Potentially Novel Antipsychotic

Philip Iredale

P2. Modulation of Dopamine-Dependent Protein Phosphorylation Provides a Novel Approach to Antipsychotic Drug Discovery

Gretchen Snyder

P3. Genetic Analysis of Whisker Barrels in SI in Recombinant Inbred Strains of Mice

Robert Waters

P4. Rapid Structural Plasticity of Astrocytes during Osmotic and Ischemic Stress in Cortical Brain Slices

Sergei Kirov

P5. Buprenorphine/Naloxone Treatment for Opioid Dependent Adolescents/ Young Adults

George Woody

P6. Promiscuous Pharmacology Complicates Distinguishing Connexin Hemichannels from Volume Activated Anion Channels in Astrocytes

Zu-Cheng Ye

P7. Inflammatory Mediators Produced by IFN-gamma Stimulated Murine Microglia Are Attenuated by Taurine Chloramine: Disruption of Signaling Pathways and Decreased Inflammatory Gene Expression

Michael Quinn

P8. Evidence for the Involvement of Ephrins and Ephs in the Guidance of the Peripheral Somatosensory System

Richard Lane

P9. Abused Inhalants May Interfere with Learning by Disrupting Hippocampal Inhibitory Circuit Function

Bruce MacIver

P10. Interactions of the Dopamine D2 Receptor with the Calcium-Binding Protein S100B

Kim Neve

P11. Neuroprotective Effect of VPS41, a Protein Involved in Lysosomal Trafficking, in Mammalian Cellular Models of Parkinson Disease

David Standaert

P12. Role of Neuronal Pentraxin 1 in the Intrinsic Program of Apoptotic Neuronal Death

Ramon Trullas

P13. Novel Roles for Aquaporin 1 in Spinal Cord Injury

Olivera Nesic

P14. Structural MRI and Cognitive Brain Measures in Methamphetamine Dependence

Malcolm Reid

P15. Reversible Silencing of the Glia-Specific Connexin-43 Produces Temporary Analgesia in a Rat Model of Orofacial Neuropathic Pain

Luc Jasmin

P16. Effects of Noggin on Oligodendrocytic Lineage Elaboration in Human Fetal Spinal Cord Tissue Derived Neural Precursor Cells

Tailoi Chan-Ling

P17. A Role for Beta 1 Integrin in Retaining Neural Stem Cells in the Ventricular Zone

Justin Lathia

P18. Analysis of ApoE-Mimetic Peptides as Novel Therapeutics for Treatment of Parkinson's Disease

Dale Christensen

P19. Ethanol Withdrawal-Induced Motor Impairment in Genetically Distinct Mice

Scott Philibin

P20. Heme Metabolism in Alzheimer's Disease

Barney Dwyer

P21. Amyloid Beta Induced Changes in Receptor Trafficking

Warren Hirst

P22. Modulating Microglial Activity and Neuroprotection

Alan Faden

P23. Gender Differences in the Time Course of Voluntary Alcohol Intake in Adolescent Mice

Sophie Tambour

P24. The Cannabinoid Agonist CP-55940 Injected into the 4th Cerebroventricle Antagonizes Cfos Induced by Intraperitoneal Cholecystokinin

Gaylen Edwards

P25. Neurotrophins Protect Cortical Cultures against Hydrogen Peroxide Toxicity

Frank Welsh

P26. Effects of Sex and Saccharin Preference on Behavioral Inhibition and Cocaine Self-Administration

Justin Anker

P27. Internal and External Shifting in an Operant Task in 6-OHDA Lesioned Rats

Arjan Blokland

P28. Acute Citalopram Potentiates Amygdala Reactivity

Kristin Bigos

Poster Session 2

Monday–Tuesday • Ballroom 2 & 3

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

P29. Age-Related Changes in Astrocyte Density, Morphology and Pax2 Expression in the Rat Retina: Imbalance between Cell Proliferation and Cell Death

Tailoi Chan-Ling

P30. Sorting Nexin-25 is a Novel Interacting Partner for D1 and D2 Dopamine Receptors and Influences their Trafficking and Expression

David Sibley

P31. Methamphetamine-Dependent Males Perform Better on Tasks Assessing Working and Episodic Memory than Matched Females

Brian Jackson

P32. Hippocampal Theta-Modulation by Inhalational (Non-)Anesthetics at Amnesic Concentrations

Misha Perouansky

P33. Time Course of Oxidative Stress and Synaptic Proteins Following Traumatic Brain Injury

Stephen Scheff

P34. Recruitment of Excitatory Serotonergic Neurotransmission to Cardiac Vagal Neurons in the Nucleus Ambiguus Post Hypoxia and Hypercapnia

David Mendelowitz

P35. Unrestricted Access to Stimulants of Abuse in the Past Is Associated with Increased Stimulant Use in the Present

Christopher Culbertson

P36. Protein Kinase C Delta Regulates Ethanol Intoxication and Ethanol Enhancement of Tonic GABA Currents

Robert Messing

P37. Seeing Is Believing? Why You Should Not Image Pain in the Anesthetized Brain

Pamela Paulson

P38. Polysynaptic Inhibitory Network among Striatal Cholinergic Interneurons

Matthew Sullivan

P39. Microglia Processes Block the Spread of Damage in the Brain

Dustin Hines

P40. Beyond TRPA1—Peripheral Neural Correlates of the Formalin Test

Tatjana Kichko

P41. Intrastriatal BDNF Infusions Restore Opioid Peptide Gene Expression in BDNF+/– Mice

Alicia Saylor

P42. Novel mGluR5 Antagonists as Potential In Vivo Probes

Amy Newman

P43. Coordinate Regulation of the GABA (A) Receptor Alpha1 Subunit by the CREB and BDNF Pathways

Ingrid Lund

P44. AMPA Receptor Trafficking after Withdrawal from Cocaine Administration: Role of Transmembrane AMPA Receptor Regulatory Proteins (Tarps)

Carrie Ferrario

P45. Coupling of Neuronal Nitric Oxide Synthase Phosphorylation to the NMDA Receptor and Signaling Pathways

Gerald Rameau

P46. Sherrington Was Right: Tail Withdrawal Responses in Rats Are Limited in Direction

Corey Cleland

P47. Bilateral Putamen Connectivity during Human Motor Task Execution

William Marchand

P48. Isolation Rearing Enhances Prepulse Inhibition Deficits in a Rat Model of Schizophrenia

Carrie John

P49. Global Gene Expression Profiling of Rat Prefrontal Cortex after Chronic Oral Risperidone Treatment

Mark Bardgett

P50. Expression of the Cannabinoid Receptor CNR1 in Schizophrenia and across Life Span in Postmortem Human Prefrontal Cortex

Ross Buerlein

P51. Expression of Ephrin-A3 and Epha4 in Somatosensory Cortical and Thalamic Neurons in Neonatal Rats

Cynthia Kenmuir

P52. Wake-Enhancing Effects of Nicotine Are Mediated by $\alpha4\beta2$ and $\alpha7$ Subunit-Containing Nicotinic Acetylcholine Receptors (Nachrs) in Rats

Maciej Gasior

P53. Orbitofrontal Cortex Does Not Signal Reward Prediction Errors (OFC VS VTA)

Donna Calu

P54. Orbitofrontal Cortex Is Critical for Conditioned Reinforcement Mediated by Outcome-Specific Representations

Kathryn Burke

P55. What Affects Resting Glutamate Levels in Striatum and Prefrontal Cortex of Awake Rats and Mice?

Peter Huettl

P56. Impaired Mismatch Negativity in Phencyclidine-Rat Model of Schizophrenia

Andrea Balla

Poster Session 3

Tuesday–Thursday • Ballroom 2 & 3

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

P57. Consolidation of Motor-Skill Memory in the Dorsal Striatum: Post-Trial Interference Reversed by Cocaine

Ingo Willuhn

P58. Neurons in the vSub Are Activated by Noxious Stimuli and Are Modulated by NE Afferents

Witold Lipski

P59. Differences in Receptor Expression and Dopamine Cell Activity during Adolescence May Predispose Adolescents to Drug Addiction

James McCutcheon

P60. Imaging Brain Activation: Looking "Through the Eyes" of Different Tracers

Nancy Cruz

P61. Potential Role of NUDEL-Oligopeptidase Enzymatic Activity in PC12 Cells Differentiation Process

Juliano Guerreiro

P62. Does the Mesocorticolimbic Dopamine System Contribute to the Subthalamic Nucleus Hyperactivity in Parkinson's Disease?

Shannon Blume

P63. Postnatal Maturation of Calcium Plateau Potentials in the Prefrontal Cortex during Adolescence: Role of L-Type Calcium Channel and Protein Kinase A Signaling

Lijun Heng

P64. Transcriptional Profiling of Postmortem Anterior Prefrontal Cortex from Cocaine Users

Elin Lehrmann

P65. Glutamate Release in the Ventral Striatum Is Regulated by Both D1 and D2 Receptor Activity

Nigel Bamford

P66. Expression of Schizophrenia Susceptibility Genes in Human Cerebral Cortex across the Lifespan

Hetal Choxi

P67. Progression of Immune Activation in Ventral Horn and Ventral Nerve Roots in the Transgenic G93A-SOD1 Rat Model of Amyotrophic Lateral Sclerosis

Brent Harris

P68. Ventral Striatal Neuronal Entrainment to Hippocampal Theta and Representation of Reward in the Awake Behaving Rat

John Wolf

P69. Investigating the Role of Oligodendroglia in Retrovirus-Induced Spongiform Neurodegeneration

William Lynch

P70. Effects of MDMA on Neurogenesis and Conditioned Place Preference in Adolescent Rats

Ashley Sponaugle

P71. Gene Delivery to Sensory Neurons Following Direct Lumbar Puncture

Carolyn Fairbanks

P72. Fast Desensitization of Synaptic GABA-A Receptors after Brief Hi-Frequency Firing as a Trigger for Seizures

David Naylor

P73. Involvement of the Ventral Tegmental Area and Nucleus Accumbens Septi in the Reinstatement of Cocaine Place Conditioning during Adolescence

Cheryl Kirstein

P74. Putative Dopamine Responses during a Dopamine-Dependent Motor Behavior in a Rodent Model of Parkinson's Disease

Kristin Anstrom

P75. Interactive Dynamics between Frontal Cortex, Basal Ganglia, and Norepinephrine in High-Conflict Decisions and Response Inhibition

Michael Frank

P76. A Demonstration and Interactive Explanation of the Inability To Perceive One's Own Eye Movements in a Mirror

Ralph Berger

P77. Neuroregulation of Non-Exercise Activity Thermogenesis (NEAT) and Obesity Resistance

Catherine Kotz

P78. Repeated Ferret Odor Exposure Induces Same-Stressor Habituation and Novel-Stressor Sensitization of Neuronal Activity across Numerous Forebrain Regions in the Rat

Marc Weinberg

P79. Does Mother Nature Always Know Best? Fetal Ethanol Experience and Olfactory Plasticity

S.L. Youngentob

P80. Initial Phase 2 Trial of a Nicotinic Agonist in Schizophrenia

Lynn Johnson

P81. Insertion of GluR1 Is Required for the Synaptic Plasticity Evoked by Addictive Drugs in the VTA

Bénédicte Balland

P82. Olfactory Marker Protein Is a Novel Modulator of Ca2+ Efflux in Olfactory Sensory Neurons

P.F. Kent

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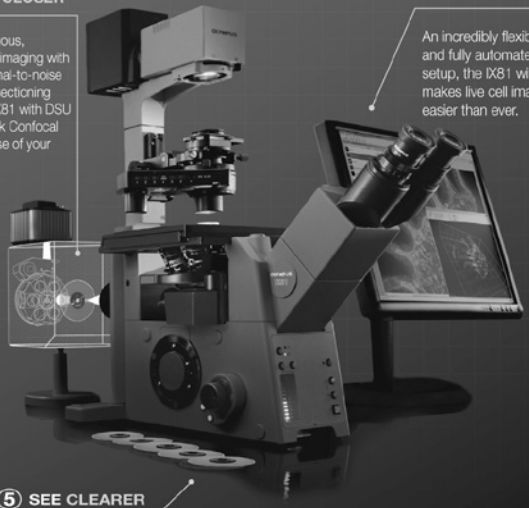

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Session Abstracts

Panel • Sunday 4:30–6:30 PM • Ballroom 1

1. Encoding Value: The Neural Basis of Decision Making

Paul Phillips, Geoffrey Schoenbaum, Joseph Paton, Shunsuke Kobayashi, Read Montague

Throughout everyday life we constantly choose between action sets to optimize outcomes for our current situation. Such decision making requires the assignment of value to each of the possible options so that they can be compared in a common currency. Value could be represented in a purely objective way and account for the measurable features of an outcome (such as its weight or color). It could be represented in a subjective form (utility) which accounts for individual preferences, as well as changed preferences across behavioral states. It could also incorporate the negative utility conferred by response costs that discount outcomes. Furthermore, outcome availability is often intermittent so the (mean) expected value (or utility) should be estimated. Ultimately, each of this metrics may be encoded in the brain and used in decision making. The emerging consensus is that proxies of value are encoded in brain areas that include the prefrontal cortex, basal ganglia and limbic system. This panel will discuss neural representation of value during decision-related tasks. First, Geoff Schoenbaum (University of Maryland) will compare and contrast neural signaling during decision-making in rodent orbitofrontal cortex and ventral tegmental area. Joe Paton (Columbia University) will present data on activity in the amygdala in monkeys during classical conditioning for rewards and punishers. Shunsuke Kobayashi (University of Cambridge) will discuss how neural activity in dopamine neurons is modulated by temporal discounting in non-human primates. Finally, Read Montague (Baylor College of Medicine) will present functional imaging data from human decision making.

Panel • Sunday 4:30–6:30 PM • Magpie

2. Assessing the Genetics of Neurocognitive Dysfunction in Schizophrenia and Bipolar Disorder: Diverse Approaches towards a Common Goal

Richard Keefe, Katherine Burdick, Anil Malhotra, David Goldstein

This panel will discuss recent advancements in methods used to elucidate the genetic bases for cognitive impairment in major psychiatric diseases, including schizophrenia (SZ) and bipolar disorder (BPD). Dr. Richard Keefe (Duke University) will present data highlighting the importance of investigating neurocognitive abnormalities in prodromal subjects (individuals who have subsyndromal symptoms but have not yet had a full psychotic or affective episode), focusing on the sensitivity and specificity of cognitive measures in predicting conversion to SZ or BPD. He will discuss how carefully targeted phenotyping of this population may enhance power in molecular genetic studies of these disorders. Dr. Katherine Burdick (Albert Einstein College of Medicine) will first review convergent evidence supporting the prevalence and persistence of cognitive impairment in BPD patients. She will then present data derived from a large family-based approach, using discordant sibling pairs, to critically evaluate the utility of neurocognition as an endophenotype in BPD. Dr. Anil Malhotra (Albert Einstein College of Medicine) will discuss the use of molecular genetics, including candidate gene approaches and a recent whole-genome association (WGA) study, to detect novel targets for cognitive enhancement in patients with SZ, BPD, and in healthy individuals. Finally, Dr. David Goldstein (Duke University) will outline the challenges inherent in whole genome association studies of neurocognitive function, and provide real-world examples from his own WGA study. He will then describe the relationship between a novel candidate gene and neurocognitive function in a large dataset of patients with schizophrenia, derived from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. The session will leave time for audience-based discussion about the multiple scientific issues raised during this symposium.

Panel • Sunday 4:30–6:30 PM • Maybird

3. Neurobiology of Aging Is Going to the Dogs

Donald Ingram, N. W. Milgram, Carl Cotman, Patrick Sullivan, Elizabeth Head

Over the past decade the number of studies utilizing canine models of brain aging has shown substantial growth. Dogs offer remarkable parallels to human aging in many parameters, including declines in cognition and deposition of amyloid-beta This session will review current research from several laboratories utilizing canine animal models of brain and behavioral aging. D. Ingram will chair and provide insight about the value of the models. N.W. Milgram will describe paradigms used to assess age-related changes in cognition and affect as well as progress for developing successful pharmacologic and dietary interventions. C. Cotman will review age effects on gene expression, neural structure, neurochemistry, and neuropathology in dog brain, with a focus on amyloid-beta deposition. P. Sullivan will focus on the impact of oxidative stress on brain aging in dogs particularly related to mitochondrial function. E. Head will discuss the value of the canine model for developing immunization strategies to treat Alzheimer's disease.

Panel • Sunday 4:30–6:30 PM • Wasatch

4. Circadian Clocks and Non-Image Forming Retinal Physiology: From Mice to Men

Susan Doyle, Michael Iuvone, Samer Hattar, Xudong Qiu, Steven Lockley

In the past decade we have witnessed the discovery of a previously unknown class of inner retinal photoreceptor, intrinsically photosensitive retinal ganglion cells (ipRGCs) that express the novel photopigment melanopsin. Together with retinal rods and cones, ipRGCs provide light information for several non-visual functions, including entrainment of circadian rhythms, pupil constriction, and suppression of pineal melatonin. In addition, the eyes contain a circadian clock that is known to regulate many aspects of intraretinal physiology. This panel will provide an overview of the anatomy, photobiology, and functional attributes of the remarkable non-image forming systems of the eye. Mike Iuvone will introduce circadian clock networks of the retina and discuss the possible roles of dopamine and cAMP in their synchronization. Samer Hattar will present intriguing new findings on the developmental time course of ipRGC specification and targeting to specific brain regions. His work

suggests that the developmental program of ipRGCs is distinct from that of conventional retinal ganglion cells. Xudong Qiu will show data from a combination of physiological, molecular genetic, and biochemical approaches indicating that inner retinal photoreceptors can function independently from the outer retinal retinoid processing machinery. Steve Lockley will discuss the effects of light on circadian entrainment and other non-image forming responses in blind and sighted humans. Collectively, these presentations will highlight the recent advances in our understanding of non-visual ocular physiology.

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

5. The Brain Does Not Live by Glucose Alone: Alternate Fuels for Brain Metabolism

Sami Harik, Joseph LaManna, Gerald Dienel, Pierre-Gilles Henry

Numerous misconceptions cloud our understanding of brain metabolism. The most common is that the brain uses only glucose for metabolic fuel. The panel will discuss recent evidence that the brain utilizes alternate substrates, including ketones and acetate. Harik will open discussion with brief historical overview of the subject and how the notion of glucose exclusivity gained prominence. He will also address ketone body utilization by the brain during starvation and ketogenic diet and when there is decreased BBB glucose transport. LaManna will present data that documents decreased brain glucose metabolism when plasma ketone concentrations are greatly increased and will offer mechanisms by which ketones might affect the TCA cycle and activate brain signaling pathways. Dienel will present evidence showing that lactate shuttling from astrocytes to neurons is not quantitatively appreciable. Instead, he will show that it is most likely that large quantities of lactate are produced during brain activation in amounts corresponding to most of the additional glucose consumed by such activation and that lactate is released from the brain by novel routes. Henry will present his findings using 13C NMR spectroscopy after infusion of 13C-labeled substrates as a unique tool for investigating compartmentalized brain metabolism. Analysis of glutamate and glutamine 13C turnover curves using a 2-compartment neuronal-glial model of brain metabolism allows measurement of metabolic fluxes such as glial and neuronal TCA cycle rates. The presentations will provide multiple lines of evidence that brain metabolism is anything but simple and that the brain is capable of using other fuel sources. Such utilization depends on the state of brain activation under physiological or pathological conditions.

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

6. The Challenge of Modeling and Therapeutic Development for Mild TBI

Edward Hall, David Hovda, Jonathan Lifshitz, Douglas Smith, Barclay Morrison

Approximately 1.5 million people in the U.S. experience a traumatic brain injury (TBI) every year. About 80-90% of those sustain a mild TBI (mTBI). Atlthough usually not life-threatening, mTBI is associated with neurological and psychiatric sequelae that are often devastating to the patient and his/her family. The societal cost of mTBI is huge and more attention has recently become focused on the problem of mTBI as a result of the high incidence of these injuries in service people in Iraq and Afghanistan. The Mild TBI Committee of the American Congress of Rehabilitation Medicine (1993) defines mTBI as a traumatically induced focal neurological deficit that may or may not be transient but does not involve a loss of consciousness of >30 minutes and post traumatic amnesia of no more than 24 hours. In the sports medicine literature, mTBIs are typically referred to as a "concussion" which may often be repetitive. Following a brief introduction of the topic of mTBI by the panel Chair (E Hall, U. Kentucky), D. Hovda (UCLA) will review metabolic and neurochemical data suggesting that mTBI can change the way information is processed and that this alters the ability of the "neurovascular unit" to respond to neuronal activity as well as change the characteristics of receptors resulting in abnormal synaptic responses. J. Lifshitz (U. Kentucky) will discuss his work on mTBI-induced subtle neuropathological and behavioral dysfunction using the rat whisker barrel circuit as a model for mTBI pathophysiology. D. Smith (U. Penn) will present work concerning modeling of single and repetitive mTBI. B. Morrison (Columbia U.) will discuss the biomechanical aspects of mild TBI in animal models and humans and their relationship to mTBI pathophysiology and injury prevention.

Panel • Sunday 8:30–10:00 PM • Ballroom 1

7. Dissecting the Role of Reactive Astrocytes in Neurotrauma, Stroke and Neural Grafting in the CNS

Milos Pekny, Ole Petter Ottersen, Yang Teng

In neurotrauma or brain ischemia, astrocytes become reactive. This phenomenon is known as reactive gliosis and is accompanied by altered expression of many genes. It has previously been shown that reactive gliosis is of major importance in neurotrauma; reactive astrocytes affect the healing process and reconstitute locally damaged blood-brain barrier. Recent data suggest that reactive astrocytes may also present an obstacle to neuroregeneration and effective neural reorganization (neuroplasticity). Interactions between the astrocytic and neuronal networks and between astrocytes and blood vessels are central in many CNS pathologies. Ole Petter Ottersen will present the role of the astrovascular unit in experimental edema and ischemic stroke and will show novel data on the role of aquaporins in neuropathologies. Yang (Ted) Teng will examine potential astrocyte impact on functional repair of the injured spinal cord via influencing neural pathways. Milos Pekny will focus on the role reactive astrocytes play in the ischemic penumbra, and on the possibilities to improve the outcome of neural grafting in the CNS by modulation of reactive gliosis.

Panel • Sunday 8:30–10:00 PM • Magpie

8. Where in the Brain Is Schizophrenia?

Sharon Eastwood, Clare Beasley, Steven Arnold, Dwight Dickinson

Although several brain regions have been implicated in the pathophysiology of schizophrenia, some have gained such prominence in the field that other, perhaps equally important regions, have been until recently largely ignored. The aim of this panel is to demonstrate that many, sometimes unexpected, brain regions are also implicated in schizophrenia. Sharon Eastwood will give an overview of the "favourite" regions of interest in neuropathological studies of schizophrenia, and present molecular data from the cerebellum and primary visual cortex which suggest that similar pathophysiological processes may occur throughout the brain in the disorder. Clare Beasley will present molecular and diffusion tensor imaging data on a relatively unexamined brain region

in schizophrenia, the internal capsule, and demonstrate that poorer cognitive performance is associated with tract changes in first episode schizophrenic subjects. Steven Arnold will present data from clinical and post mortem studies of primary olfactory, auditory and visual processing pathways to support a view of relatively diffuse, elementary neuronal dysfunction in schizophrenia. To conclude, Dwight Dickinson will talk about an often overlooked neuropsychological measure in schizophrenia, the 5 minute digit symbol coding task, and suggest that generalized failures of coordination or effective connectivity among widely distributed brain networks may occur in schizophrenia. Together the data presented will suggest that conceptualising schizophrenia as a whole brain disorder (rather than focussing on specific regions or circuits), may lead to a better understanding of the underlying molecular mechanisms involved.

Panel • Sunday 8:30–10:00 PM • Maybird

9. Sleep and Drug Dependence: Some Stimulating Data

Colleen McClung, Peter Morgan, Una McCann

Emerging data indicate that the effects of drugs of abuse on sleep and circadian rhythms may play a key role in the addiction process and, in some cases, may be a lasting adverse sequela. This panel will focus on recent advances in our understanding of the effects of drug abuse on sleep and circadian rhythms, and the role that these changes may have in the addiction process. Dr. McClung will present data implicating the circadian genes CLOCK and NPAS2 in the regulatation of mesolimbic dopamine neurons known to play a role in drug reward. She will also review findings demonstrating that drugs of abuse, such as cocaine, regulate these genes. Dr. Morgan will present clinical data indicating protracted alterations in sleep following controlled cocaine administration that were found to be directly correlated with diminished vigilance and learning. The role of persistent sleep and cognitive dysfunction in cocaine addiction, and potential therapies for cocaine-related sleep disturbance will be discussed. Dr. McCann will conclude the session by presenting recent sleep data in abstinent users of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'), a drug of abuse that damages brain serotonin neurons. These results raise the question of whether sleep and cognitive changes in abstinent MDMA users are interrelated.

Panel • Sunday 8:30–10:00 PM • Wasatch

10. Of Pain and Chocolate: Exploring the Opioid-Feeding Link across the Neural Axis

Wayne Pratt, Kenny Simansky, Charles Billington, Kyle Smith, Robin Kanarek

The activation of opioid systems in the brain plays an important role in recruiting and maintaining motivated behaviors directed toward food and away from pain. This panel will focus on the interacting relationships between central opioid systems and food-directed behaviors. Dr. Simansky will demonstrate that mu opioid receptor stimulation within the parabrachial nucleus of the pons robustly increases consumption of standard and palatable diets, and activates c-fos expression in regions associated with both reward and energy homeostasis. This suggests a gate-keeping role for pons opioid receptor ligands in modulating visceral and gustatory sensory access to forebrain areas involved in eating and satiation. Dr. Billington will consider the role that opioids, acting in the amygdala, hypothalamus and striatum, play in modulating the action of appetitive stimuli and direct actions on feeding. Of particular focus will be the role of opioids on the consumption of palatable diets across these disparate brain regions. Dr. Smith will discuss opioid hedonic signals in the ventral striatopallidal circuit. He will present research demonstrating how the hedonic impact of a sweet taste can be enhanced by opioid activity in the nucleus accumbens, and how this enhancement is represented in neurobiological and electrophysiological activity profiles downstream in the ventral pallidum. In addition to opioid peptides influencing feeding behavior, food consumption can moderate the behavioral consequences of opioid drugs. To evaluate this bidirectional pathway, Dr. Kanarek will present research investigating the effects of palatable food intake on the behavioral effects of opioids on pain sensitivity and drug tolerance.

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

11. The Emerging Role of HDACs in Neuronal Function and Disease

Michael Ahlijanian, William Renthal, Ghazaleh Sadri-Vakili, Andre Fischer

Histone deactylases (HDACs) are enzymes that remove acetyl moieties from lysine amino acids from histones and other proteins. Histones complex with DNA to form chromatin and the degree of histone aceylation regulates the accessibility of chromatin to RNA polymerases thereby

regulating transcription. Thus, inhibition of HDACs can alter gene transcription and result in changes in a wide variety of physiological processes. This panel will focus on the role of HDACs and the potential of HDAC inhibitors in models of CNS diseases. Michael Ahlijanian (EnVivo, Boston) will present an introduction to the field and report on progress towards CNS penetrant, orally bio-available HDAC inhibitors. William Renthal (UT Southwestern) will discuss the identification of long lasting changes in chromatin structure in animal models of addiction and depression, the upstream chromatin modifying enzymes that mediate these changes, and downstream gene targets that are affected. Jim Wang (High Q Foundation, New York) will describe studies testing available HDAC inhibitors for efficacy in Huntington's disease, in which transcriptional dysregulation is implicated. Andre Fischer (Gottingen) will discuss recent data that support an unexpected role for HDACs during learning and memory including experiments demonstrating that administration of HDAC inhibitors reinstate neuronal plasticity and learning behavior in mice that have already developed Alzheimers's-like pathology including severe synaptic and neuronal loss. These talks will highlight the emerging excitement around the role of HDACs in neuronal function and disease.

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

12. Synaptic Signal Transduction and Striatal Neurodegeneration in Huntington's Disease

Edoardo Marcora, Ilya Bezprozvanny, Lynn Raymond, Veronique André

Huntington's disease (HD) is a neurodegenerative disorder caused by an unstable expansion of CAG repeats in the HD gene, leading to polyglutamine (polyQ) expansion in the huntingtin protein (htt). In HD patients, selective alteration of striatal medium spiny neurons (MSN) might be responsible for some of the motor and psychological symptoms of the disease. Activation of glutamate signaling pathways reproduces MSN degeneration.

This panel will deal with different aspects of the synaptic mechanisms and cascades suspected to be involved in cellular and physiological alterations of MSNs in mouse models of HD. E. Marcora will present live-imaging assays showing how polyQ expansion blocks retrograde transport of transcription factors such as NF-κB from the synapse to the nucleus, and inhibits the induction of neuroprotective genes in cell cultures. I. Bezprozvanny will talk about interactions between mutant htt

and intracellular Ca^{2+} channel (type 1 inositol 1,4,5-trisphosphate receptor ($InsP_3R1$)) and how blocking those interactions can be neuroprotective in primary cell cultures. L. Raymond will present how potentiation of NMDA receptor subunit NR2B surface expression and excitotoxicity by mutant htt may be mediated by interaction with membrane-associated guanylate kinases (MAGUKs) such as PSD-95 or SAP102 in primary striatal cell cultures. Finally, V. André will show the differential regulation of NR2B subunit in the two sub-populations of MSNs (expressing dopamine receptors D1 or D2) at different stages of the disease using electrophysiology in acutely dissociated neurons.

Panel • Monday 7:30–9:30 AM • Ballroom 1

13. Regulation of Excitatory Synapses

Katherine Roche, David Bredt, A. Villu Maricq, Roger Nicoll

The dynamic regulation of glutamate receptors at excitatory synapses underlies changes in excitatory neurotransmission in paradigms of synaptic plasticity and during development. Presentations in this panel will describe recent findings on the regulation of several subtypes of glutamate receptors, discussing the molecular mechanisms regulating receptor function in neurotransmission, synaptic plasticity, and behavior. Katherine Roche will discuss the trafficking and functional regulation of NMDA receptors. She will describe the role of subunit-specific phosphorylation and protein-protein interactions of NR2 subunits in NMDA receptor trafficking and channel function. David Bredt will present research on stargazin and related transmembrane AMPA receptor related proteins (TARPs), which serve as receptor auxiliary subunits. The expanding family of TARPs control diverse components of AMPA receptor function including receptor trafficking, agonist pharmacology and channel gating. Through these regulatory mechanisms TARPs underlie fundamental aspects of synaptic transmission and plasticity. Villu Maricq will describe the regulation of RIA interneurons as part of a neural circuit that controls thermotaxis behavior in C. elegans. These interneurons express GLR-1/GLR-2 AMPA receptors and GLR-3/GLR-6 kainate receptors, and deletion mutations in glr-3 and glr-6 disrupt thermotaxis. The glr-3 and glr-6 promoters drive expression exclusively in RIA allowing for unambiguous identification of the neuron and synapses being studied. This offers great advantages for the study of receptor dynamics and their contribution to behavior. Roger Nicoll will present new findings addressing the role of NMDARs in synapse development. AMPA receptor-mediated synaptic transmission is present when NMDARs are deleted, either embryonically, prior to synapse formation,

or in neonatal neurons. Thus, acquisition of synaptic AMPARs is independent of NMDAR activity. This panel provides information on the latest findings on regulation of excitatory synapses and allows comparison between different subtypes of glutamate receptors and in different organisms.

Panel • Monday 7:30–9:30 AM • Magpie

14. Can't Stop Loving You: Role of Impulsivity in Drug Seeking Behavior

Catharine Winstanley, Jeffrey Dalley, Tommy Pattij, Harriet de Wit

It is increasingly recognized that addicts are more impulsive. However, it is not known to what extent impulsivity predicts the development of addiction, or results from exposure to addictive drugs. Catharine Winstanley will review evidence that a similar neural circuitry is implicated in both addiction and impulse control. Her recent data indicate that rats do become more impulsive, as assessed using the 5-CSRT task, during the initial acquisition of cocaine self-administration (SA), although this effect is transient. She also reports that withdrawal from cocaine SA increases impulsive responding, and this can be exacerbated by enhancing drug-induced changes in gene transcription within the orbitofrontal cortex. Jeffrey Dalley will address the causal influence of dopamine dysfunction in the ventral striatum in impulsivity and stimulant abuse vulnerability using several interrelated techniques, including PET, selective DA depletion and infusions of selective D2 and D3 receptor compounds. He will also discuss evidence for a relationship between impulsivity and compulsive drug seeking. Tommy Pattij will present evidence that sub-dimensions of impulsivity predict vulnerability to distinct stages of nicotine seeking behavior in rats. He proposes that individual differences in impulsive action and impulsive choice may relate to differences in release of dopamine in accumbal and prefrontal brain areas. Current studies on alcohol and food SA will also be presented at the meeting. Harriet de Wit's angle will be from the human perspective. There is growing evidence that 'impulsivity' refers to several independent processes, which are likely to affect behavior in different ways at different stages of drug use. She will review new evidence for separate behavioral mechanisms of impulsive behavior in healthy human volunteers, and discuss how these different mechanisms can influence inappropriate drug-seeking behavior.

Panel • Monday 7:30–9:30 AM • Maybird

15. Sorting Out Morphological and Electrophysiological Differences between Striatal D1 and D2 Receptor-Containing Striatal Neurons: Myths and FACS

Anton Reiner, Carlos Cepeda, Michelle Day, William Yang

Striatal medium-sized spiny neurons (MSSNs), although seemingly homogeneous, differ in terms of expression of dopamine receptors (D1 and D2 subtypes), peptide content, projection patterns and cortical inputs. MSSNs containing D1 receptors mainly project to the substantia nigra (direct pathway) and those containing D2 receptors project to the external globus pallidus (indirect pathway). This segregation has shaped current theories of striatal function in normal and pathological conditions. The recent development of mice engineered to express enhanced green fluorescent protein (EGFP) in D1 and D2 receptor-expressing neurons, has allowed a better characterization of MSSNs at the origin of the direct and indirect pathways. Anton Reiner will discuss findings in rats and monkeys showing that the two main types of layer V pyramidal neurons preferentially target different striatal projection neurons. Electron microscopy studies demonstrate that synaptic connections to direct and indirect pathway MSSNs are different. Carlos Cepeda will follow up this idea providing electrophysiological evidence that membrane properties and synaptic inputs also are different in D1 and D2 EGFP-positive neurons. Michelle Day will present combined electrophysiological and 2-photon imaging data showing that the distal dendrites of D1 and D2 MSSNs respond differently to both DA and acetylcholine receptor activation. Finally, William Yang will discuss recent studies using fluorescent-activated cell sorting (FACS) and gene arrays demonstrating the effects of deletion of genes selectively expressed in D1 or D2 MSSNs.

Panel • Monday 7:30–9:30 AM • Wasatch

16. Will Genome-Wide Association Studies Rewrite the Genetics of Bipolar Disorder and Schizoprhenia?

William Bunney, Francis McMahon, Anil Malhotra, Steven Potkin, David Goldstein

Genome-wide association (GWA) studies to rapidly identify novel susceptibility genes have recently become possible due to advances

in gene chip technology. Reliable and cost effective genotyping with 1 million SNPs is now routine. The panel will discuss recent experiences with GWA studies in schizophrenia and bipolar disorder, highlighting their strengths and the challenges. McMahon will describe a GWA study of bipolar disorder genotyping 550,000 markers in pooled DNA from 2 independent samples comprising 1200 cases and controls. The results implicated 88 SNPs in 80 genes, about half were confirmed by individual genotyping. He will contrast the results when clinical variables such as age of onset and the presence of psychosis are included. Malhotra will present a GWA study in a case control schizophrenia sample using 500,000 SNPs that implicated CSF2RA and IL3RA as novel candidate genes for schizophrenia. These candidates were sequenced in a new sample and revealed several missense variants. Exploiting the improved power that may characterize studies of quantitative traits (QT), Potkin used activation in the dorsolateral prefrontal cortex as a quantitative trait. He examined which of 109,000 SNPs influenced the QT as a gene discovery approach in schizophrenia. SNPs associated with two novel genes, surviving a permutation test for multiple comparisons, were identified and were verified in an independent sample. Adjustment for multiple comparisons with literally millions of statistical tests presents unique challenges and the need for improved methods of replication and biological validation. Goldstein will review these issues and propose new statistical methods and analytic approaches to address this wealth of genetic information and their application in two independent GWA studies in schizophrenia.

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

17. Neuroprotective Therapies for Parkinson's Disease: How Much Help Can We Get from Animal Models?

Yoland Smith, Erwan Bezard, Joel Perlmutter, Warren Olanow

An important challenge for the development of novel therapeutics in neurodegenerative diseases is to develop drugs that have symptomatic effects and slow down the disease progression. Despite the advances that have been made in Parkinson's disease (PD) pharmacotherapy during the last twenty years, none of the antiparkinsonian drugs currently used in humans have significant "neuroprotective" effects on the degeneration of midbrain dopaminergic neurons. Although promising evidence for neuroprotection resulted from pre-clinical studies in animal models of parkinsonism, these compounds had limited success

when tested in patients. These observations and others gathered from animal models highlight the complexity of PD pathology and led us to examine the advantages and limitations of the "gold standard" non-human MPTP-treated primate model of parkinsonism to develop and test neuroprotective therapies for PD. In a first talk, Yoland Smith will provide some historical perspectives about MPTP, highlight some of its current use and discuss the relevance of the MPTP-treated non-human primate model of parkinsonism for the study of PD. This will be followed by Erwan Bezard who will describe experimental results that used the MPTP-treated non-human primate to test neuroprotective therapies for PD. In a third presentation, Joel Perlmutter will discuss the limitations and advantages of PET imaging to assess neuroprotection of the dopaminergic system in human parkinsonians. Finally, Warren Olanow will conclude with a discussion of the etiology and progressive characteristics of PD that likely contribute to the problems in translating pre-clinical data from animal models to effective human neuroprotective therapies for Parkinson's disease.

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

18. Synaptic Mechanisms in the Outer Retina

Ron Gregg, Teresa Nicolson, Stephen Massey, Catherine Morgans

The first stage of image processing in the visual system occurs within the outer plexiform layer of the retina. Here photoreceptors form specialized ribbon synapses with bipolar cells, which transmit the visual signals to the inner retina, and with horizontal cells, which provide lateral inhibition in the outer retina. The unique structure and proteins of the ribbon synapse allow the photoreceptor to precisely modulate the release of the neurotransmitter, glutamate, in response to graded changes in light intensity. A complex interplay of pre- and post-synaptic mechanisms allow the output of the synapse to be adjusted depending on the light conditions. This panel will discuss new findings on the functional organization of the outer retinal circuitry.

Ron Gregg will discuss the role of functional domains of nyctalopin, a protein required for glutamate mediated signaling through ON-bipolar cells. He will also present data on the mechanism by which the absence of nyctalopin disrupts retinal ganglion cell function. Teresa Nicolson will contrast hair cell and photoreceptor ribbon synapses with respect to genetic mutations that affect ribbon synapse function in zebrafish. Steve Massey will discuss Cx36 gap junctional coupling between cone telodendria in the primate retina. He will also describe gap junctions

between rod and cone photoreceptors and their role in mediating visual responses at intermediate light intensities. Lastly, Catherine Morgans will present new findings on the role of Gbeta5-RGS complexes in the mGluR6 signal transduction pathway of ON-bipolar cells.

Panel • Monday 4:30–6:30 PM • Ballroom 1

19. The Adolescent Reward System: Too Much of a Good Thing?

Susan Andersen, Patricio O'Donnell, Adriana Galvan, Monique Ernst

Adolescence is a time of tumultuous changes in body, brain, and behavior. The adolescent brain undergoes numerous changes that include remodeling of synapses and signaling pathways, quite dramatically in the neural systems involved in reward and motivation. As adolescents exhibit a propensity for risk-taking, novelty/reward-seeking and impulsive behavior, this stage in life becomes a critical developmental window during which psychopathological conditions can emerge. There has been a recent surge in interest in studying brain changes that may be responsible for behavioral maturation (or propensity for psychopathology) during adolescence. This panel will cover recent developments in this field, combining human imaging studies with mechanistic studies in rodents. Dr. Andersen will present data on over-expression of D1 dopamine receptors in the striatum and prefrontal cortex during adolescence. Prefrontal projections to the nucleus accumbens core are particularly involved, and the changes are related to behavioral responses to environmental cues. Dr. O'Donnell will present electrophysiological data on the maturation of dopamine-glutamate and dopamine-GABA interactions in the prefrontal cortex of rats during adolescence and their abnormal maturation in developmental models of schizophrenia. Dr Galvan will present data on how circuitry involved in reward processing is related to risk-taking behavior in the real world and will also summarize recent work on reward processing in youth with psychopathology (e.g. Tourettes syndrome) and drug addiction (e.g. methamphetamine addicts). Dr. Ernst will present data on reward processes, their changes during adolescence and their role in the predisposition for psychopathology. Overall, the presentations can provide a theoretical framework that allows testable hypotheses and perhaps provide critical anchors for the development of policies and preventive interventions that both protect youth from risky behaviors and decrease incidence of pathologies related to alterations in the neural substrates of motivation.

Panel • Monday 4:30–6:30 PM • Magpie

20. To Be or Not To Be: Hanging in the Balance

Joseph LaManna, Paula Dore-Duffy, Gregory del Zoppo, Denson Fujikawa, Dale Pelligrino

Under conditions of environmental stress such as that produced by injury, infection, inflammation, or a stress signal such as hypoxia, the CNS microvasculature undergoes a number of adaptive processes that maintain energy requirements, promote cell survival, repair and maintenance of homeostasis and hemostasis. Nowhere is this more crucial than in the brain where there is a delicate balance within the microenvironment that involves highly regulated cross talk between cells of the neurovascular unit and parenchymal cells. Perturbation of that balance such as seen following cerebral ischemia can lead to a destructive sequence of events where normal adaptive mechanisms are either dysregulated, ineffective or even deleterious to tissue survival. A better understanding of normal physiological adaptation to stress is needed to completely interpret maladaptive mechanisms. Is programmed cell death a normal aspect of vascular adaptation gone terribly wrong? Are inflammatory mediators and regulatory cytokines protective or do they contribute to neuropathology? An overview of physiological adaptation to stress will be discussed by Joseph C. LaManna. He will focus on hypobaric hypoxia-induced changes in angiodynamics. The role of TNF family members TWEAK and APRIL in regulation of angiogenesis will be discussed by Paula Dore-Duffy. She will consider both pathological and physiological responses. Changes in extracellular matrix proteins leading to altered hemodynamics will be discussed by Gregory del Zoppo. Programmed cell death in ischemic neuronal cell death will be discussed by Denson Fujikawa. The role of vascular proinflammatory factors—saviors or cursed proteins—will be summarized by Dale Pelligrino.

Panel • Monday 4:30–6:30 PM • Maybird

21. Using Biomarkers To Guide Drug Activity in Psychiatric Indications

Menelas Pangalos, Anne Olincy, Mitchel King, Eve Johnstone, Mark Day

50–70 % of all CNS clinical trials fail in clinical development due to lack of efficacy in patients. As such, there is a clear need for improved pre-clinical and clinical biomarkers in early clinical development to gauge whether drugs are likely to be efficacious in humans. Successful identification and employment of such biomarkers will depend on

successful partnerships between pre-clinical and clinical scientists and between academia, industry and regulators. Several novel approaches are yielding early efficacy biomarkers for use in schizophrenia employing intermediate phenotypes, CSF sampling, neuroimaging technologies, genetic association studies and surrogate populations. This session will bring together four leading figures that are currently pioneering the way we look for early efficacy in the clinic. Within the symposium we will explore the use of intermediate phenotypes to reveal positive and cognitive symptom attenuation in schizophrenia. Professor Johnstone will focus on the genetic basis of schizophrenia and how brain imaging can aid in the identification of people at risk of developing schizophrenia. She will share her recent results that shed light on different fMRI profiles associated with risk alleles in schizophrenia and bipolar disorder. Professor Ann Olincy will review the relationship between P50 auditory evoked responses and the effects of alpha 7 nicotinic receptor partial agonists on the symptoms associated with schizophrenia. Dr. Mark Day will discuss how preclinical efficacy studies may be used to identify novel markers of efficacy in humans and help to drive dose selection, translating results from animal models of attention, spatial memory and impulsivity into early human psychiatric clinical testing. Dr Mitchel Kling will present on "Developing Biomarkers to aid drug development in mood and anxiety disorders."

Panel • Monday 4:30–6:30 PM • Wasatch

22. New Insights into Glial-Neuronal Interactions

Ken McCarthy, Stephen Traynelis, Michael Robinson, Aude Panatier

Glial cells have been known to influence neuronal function for decades. In recent years, new data supports detailed molecular hypotheses for glial modulation of neuronal function, which shows a surprisingly number of important roles. This panel presentation will summarize the latest findings involving glial neuronal cross-talk. Dr. Ken McCarthy will initially provide a brief historical overview of the idea that glial cells can influence neuronal signaling through activation of G-protein coupled receptors. He will outline key questions in the field, and provide an overview of his recent data showing how he has addressed these problems. Dr. Stephen Traynelis will discuss the various ways astrocytes might control glutamate concentration and time course in the synaptic cleft, and present data showing regulation of these parameters by astrocytic G-protein coupled receptors. Dr. Mike Robinson will subsequently

describe translational regulation of the astrocytic glutamate transporter GLT1, which ultimately sets the spatial and temporal profile of glutamate in the synaptic cleft. Dr. Aude Panatier will discuss evidence that indicate that glial cells are active partners modulating neuronal activity and synaptic strength. He will present evidence that glial cells are necessary for the establishment of synaptic plasticity. Each of these four presentations touches on the regulation of synaptic function by astrocytes, and should provide a cohesive overview of this important area.

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

23. Voxel-Based Meta-Analysis: Neural System Models Emerge from Data Mining

Peter Fox, Angela Laird, Tomas Paus, Simon Eickoff, Jane Neumann

The human neuroimaging literature contains tens of thousands of studies which report task-related (functional) and disease-related (functional and structural) regional effects in standardized coordinates. Over the past 5 years, there has been an explosion of methods which mine this enormously rich, well-standardized literature to create meta-analytic models of functional and structural human neural systems. The most widely used mathematical model for meta-analysis is the Activation Likelihood Estimation (ALE) method of Turkeltaub (2002). ALE models activation/structural foci as spatial probability distributions to generate quantitative meta-analyses. The ALE algorithm was extended by Laird to add permutation testing and between-study contrasts (Laird et al., 2005). The ALE algorithm was extended by Eickhoff to add between-experiment clustering and tissue-class specification (Eickoff et al., in review). The ALE method has enabled network modeling constructs, including replicator dynamics network analysis (RDNA; Neumann, 2005) a task-specific (e.g., Stroop task) modeling method. Paus and Toro extended ALE to extract between-task systems, including the "resting-state network" (Toro et al, in review). This minicourse is introduced and motivated by Peter Fox. The ALE method(s), original and improved, are presented by Simon Eickoff. Extension of ALE to voxel-based morphometric (VBM) structural studies is presented by Angela Laird, including examples in Schizophrenia and Depression. Within-task network modeling (e.g., a consensus model of nodal interaction in the Stroop Task) and the use of ALE-derived models to seed Structural Equation Models (SEM) is presented by Jane Neumann. Between-task network modeling, to extract task-independent, quasi-anatomical networks is presented by Tomas Paus. Several presentors receive support from RO1MH074457 (P. Fox, PI).

Minicourse • Monday 4:30–6:30 PM • Superior B

24. Homeostasis in the Visual System

Arianna Maffei, Michael Crair, Hey-Kyoung Lee, Ronald Meyer

Although homeostasis in most physiological systems has been known for a long time, the focused investigation of homeostasis in the nervous system is relatively recent. Work in this emerging field has progressed in diverse systems and preparations. Salient differences in the regulation and type of compensatory mechanisms have arisen between studies. These differences might reflect the different systems which would have different functions and physiological states and consequently different characteristics and performance demands of the underlying circuitry. It may be informative to focus on one system to see what is common and different between diverse studies on the same system.

The visual system is one of the most intensely studied CNS systems. Neuronal function is well characterized and can be accurately monitored. Importantly, it also lends itself to experimental manipulations of the intact system and thus can provide insight into the in vivo situation.

This session will focus on homeostatic responses of the developing and mature vertebrate visual system. Arianna Maffei will describe homeostatic changes in network excitability that occurs in the visual cortex following altered visual input during the critical period of development. Michael Crair will show that during the development of the retinocollicular system homeostatic mechanisms underly the development of receptive field properties. Hey-Kyoung Lee will discuss experience dependent plasticity in the cortex showing that these involve homeostatic regulation of AMPA receptors and persist in the adult. Ronald Meyer will describe rapid homeostatic compensation in the retinotectal system of adult goldfish that is reversible and shows dynamic scaling.

Panel • Monday 8:30–10:00 PM • Ballroom 1

25. Exactly How Does "Ecstasy" Produce Long-Term Effects?

George Ricaurte, Glen Hanson, Terry Monks, Bryan Yamamoto

Methylenedioxymethamphetamine (MDMA, 'ecstasy') and related amphetamine-type stimulants are widely abused and some of these drugs are also used therapeutically (e.g., amphetamine for the treatment of ADHD). Over the last two decades a large body of data has accrued indicating that some amphetamine-type stimulants [e.g., methamphetamine (METH)] have the potential to selectively damage brain dopamine

and/or serotonin neurons. Mechanisms implicated in amphetamine neurotoxicity may bear directly on processes involved in neural degeneration in Parkinson's disease and other neurodegenerative disorders that involve dopamine and/or serotonin neurons. This panel will focus on recent advances in our understanding of mechanisms of MDMA neurotoxicity and the relevance of these data to human disease states. Ricaurte will set the stage by outlining the major hypotheses to be discussed and neurodegenerative conditions to be considered. Hanson will present data implicating brain dopamine in METH and MDMA neurotoxicity, and discuss the possible role of dopamine in the pathogenesis of Parkinson's disease. Monks will present findings suggesting that toxic drug metabolites are involved in the long-term effects of MDMA. He will also discuss how formation of such reactive metabolites may be relevant to the development of neurodegenerative disorders. Yamamoto will conclude by presenting data implicating glutamate and a novel role of tyrosine in substituted amphetamine neurotoxicity. He will discuss how neurodegeneration may be a complex, multifaceted process, both in animal models and in disease states. Each panelist will highlight areas where there is consensus and identify gaps where more research is needed.

Panel • Monday 8:30–10:00 PM • Magpie

26. Imaging of Pain

Richard Gracely, Bruce Naliboff, Pamela Paulson, Thomas Morrow

Functional imaging of pain-related brain activity provides a powerful method for investigating the complex neural mechanisms that support the pain experience. This panel will discuss recent applications of these technologies in man and animals to explore the underlying mechanisms of chronic pain syndromes. The advantages and limitations of various imaging techniques will be stressed. Gracely will describe a series of functional magnetic resonance imaging (fMRI) studies of pressure pain sensitivity in fibromyalgia patients and healthy controls, providing evidence for pain augmentation, descending inhibitory modulation, stimulus encoding, and evidence of individual differences suggesting modulation of pain processing by cognition and mood. Naliboff will present recent data using fMRI and positron emission tomography (PET) showing altered cortico-limbic pontine interactions in patients with Irritable Bowel Syndrome to both noxious visceral stimulation and anticipation of visceral pain. Data will highlight the role of the amygdala in visceral hypersensitivity and its role in preparation for a painful stimulus. Paulson will first describe animal experiments using high-resolution autoradiographic regional cerebral blood flow (rCBF) imaging of

muscular and visceral pain and relate these results to imaging studies of chronic pain in humans. Secondly, she will present data highlighting the effects of restraint and anesthetics on pain processing in animal imaging studies. The speakers will conclude with a discussion of the potential convergence of animal and human pain neuroimaging and the critical issues in future imaging studies of pain and pain control.

Panel • Monday 8:30–10:00 PM • Maybird

27. Novel Views of Myelin

George Bartzokis, Michael Georgieff, James Connor

This panel will cover novel investigations into myelin relationships with aging, development and interactions with the immune system. George Bartzokis M.D. will present data showing how imaging data support the hypothesis that premature myelin breakdown and subsequent homeostatic remyelination attempts may contribute to pathogenesis in several neurodegenerative diseases. A unique combination of in vivo tissue integrity and iron level assessments can examine such hypotheses; including the influence of gender and genetic risk factors affecting iron metabolism. Tracking the effects of novel interventions that reduce myelin breakdown and iron accumulation in preclinical stages of disease could hasten the development of preventive treatments. Michael Georgieff M.D. will show how early postnatal iron deficiency that occurs commonly in humans alters behaviors and alters metabolites in the striatum indexing energy metabolism, neurotransmission, glial integrity, and myelination, Correction of anemia normalizes the striatal metabolome but not the behaviors. These novel data imply that alterations in the metabolite profile of the striatum likely influence later neural functioning associated with hypomyelination in early iron deficiency. James Connor, Ph.D. will reveal a novel receptor for ferritin that has been identified on oligodendrocytes. This receptor is Tim 2(T cell immunoglobulin and mucin domain 2). Tim-2 is expressed on CD4+ T lymphocytes and was originally described as a receptor for Sema4a. Sema4a is expressed on antigen presenting cells, including activated macrophages. The shared expression of Tim-2 between the oligodendrocytes and the immune system offers a new possibility for cross-signaling during inflammatory interactions that could lead to demyelination.

Panel • Monday 8:30–10:00 PM • Wasatch

28. Using Transport To Map the Brain: Live Imaging of Neuronal Connections with MRI

Elaine Bearer, Russell Jacobs, Arthur Toga

A major challenge in understanding how the brain processes information is defining the circuitry that links neurons into a functional distributed parallel processing network. Intracellular transport provides a biological process that allows the anatomy of circuitry to be defined. Axonal transport in neurons occurs in two directions: towards the synapse or away from it. Transport has recently been implicated in many neurological diseases, including neurodegeneration of Alzheimers, Huntingtons and Parkinsons disease and in Downs syndrome and in the optic tract in normal-pressure glaucoma. Recent ground-breaking work has demonstrated that Mn2+, an MRI contrast agent, is picked up and transported within neurons. Thus for the first time dynamics of transport (rates, directionality, trans-synaptic transmission) and changes in circuitry over an animals lifetime can now be studied with MEMRI. Here three laboratories with complimentary expertise in molecular microscopy and neuropathology (Brown University), in μMRI imaging (Caltech), and in computational analysis (Center for Computational Biology (CCB) at UCLA, one of the centers of the National Centers for Biological Computing) will present recent work developing and exploiting magnetic resonance microscopy (MRI), the biology of the axonal transport system, and computational analysis towards the problem of mapping cerebral circuitry in living brains.

Panel • Monday 8:30–10:00 PM • Superior A

29. Novel Functions of Intracellular Loops in Ligand-Gated Channels

Tim Hales, David Weiss, Sheryl Smith

Cys-loop receptors constitute a family of ligand-gated channels with 4 transmembrane-spanning domains and 2 intracellular loops. Although the extracellular domains and pore region have been well-characterized, less is known about the function of the intracellular loops. The 4-Å resolution structural model of the *Torpedo Marmorata* nicotinic acetylcholine (nACh) receptor reveals that residues within the TM3-4 loop frame five cytoplasmic portals that appear to be part of the conduction pathway. Tim Hales will discuss homologous models of 5-HT^3 and nACh receptors used to identify residues that lie at the mouths of their portals.

His functional studies demonstrate that the residues influence single channel conductance, rectification and ionic selectivity of the 5-HT^3 receptor, properties previously thought to be dictated by amino acids located in the TM2 domain. Then, David Weiss will provide evidence from mutagenesis and cysteine scanning studies that the intracellular loop between TM1 and TM2 is along the ion permeation pathway. Finally, Sheryl Smith will discuss recent findings in the novel $\alpha4\beta2\delta$ GABA-A receptor. The TM3-4 loop of $\alpha4$, which has less than 10% homology with other α subunits, contains a basic residue which controls neurosteroid effects on GABA-gated current, an effect dependent upon the direction of Cl- flux. When mutated to a neutral amino acid, this effect is prevented, suggesting that it is part of an ion-permeation pathway. Taken together, these novel findings suggest that the intracellular loop of cys-loop receptors plays a pivotal role in regulating channel properties and the response to modulators.

Workshop • Monday 8:30–10:00 PM • Superior B

30. All for One and One for All: Emerging Ideas of Population Coding in the Brain

Vivien Casagrande, Kristina Nielsen, Walter Jermakowicz, Andrew Schwartz

Is firing rate really a sufficient neural code? Many have argued that a frequency code is insufficient by itself as a neural code. If it is insufficient then exactly how do neurons cooperate to represent information? This workshop will give some examples from current work to set the stage for an open debate about this issue. Implications for the development of neural prosthetics will also be discussed. Casagrande will provide a brief introduction and will moderate the session. Nielsen will discuss what a comparison of the local field potentials to single neuron activity reveals about the encoding of complex visual features in the inferotemporal cortex. Jermakowicz will address how firing rate and local network synchrony compare in encoding simple features at early levels of the visual system and will examine how well such codes can propagate information to higher levels of the visual system. Finally, Schwartz will consider the role of advances in theories of population coding in the development of robotic neuron-prosthetic devices. We hope that each of the examples presented will engender a lively discussion. Support contributed by EY01778 (VAC).

Panel • Tuesday 7:30–9:30 AM • Ballroom 1

31. The Role of the Medial Prefrontal Cortex in Fear and Drug Memories

Jacqueline F. McGinty, Suzanne Haber, Ronald See, Jamie Peters, Douglas Bremner

The purpose of this panel is to explore comparative similarities and differences in the function of prefrontal cortex in the recall and extinction of anxiety/fear and reward-related memories in rodents and primates. The differential connections of adjacent prefrontal cortical regions, implicated in fear/anxiety and substance abuse, in rodents and primates predict specific excitatory/ inhibitory (GO/STOP) neurocognitive networks that will be described. Dr. Suzanne Haber will present recent 3-D reconstructions of the ventral medial prefrontal (vmPFC), orbital prefrontal (OFC) and dorsal medial prefrontal cortical (dmPFC) neural networks that allow a comparison between these networks in the striatum, thalamus, and amygdala. Dr. Ronald See will present data demonstrating that the role of medial PFC subregions differs in cue-induced reinstatement of cocaine vs. heroin-seeking and after forced abstinence or daily extinction in rats. Dr. Jamie Peters will present studies that highlight dorsal/ventral differences in mPFC for the expression of drug-seeking memories in rats. Dr. Douglas Bremner will present functional imaging data demonstrating a decrease in mPFC activity in veterans with PTSD vs. veterans without PTSD after exposure to traumatic combat-related slides. Animal studies support human neuroimaging studies that demonstrate changes in the activation of the medial PFC in fear and reward-related memories and memory extinction. Discovery of opposite functions mediated by the dorsomedial and ventromedial prefrontal cortex reinforces the concept that distinct GO/STOP neurocognitive networks modulate emotional memory recall. Understanding the homologous role of prefrontal networks in both addiction and fear disorders could lead to generalized treatments aimed at strengthening prefrontal inhibition.

Panel • Tuesday 7:30–9:30 AM • Magpie

32. No Gene Is an Island: COMT and Its Interactions Contribute to Complex Brain Phenotypes

Paul Harrison, Daniel Weinberger, Yoshi Sei, Elizabeth Tunbridge, Joshua Roffman

Complex brain phenotypes, including neuropsychiatric disorders, are likely modulated by interactions between multiple genes. It has been a hard task to identify individual genes involved; identification of the interactions is an even more daunting yet critical one. Nevertheless, progress is being made. This panel will review the approaches and the advances, using catechol-o-methyltransferase (COMT), an enzyme that degrades dopamine and is strongly linked with prefrontal function and diverse psychiatric phenotypes, as the exemplar. Daniel Weinberger will discuss gene-gene interactions at the genetic level, focussing on evidence that COMT interacts with other genes (e.g. Dysbindin, Akt1) to increase risk for schizophrenia. Yoshi Sei will discuss biological interactions between COMT and neuregulin 1, another schizophrenia risk gene. He will demonstrate effects of the COMT Val/Met polymorphism, which affects enzyme activity, on neuregulin1/erbB receptor-induced cell adhesion and migration, and will discuss the possible mechanisms underlying defects in adhesion/migration in schizophrenia. Liz Tunbridge will focus on new evidence showing that COMT interacts with methylenetetrahydrofolate reductase (MTHFR) to modulate homocysteine levels, indicating that COMT may contribute to the various adverse neurologic and psychiatric effects (including depression and neurotoxicity) that are associated with elevated homocysteine. Joshua Roffman will show how gene-gene interactions may impact on cognition, demonstrating an interaction between COMT and MTHFR on executive function in schizophrenia. These talks will highlight how COMT interacts with other genes at the genetic, biological and systems levels to modify multiple brain phenotypes, and will illustrate more broadly how epistatic interactions of different kinds are of increasing importance to neuroscience.

Panel • Tuesday 7:30–9:30 AM • Maybird

33. Neuroinflammation: Is There an Alternative?

Carol Colton, Fredrik Kamme, David Wink, Michael Vitek

Inflammation in the brain has been traditionally viewed as a "death sentence "caused by the release of multiple cytotoxic cytokines and redox-active agents from microglia or astrocytes during an acute and/or chronic innate immune response. But, recent data suggest an alternative activation state that orchestrates "repair" can be induced in microglia. Consequently, a re-interpretation of the meaning of microglial "activation" is required. Carol Colton will define alternative activation in microglia and provide ways to identify an alternatively activated state in vitro and in vivo. Mouse models of Alzheimer's disease will be used to show how classical activation can be shifted to alternative activation and vice versa and the role Abeta fibrosis plays in this process. Fredrik Kamme will further define "neuro-beneficial" genes expressed by alternatively activated microglia using expression profiling following transient forebrain ischemia in rat. Accelerating the acquisition of the alternative activation state using pharmacological means reduces neuron death after ischemia and provides evidence that alternative activation can be protective. David Wink will talk about the role of alternative activation genes such as thrombospondin, MMP, and VEGF in angiogenesis after injury and in wound healing and how nitric oxide contributes to this process. Finally, Mike Vitek will discuss the role of apolipoprotein E as an "endogenous" switch that triggers the conversion of classically activated microglia to alternatively activated microglia and the induction of repair after injury and infection.

Panel • Tuesday 7:30–9:30 AM • Wasatch

34. Connexins in Physiology and Pathology of CNS

David Spray, Vladimir Parpura, Christian Giaume, Christian Naus

Gap junction channels (GJC) are formed by coupling of the two connexons provided by apposed cell membranes. The proteins, connexins and perhaps pannexins, forming GPCs are linked into macromolecular signaling complexes (the Nexus) and the expression of connexin genes is linked to that of genes with a wide variety of other functions. This symposium will provide an excellent opportunity to learn more about the new roles of connexins in physiology and pathophysiology of CNS.

Spray will focus on connexin protein and gene linkages and implications for changes in intercellular communication in CNS (dys)function. Next, Parpura will present the evidence that astrocytes under physiological conditions can exocytotically release glutamate; the location of astrocytic exocytoyic sites is regulated by connexin 43. Giaume will discuss astrocytic connexins as a target for neuron-glial interactions, where, among many other ligands, glutamate can regulate the permeability of astrocytic GJCs. Finally, Naus will discuss the role of connexins in neuroprotection during ischemic and metabolic insults; also, connexin/pannexin-mediated growth control in gliomas will be presented.

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

35. Seizures from Broken Channels: Regulation and Therapeutics of Acquired Channelopathies in Epilepsy

Anne Anderson, Nicholas Poolos, Shelley Russek, Amy Brooks-Kayal

Ion channel dysfunction in inherited human epilepsy syndromes is now well-established, with the discovery of disease-causing gene mutations that produce either loss of function or altered biophysical properties of ion channel subunits. However, epilepsy often results from insults to the CNS such as head trauma or early life prolonged seizures (status epilepticus, SE). An emerging hypothesis is that such acquired epilepsy also results from ion channel dysfunction or "acquired channelopathy". This panel will present accumulating evidence that alterations to a variety of voltage- and ligand-gated ion channels, including potassium (Kv) and hyperpolarization-activated cation (HCN) channels, and type A GABA receptors (GABAARs), occur in animal models of acquired epilepsy. Uncovering the role that intracellular signalling processes play in acquired channelopathy may provide clues for the eventual treatment of this often medically-intractable problem. Anne Anderson will present recent data showing altered post-translational regulation and trafficking of Kv4.2 channels in hippocampal synaptic regions following SE, and their contributions to increased postsynaptic excitability. Nicholas Poolos will discuss the progressive downregulation of HCN channels in hippocampal pyramidal neuron dendrites during epileptogenesis and how this reflects multiple changes in HCN channel biophysical properties. Shelley Russek will describe the molecular pathways that regulate the transcription of alpha 1 and alpha 4 GABAAR subunit genes

in developing neurons and after SE in adult animals. Amy Brooks-Kayal will review evidence that subunit changes are functionally important and discuss potential therapeutic interventions, including gene therapy, to block altered subunit composition of GABAARs and reverse neuronal hyperexcitability.

Panel • Tuesday 7:30–9:30 AM • Superior B

36. Sex Hormones—and Why the Lack of Them Makes You Fat

Thomas Lutz, Debbie Clegg, Richard Simerly, Stephen Benoit

An important biological action of estradiol is its effect on eating. Here, we will elaborate on recent findings regarding the role of estradiol in the brain linked to the control of energy balance. Dr. Lutz will present data on hindbrain estradiol signaling. Low dose estradiol in the hindbrain is sufficient to reduce food intake in ovariectomized rats. This effect seems to be associated with an interaction with the satiating peptide cholecystokinin (CCK). Dr. Clegg will focus on hypothalamic estradiol signaling through nuclear and membrane receptors, demonstrating that estradiol signaling through specific hypothalamic nuclei is critical for body weight, food intake, and energy homeostasis. Additional data suggest that rapid signaling effects initiated by estradiol are critical for mediating the feeding effects of CCK. Dr. Simerly will provide examples of how leptin and estrogen receptors direct molecular mechanisms that influence the developmental neurobiology of the hypothalamus. Leptin and sex steroids act on discrete subsets of forebrain neurons and regulate the development and activity of hormone-sensitive neural pathways. In rodents postnatal surges in secretion of sex steroids and leptin appear to function as developmental signals directing development of sexually dimorphic circuits and feeding pathways. In the last presentation, Dr. Benoit will discuss findings regarding the mediation of estrogenic action on energy balance by extra-cellular matrix proteins and the matrix metalloprotease (MMP) family of enzymes that regulate the cellular location of these proteins. MMP-3 seems to mediate the effects of peripheral and central estradiol to influence food intake, energy balance and body fat distribution.

Panel • Tuesday 4:30–6:30 PM • Ballroom 1

37. To Move, or Not, to the Rhythm: Physiological and Pathological Oscillations in Cortico-Basal Ganglia Networks

Peter Magill, Andrew Sharott, Rui Costa, Nicolas Mallet, Thomas Boraud

Oscillations might be important for optimal somatosensory/motor information processing in cortico-basal ganglia networks. However, synchronized oscillations at certain frequencies could be disadvantageous or even pathological. This panel will discuss new insights gained at the cutting edge of this research field. Sharott will describe how the coordinated activity of putative GABAergic interneurons could support the emergence of synchronized gamma oscillations (40-80 Hz) in the striatum of intact animals, and will discuss findings in light of the coherent expression of these network oscillations in striatum and cortex. Charpier will present data from a rat model of absence epilepsy showing how and where thalamocortical paroxysmal oscillations (7-10 Hz) propagate within basal ganglia, and will provide evidence that basal ganglia outputs constitute a control point for absence seizures. Mallet will demonstrate that dopamine loss in a rat model of Parkinson's disease (PD) potentiates synchronous beta oscillations (15-30 Hz) in cortical-basal ganglia circuits, with a focus on the expression of these abnormal rhythms in the globus pallidus and subthalamic nucleus (STN). Finally, Boraud will present recent investigations of a causal link between exaggerated beta oscillations in STN and the manifestation of parkinsonian dysfunction. Neuronal activity recorded in STN of parkinsonian monkeys was used as a stimulus for injection into STN of normal monkeys. The behavioral effects of these injected activities, specifically concerning the cardinal motor symptoms of PD, will be discussed. By examining neural substrates/mechanisms and behavioral contexts, we will highlight the potential functional significance of both physiological and pathological oscillations in cortico-basal ganglia networks.

Panel • Tuesday 4:30–6:30 PM • Magpie

38. Diverse Mechanisms Underlying Brain Reward

Sarah Leibowitz, Friedbert Weiss, Rainer Spanagel, Charles O'Brien

Diverse neurochemical mechanisms are now known to be involved in mediating reward pathways in brain. This panel will review recent evidence supporting a role for different neuropeptides and glutamate. Leibowitz will provide evidence for positive feedback loops or "vicious cycles" involving orexigenic peptides, in hypothalamus and accumbens, which promote overconsumption of fat, sugar and alcohol. Findings support the existence of systems (e.g., galanin, orexin, enkephalin) affected by fat, alcohol and circulating lipids and others (neuropeptide Y, agouti-related protein) responsive to sugar and circulating glucose. Weiss will describe results showing that stimuli previously associated with drug reward, but not cues conditioned to palatable natural reward, recruit hypothalamic orexin neurons that converge onto the paraventricular thalamus. Together with evidence that orexin antagonist reverses cocaine-seeking behavior, these findings identify the orexin system as important mechanism mediating conditioned incentive effects of abused drugs. Spanagel will describe his research on cocaine CPP, sensitization and extinction processes in different conditional and inducible mouse mutants. To study glutamatergic components of addictive-like behavior, this research targets NR1, GluR1, GluR2, mGlu5, CREB/CREM, CamKIV, and SRF in dopaminergic (DATcre-driven) and dopaminoceptive (D1-Cre driven) neurons. O'Brien will focus on the role of endogenous opioids in the rewarding value of alcohol. The evidence in humans that opioids are activated by alcohol, especially in individuals with genetically determined sensitivity, has allowed the development of a completely novel treatment for alcoholism and a demonstration of genomically informed medical treatment. These presentations underscore the diversity of brain mechanisms mediating different components of the reward pathway.

Panel • Tuesday 4:30–6:30 PM • Maybird

39. Exploiting DISC1 To Understand the Biology of Schizophrenia and Develop New Preclinical Disease Model

Nick Brandon, Mirian Hayashi, Kozo Kozo Kaibuchi, Steve Clapcote, Akira Sawa

Disrupted in Schizophrenia 1 (DISC1) was initially identified in a Scottish family by a balanced translocation associated with schizophrenia, bipolar disorder and depression but has now been linked more generally to a range of psychiatric disorders and to reduced cognitive function, altered brain structure and function. The biology of DISC1 is being understood through a combination of elegant cell biology around its protein interaction partners and through the development of a wide range of DISC1 animal models. This has the potential to change our level of understanding of psychiatric disease. This symposium will cover both of these developments in this exciting area. Nick Brandon will introduce the "DISC1 Interactome", a comprehensive protein-protein interaction map around DISC1. He will show that detailed bioinformatic analysis of this resource allows multiple predictions of DISC1 function and will describe the impact to date on our understanding of DISC1 and schizophrenia. In particular he will describe new data on biology of sections of this interactome and put them in the context of understanding DISC1 from a therapeutic perspective. Mirian Hayashi will describe the exciting relationship between DISC1 and the peptidase activity of Ndel1. Ndel1-oligopeptidase is a cysteine endooligopeptidase, which is known to cleave small neuropeptides in vitro. DISC1 binds Ndel1 in the vicinity of the active site of this enzyme, inhibiting its catalytic activity. For the first time, an in vivo role for the enzymatic activity will be described and shown to be critical for neurite outgrowth. This activity will be discussed in the context of a possible role in the etiology of schizophrenia.

Panel • Tuesday 4:30–6:30 PM • Wasatch

40. Roles of Mitochondria in Synapse Formation and Dysfunction

Leonard Kaczmarek, George Spirou, Elizabeth Jonas, Gordon Rintoul, Ella Bossy-Wetzel

In all cells, mitochondria are responsible for routine metabolic activities and for life/death decisions during development or in response to changes in cellular environment. In neurons, however, mitochondria appear to have additional specialized functions that contribute to regulation of synaptic transmission. This session will cover recent evidence that biogenesis, fission, fusion, trafficking and degradation of mitochondria are key elements of synapse formation and are required for normal synaptic function, and that impairment of mitochondrial function is a central aspect of the neuronal pathology that occurs in disease states such as hypoxic injury and Huntington's disease. George Spirou will describe the unusual morphology of mitochondria that are tethered to active zones in presynaptic terminals of neurons capable of releasing neurotransmitter at very high rates. Elizabeth Jonas will discuss the mechanism by which the outer mitochondrial membrane protein Bcl-XL regulates the number of mitochondria in neurons, and their targeting to presynaptic terminals though its interaction with the mitochondrial fission factor dynamin-related protein 1 (Drp1). Gordon Rintoul will describe imaging experiments demonstrating that the morphology and movement of mitochondria is tightly regulated by neurotransmitters and cytoplasmic signaling pathways and that changes in mitochondrial dynamics contribute to neuronal injury. Finally, Ella Bossy-Wetzel will present data indicating that the mutations in the Huntingtin protein that give rise to Hundington's disease alter mitochondrial fission/fusion machinery, triggering chronic, unbalanced mitochondrial fission. Like Bcl-XL, the mutant Huntingtin protein interacts with Drp1 and modifies its GTPase activity, providing a potential mechanistic explanation for the mitochondrial dysfunction in Huntingon's Disease.

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

41. Cerebellar Plasticity: James McElligott Memorial Panel

Robert Baker, James Bloedel, Edward Keller, Laurence Young

One of the longest-term participants in WCBR, Jim McElligott, Professor of Pharmacology at Temple University, passed away last winter.

To honor him and his contributions to the basis of plasticity, particularly in the vestibulo-ocular system, this panel will examine the nature and mechanism of sensori-motor adaptation. Baker will summarize Jims experimental perspective on cerebellar function, in particular the surmises from his extensive pharmacological analysis of the vestibulocerebellum in goldfish as it pertains to the mechanisms underlying cerebellar plasticity. Bloedel will examine non-cerebellar plasticity in the context of new advances regarding the cerebellums role in the classical conditioning of the eyeblink reflex. Keller will discuss oculomotor plasticity regarding adaptation to altered color/location associations in a choice response saccadic task. Young will relate the experimental findings to models for vestibulo-ocular adaptation.

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

42. Chronic Pain New Mechanisms for Few Analgesics

Peter Reeh, Michael Costigan, William Lariviere, Simon Beggs

Chronic pain affects one in five American adults, but for many current pain medications remain ineffective. Genetic studies using animal models tallied with human data have begun to define the molecular mechanisms chronic pain. This panel will discuss recent advances in our understanding of these mechanisms. Peter Reeh will detail work on sensory and signal transduction in peripheral nerve axons, leading to ectopic discharge as in neuropathies. He will discuss the role of different TRP channels along the axons and of calcium channels controlling axonal neuropeptide release. The NaV1.8 sodium channel will be shown to propagate cold pain and contribute to cold hyperalgesia. Michael Costigan will discuss finding genes expressed by sensory neurons that regulate pain sensitivity. Work on one of these genes GTP cyclohydrolase, has defined a gene haplotype (population frequency 15.4%) which is significantly associated with less pain in humans. In contrast to the adult, peripheral nerve injury in the neonate rat does not result in neuropathic pain. Microarray analysis of young versus adult dorsal horn tissue following SNI has identified key differences in the glial response. Andrew Moss will detail the specific contribution of glial cell activation to pain sensitivity and discuss how this differs significantly in the neonatal rat. BDNF release from activated microglia causes a shift in the anion reversal potential in spinal lamina I neurons, leading to an excitatory response to GABA instead of inhibition, Simon Beggs will discuss the implications of these data. These findings are a first step to enable the development of mechanism-based analgesics.

Workshop • Tuesday 8:30–10:00 PM • Ballroom 1

43. Hemichannels or Giant Ion Channels: The New World of Gap Junction Proteins

Brian MacVicar, Michael Bennett, Bruce Ransom, Roger Thompson, David Spray

Gap junction proteins (connexins and pannexins/innexins) have a new role as unapposed membrane ion channels called hemichannels (or connexons, pannexons, and innexons). The evidence for hemichannels is extensive but still controversial. Pannexins may only act as hemichannels and not gap junctions in mammals and may more properly be considered giant membrane ion channels and not direct intercellular pores. Hemichannel opening may underlie certain forms of non-synaptic release of neurotransmitters such as glutamate and ATP. The participants of this workshop will discuss recent evidence for connexin and pannexin hemichannel opening under different conditions. Bennett will show that Cx43 hemichannels in HeLa cells have the conductance and gating properties predicted from the cell-cell channels which are formed by two hemichannels in series. Metabolic inhibition (oxidative stress) increases Cx43 hemichannel opening in astrocytes, which is reversed by reducing agents. Surprisingly, reducing agents increase opening under normoxic conditions. Ransom will show opening by modestly decreased extracellular [Ca2+] and release of glutamate from cultured astrocytes and acutely isolated white and gray matter. Thompson will show that excitotoxic stimuli such as oxygen-glucose deprivation and NMDA receptor activation open pannexin hemichannels possibly contributing to necrosis. Spray will present evidence that pannexin opening is secondary to P2X7 receptor activation and will describe possible molecular mechanisms. In addition Spray will present data suggesting that genes encoding pannexin1 and Cx43 represent nodes in gene expression regulation with remarkable similarity in linkage to expression of other genes, implying similar roles in cellular processes.

Panel • Tuesday 8:30–10:00 PM • Magpie

44. Sequestosome 1/p62, Aggregation and Neurodegeneration

Marie Wooten, Henry Paulson, Haning Zhu, Geir Bjorkoy, Ted Dawson

Ubiquitin along with Sequestosome 1/p62 are common components of inclusions associated with numerous neurodegenerative diseases. P62 is a multi-domain protein which serves as a scaffold. At its N-terminus the

protein has a PB1 domain involved in oligomerization, a site for recruitment of the atypical PKC, a site for interaction with the E3-ubiquitin ligase, TRAF6, and a C-terminal UBA domain. There is growing evidence that p62 plays a role in recruitment of polyubiquitin to an inclusion. The panel will discuss new findings on the relationship between p62 and its role in neurodegeneration in various models. Wooten will briefly overview the characterization of p62 knock out mouse brain. Paulson will discuss the role of p62 in polyglutamine disorders with an emphasis on its links to the polyglutamine disease protein ataxin-3, a mixed chain deubiquitinating enzyme. Zhu will discuss recent data on the interaction of p62 with mutant SOD1, modulation of aggregation and contribution to amyotrophic lateral sclerosis (ALS). Bjorkoy will discuss the interaction of p62 and LC3 that enables autophagic degradation of ubiquitinated protein aggregates. Dawson will describe findings relating to p62's role in sequestering K63-linked ubiquitinated proteins and their contribution to aggregation in relation to Alzheimer's and Parkinson's disease. Altogether these studies will shed light on the cellular and molecular mechanisms that contribute to p62's role in formation of inclusions and turnover of protein aggregates.

Panel • Tuesday 8:30–10:00 PM • Maybird

45. Reeling Rats and Mice of Vice: Novel Rodent Models of Addiction

John Crabbe, Nick Gilpin, Chris Olsen, Andrew Holmes

Addiction is a disease of motivation and/or impulse control that affects millions of people. A powerful approach to the study of this disease is the use of animal behavioral models that mimic the motivated seeking and consumption seen in the human condition. The focus of this panel will be on recent developments of rodent behavioral and genetic models to study addiction. John Crabbe will discuss a "drinking in the dark" model, which rapidly induces alcohol drinking to intoxication in mice without significant food or water restriction. Through selective breeding strategies, his lab is successfully generating mice that will reach high levels of voluntary intoxication. Nick Gilpin will also talk about behavioral methods to achieve voluntary alcohol intake and compare neural systems recruited by two such pathological drinking paradigms. Chris Olsen will present data on operant novelty seeking in mice, which

suggests that novelty "self-administration" may have predictive validity in regards to drug self-administration studies as well as non-pharmacological "behavioral addictions" in humans. Finally, Andrew Holmes will discuss a "loss of behavioral control" phenotype in mice lacking the GluR1 subunit of the AMPA glutamate receptor. This panel will discuss recent advances in modeling addictive behavior that can be useful to all scientists, whether or not they are hooked on addiction research.

Panel • Tuesday 8:30–10:00 PM • Wasatch

46. Neurological Emergencies with Methamphetamine & MDMA (Rodent Models)

Jerry Frankenheim, Daniel Rusyniak, Jon Sprague, Bryan Yamamoto, Gary Gudelsky

The mechanisms of the acute, severe neurological sequelae of the methamphetamines (methamphetamine itself, MDMA, and analogs)—including malignant hyperthermia, cerebral edema, and psychotic episodes—are insufficiently understood, and the medical management of these emergencies is controversial and far short of optimal. The hyperthermia induced by acute abuse of these drugs is dependent on activation of the hypothalamic-pituitary-thyroid-adrenal axis and the sympathetic nervous system. Daniel Rusyniak will describe the roles of the dorsomedial hypothalamus (DMH) in mediating MDMAs activation of neuroendocrine and sympathetic nervous systems. Jon Sprague will focus on the role of the hypothalamic-pituitary-thyroid axis, cellular mechanisms of thermogenesis, and the effects of ambient temperature on substituted amphetamine-induced hyperthermia. The emergency department treatment of methamphetamine-induced psychoses typically involves haloperidol, a dopamine D2 receptor antagonist. Bryan Yamamoto found that sub-chronic haloperidol administration after a high-dose regimen of methamphetamine produces a heretofore unrecognized, specific toxicity to GABAergic cells (cell death) in the rat substantia nigra via acute glutamatergic excitotoxicity. His findings suggest that the management of methamphetamine-induced psychoses with haloperidol may be contraindicated. Gary Gudelsky will discuss his findings relating acute effects of substituted amphetamines to long-term consequences of exposure to these drugs.

Panel • Tuesday 8:30–10:00 PM • Superior A

47. Toll-like Receptors in CNS Injury and Infection

Tammy Kielian, Trevor Owens, Phillip Popovich, Timothy Vartanian

Toll-like receptors (TLRs) are pivotal for recognizing conserved structural motifs on a wide variety of pathogens by the innate immune system including bacteria, viruses, and fungi. Although the role of these receptors has been well established in peripheral infections, only in recent years has the importance of TLRs been demonstrated in infections of the CNS. In addition, intriguing new information is emerging suggesting that TLRs also shape host responses that occur following non-infectious CNS insults such as stroke, spinal cord injury, and neurodegeneration. Participants in this panel will present ground-breaking studies highlighting the dual role of TLRs in response to infectious versus injury or traumatic insults to the CNS. Dr. Tammy Kielian will demonstrate the functional importance of TLRs during bacterial infections affecting the brain parenchyma (brain abscesses) and in glial recognition of bacterial motifs. Dr. Trevor Owens will discuss the role of TLRs as transducers of neuronal-glial signals using a model of nerve transection injury. Dr. Phillip Popovich will present evidence demonstrating that TLRs dictate functional recovery following spinal cord injury and the nature of the glial scar. Finally, Dr. Timothy Vartanian will discuss the functional importance of TLRs in regulating the ensuing innate immune response following stroke. An appreciation of the dual role that TLRs can play during both infectious and non-infectious diseases of the CNS may lead to the identification of common pathways that may be exploited for the therapeutic management of various autoimmune and neurodegenerative disorders that affect the CNS.

Workshop • Tuesday 8:30–10:00 PM • Superior B

48. Neonatal Programming of Neuroendocrine Function

Greti Aguilera, Karen Bales, Stafford Lightman, Tallie Baram, Michael Meaney, Jonathan Seckl

Events during fetal and neonatal life have long-term impact on neuroendocrine function and behavior. This workshop aims to explore current knowledge and unanswered questions on the mechanisms by which early life experience leads to programming of neuroendocrine responses. Following a brief outline of points to be addressed by Greti

Aguilera, Karen Bales will lay ground for discussion on how early handling or pharmacological manipulations of the oxytocinergic system in prairie voles can lead to programming of oxytocinergic and vasopressinergic systems and affect adult behavior, such as pair bonding and parenting. Stafford Lightman will promote discussion on how neonatal interventions induce long-term modifications of hypothalamic-pituitary-adrenal (HPA) axis responsiveness and behavior, with involvement of serotoninergic pathways in a context-specific manner. Tallie Baram will provide points for discussion on how HPA axis programming requires recurrent recruitment of stress-regulating brain regions, with activation of specific signaling systems and transcription factors, ultimately resulting in long-term alteration of stress-related gene expression. Michael Meaney will extend this discussion by showing that epigenetic programming of glucocorticoid receptor levels in the brain can mediate long-term effects of early life experience on HPA axis activity. Finally, Jonathan Seckl will critically evaluate the current knowledge and missing links on the mechanisms of long-term effects of early life exposure to excessive levels of glucocorticoids, and the involvement of 11beta-hydroxy steroid dehydrogenase in programming neuroendocrine and metabolic function. Discussion of these issues could lead to new integrated approaches aimed to understand pathogenic, preventive and therapeutic aspects of disorders related to early life events.

Panel • Wednesday 7:30–9:30 AM • Ballroom 1

49. New Directions in Behavioral Neurogenetics: Genetic Dissection of Brain, Behavior and Disease Pathways

Amanda Law, Daniel Weinberger, Colin Hodgkinson, David Goldman

Genes control simple and complex behaviors, but generally the biological mechanisms involved are unclear. The identification of susceptibility genes for schizophrenia and other neuropsychiatric disorders demands novel approaches to address the complex issue of how human genetic variation relates to brain development, function and contributes to disease. This panel will present data focused on elucidating the biological mechanisms underlying the association of key genes with risk for schizophrenia or anxiety disorder, showing that genetic risk influences specific molecular, cellular and biochemical pathways which ultimately regulate human brain function. Dr Amanda Law will focus on recent evidence that the PI3K/PIP3 pathway represents an integrator of altered signaling inputs in schizophrenia related to polymorphic variation in the susceptibility gene ErbB4, potentially limiting the efficiency of

NRG1's effects on cortical neural development, plasticity and adult brain function. Dr Daniel Weinberger will describe a novel schizophrenia susceptibility gene, KCNH2, a potassium channel critical for neuronal repolarization and the discovery of a novel, brain selective KCNH2 isoform that is regulated by risk genotype. Dr Colin Hodgkinson will present evidence showing that mis-sense polymorphisms in the schizophrenia susceptibility gene, DISC1, alter the interaction of DISC1 proteins with known binding partners, subsequently altering the cellular distribution of the DISC1 protein and providing a potential molecular mechanism underlying DISC1 associated psychosis. Dr David Goldman will present evidence that a novel, functional Neuropeptide Y promoter variant, associated with in-vivo transcription of the gene, predicts at the behavioral level trait anxiety and brain responses to pain, stress and emotional challenge.

Panel • Wednesday 7:30–9:30 AM • Magpie

50. CRF Effects on Midbrain Dopamine Neurons: Implications for Psychostimulant Action

Roy Wise, Matt Wanat, Michael Beckstead, Arthur Riegel

Increasing evidence suggests that hypothalamic neuropeptides have a neuromodulatory role on synaptic transmission in brain regions outside of the hypothalamus. Physiological and behavioral studies have recently identified specific actions of peptides on neural pathways implicated in psychostimulant-related reward. This session will describe ongoing investigations into the actions of the stress-related neuropeptide corticotropin-releasing factor (CRF) in dopamine neuron cell body regions in the ventral midbrain. Roy Wise will describe an indirect effect of CRF (involving presynaptic control of local glutamate release) on dopamine systems implicated in cocaine reward and motivation. CRF can reinstate cocaine-seeking behavior when infused into the ventral tegmental area (VTA) in an animal model of relapse, and cocaine-induced neuroadaptations are required for the effectiveness of CRF. Matthew Wanat will discuss how CRF increases the firing rate of VTA dopamine neurons. This effect is mediated by the CRF-R1 receptor via a PKC-dependent increase of I_h. Activation of this pathway also produces locomotion. Mike Beckstead will describe a CRF-induced increase in dopamine- and GABA-mediated inhibitory synaptic transmission in VTA dopamine neurons. This effect is attenuated following repeated exposure to cocaine, methamphetamine, or restraint stress, suggesting a psychostimulant-induced adaptation of this stress response. Finally, Art Riegel will describe a CRF-induced potentiation of metabotropic glutamate

receptor (mGluR)-mediated synaptic transmission in dopamine neurons. CRF enhances mGluR-mediated potassium channel activation through a mechanism dependent on the stimulatory G-protein Gs and intracellular calcium stores.

Panel • Wednesday 7:30–9:30 AM • Maybird

51. Deep Brain Stimulation for Obsessive-Compulsive Disorder: From Clinical Perspectives to Basic Mechanisms

Benjamin Greenberg, Darin Dougherty, Suzanne Haber, Clinton McCracken

High-frequency electrical stimulation of specific brain structures, commonly known as deep brain stimulation (DBS), has begun to attract substantial attention for use in treating highly refractory neurological and psychiatric disorders that fail to respond to traditional pharmacotherapies. In particular, DBS of the ventral striatum and ventral internal capsule has produced encouraging results for treatment of severe obsessive-compulsive disorder (OCD) and depression. Despite this demonstrated clinical utility, the mechanisms by which DBS produces therapeutic effects remain unclear. This panel will discuss how DBS acts to alleviate OCD and depression from a wide range of perspectives; incorporating clinical outcomes, human imaging studies, nonhuman primate neuroanatomy and rodent electrophysiology.

Ben Greenberg will begin by discussing the results of long-term clinical studies using DBS for OCD, which demonstrate improved results using a modified (more posterior) implantation target. Darin Dougherty will report on what human neuroimaging studies have revealed regarding the pathophysiology of OCD and how DBS may impact dysfunctional brain regions and neurocircuitry associated with OCD. Suzanne Haber will use 3-D reconstructions of cortical pathways and their targets in nonhuman primates to demonstrate the neural networks that are likely to be affected by DBS for OCD. Finally, Clint McCracken will discuss some basic electrophysiological studies examining the effects of ventral striatal DBS on neuronal activity in the rodent orbitofrontal cortex. It is hoped that the broad scope of this panel will stimulate discussion on a number of different fronts and lead to greater understanding of this promising therapy for severe, otherwise treatment-resistant psychiatric disorders.

Panel • Wednesday 7:30–9:30 AM • Wasatch

52. Sex Differences in the Brain: It's Not Just About Sex Anymore!

Margaret Altemus, Victoria Luine, Jill Becker, David Standaert

Research on humans and non-human animals has increasingly documented sex influences areas of brain that have no direct impact on reproduction or sexual behavior. These include sex differences in emotion, learning and memory, drug abuse, anxiety, stress hormone action on the brain, and Parkinson's Disease. Altemus will begin discussing sex differences in mood and anxiety. Anxiety disorders are common in both men and women, but women suffer with disproportionately higher rates of illness. Her work, in humans and rodents, suggests hormonal modulation of anxiety disorders are likely to provide an important window into the pathophysiology of these illnesses. Luine will discuss sex differences in stress effects on cognitive function in rodents. While there are deleterious effects of stress on cognitive function in males, female rodents show enhanced performance on the same memory tasks. Moreover, stress is anxiolytic in males and anxiogenic in females. Sex differences are present for all of the phases of drug abuse, which includes initiation, then escalation of use and the progression to addiction, with subsequent withdrawal followed by relapse. Becker will discuss this and the underlying neurochemical processes that mediate sex differences in drug abuse. Standaert will conclude with a discussion of his work on sex differences in Parkinson's Disease. Men have a higher incidence of PD, but the rate of progression and survival are similar in men and women. Thus, gender influences the initiation of the disease, but has only a limited effect on the factors which drive progression once the disease is established.

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

53. New Insights into the Cellular Basis for Familial Epilepsies and Other Sodium Channelopathies

Todd Scheuer, Massimo Mantegazza, Alan Goldin

Increasing numbers of mutations in ion channels are being linked to syndromes and diseases termed channelopathies. Initial investigations targeted effects on channel gating. However, recent studies of mutant sodium channels concentrating on other effects of the mutations in

heterologous systems and in mice have resulted in novel and unexpected insights into the basis for several sodium channel-linked diseases. Mutations underlying disorders including muscle paralyses, familial migraine and cerebellar ataxia target arginines of S4 segments in ion channels. Scheuer will discuss how mutations in S4 arginines of Nav1.4 channels cause hypokaelemic periodic paralysis by creating a pathway for cation leak into cells through the gating pore surrounding the S4 segment. Similar gating pore current may underlie other S4 arginine-linked channelopathies. Sodium channel mutations underlying Generalized Epilepsy with Febrile Seizures (GEFS+) and Severe Myoclonic Epilepsy in Infancy (SMEI) are primarily caused by mutations in Nav1.1 sodium channels. Most studies have linked GEFS+ to gain of function mutations and SMEI to loss of function. Mantegazza will present evidence that loss of Nav1.1 function can be linked to both GEFS+ and SMEI, despite divergent gating phenotypes. Goldin will present studies in heterologous systems and genetically engineered mice probing the role of neuron-specific reduction of current in mediating the epileptic phenotype in vivo. The latter studies underline the particular role of loss of Nav1.1 function in inhibitory interneurons as a unifying theme in understanding the basis for these familial epilepsies.

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

54. New Pistes for IGF Signaling in the Nervous System

Steve Levison, Cunming Duan, Kim Heidenreich, Terri Wood

Insulin-like growth factor-I (IGF-I) is essential for normal brain development and promotes survival and regeneration of neurons and glia following injury. The IGF type I receptor (IGF-IR) is present on all cell types in the brain and IGF-I has known actions on neural stem and progenitor cells as well as on neurons and glia. While IGF-I has diverse roles in the CNS including promoting cell proliferation, survival, and differentiation, the precise mechanisms for its actions on individual cell populations are poorly understood. The participants in this panel will present new studies on IGF-I and IGF signaling in the CNS. Steve Levison will discuss data on IGF actions on neural stem/progenitor populations both in the normal brain and in the immature brain during recovery from hypoxia-ischemia. Cunming Duan will present data on IGF receptor signaling in the proliferation and survival of specific neural cell populations in zebrafish. Kim Heidenreich will discuss signals downstream of IGF-I receptor activation that prevent apoptosis as

well as in autophagic cell death in neurons. Terri Wood will discuss the mechanisms for IGF receptor signaling and sustained Akt phosphorylation in promoting survival and development of oligodendrocyte progenitors. From these presentations, meeting delegates will have a better appreciation for the critical roles of IGF-1 in CNS development, neuronal and glial cell maintenance and regeneration.

Panel • Wednesday 4:30–6:30 PM • Ballroom 1

55. Learning and Brain Plasticity, the Schizophrenics Dilemma

Henry Holcomb, Robert Astur, Laura Rowland, Carol Tamminga

Learning is particularly impaired in schizophrenia even when attention and working memory are held accountable. This deficit contributes heavily to poor psychosocial function throughout the course of the disease and promotes high public health costs. There is now a broad effort to determine effective treatments for cognitive dysfunction in schizophrenia. Errors in cellular plasticity, long-term potentiation (LTP) or long-term depression (LTD), probably contribute to the deficits observed in schizophrenia. Although some research has demonstrated aberrations in LTP in animal models of schizophrenia, little research has investigated neuroplasticity during learning in schizophrenia. This panel will discuss neural plasticity during various forms of learning and memory in schizophrenia. These studies provide indirect evidence of altered cellular brain mechanisms during learning in schizophrenia, and could provide a framework for testing novel cognitive treatments. Henry Holcomb will begin the Panel with a presentation on brain activity changes underlying motor learning assessed with positron emission tomography. He will also describe visual-spatial learning assessed with functional magnetic resonance imaging (fMRI), in schizophrenic subjects learning with and without performance feedback. Robert Astur will provide data from fMRI studies of hippocampal function assessed with the virtual Morris water maze, and amygdala function assessed with a fear-conditioning paradigm. Laura Rowland will discuss fMRI and 1H-MRS studies of neural changes during relational learning and memory assessed with the transverse patterning paradigm in schizophrenia. Carol Tamminga will discuss the impact of antipsychotic drugs on declarative memory and will also review learning studies employing novelty and inferential cognition in schizophrenic participants.

Panel • Wednesday 4:30–6:30 PM • Magpie

56. Drug of Abuse: What Dopamine Neurons Do and Don't Do!

Christopher Ford, Christian Luscher, Michela Marinelli, François Georges

The dopamine (DA) neurons and their projections are involved in both acute and chronic responses to drugs of abuse. The focus of this panel will be to understand: 1) how dopaminergic and glutamatergic synaptic transmission in the ventral tegmental area (VTA) regulate the activity states of DA neurons and 2) how do drugs of abuse modify DA neurons physiology and thereby lead to addictive behaviour. The science discussed will be highly interdisciplinary, encompassing behavioral paradigms for addiction, electrochemical technology and in vivo and ex vivo electrophysiological approaches. To understand the manner in which DA regulates the activity of local DA neurons, Christopher Ford recorded dopaminergic IPSCs while simultaneously measuring DA release with fast-scanning voltammetry. He will present evidences describing the mechanisms by which DA is released somatodendritically. Christian Lüsher will discuss new data where he characterized the mechanism of mGluR-LTD in the VTA of mice exposed to a single dose of cocaine. LTD in this system is not due to the simple removal of AMPA receptors (AMPARs) from the synapse. Instead, AMPARs are replaced by new ones that contain newly synthesized GluR2 subunits. Michaela Marinelli will present in vivo data showing how DA neurons respond and adapt to acute and repeated exposure to cocaine and nicotine. She will show how the effects of these drugs show individual variability across animals, ages, and stress states. François Georges will present recent in vivo electrophysiological experiments showing that prolonged morphine exposure and nicotine self-administration triggers a similar hyperactivity in tonic DA neurons firing.

Panel • Wednesday 4:30–6:30 PM • Maybird

57. Polyphenols and Polyunsaturated Fatty Acids: The Pollyannas of Brain Neurodegeneration

James Joseph, Marva Sweeney, Henriette van Praag, Tom Kuhn

Inflammation and oxidative stress contribute substantially to the progression of neurodegeneration in aging as well as in chronic, acute, and psychiatric CNS pathologies. Persistent stimulation of signaling pathways by inflammatory mediators accounts for the generation of

oxygen radicals and other neurotoxic intermediates, which compromise neuronal survival by damaging proteins, lipids, and nucleic acids. Diets rich in polyphenols and polyunsaturated fatty acids are long known to alleviate cognitive decline associated with aging and CNS pathologies. This panel will focus on molecular mechanisms of neuroprotection associated with dietary compounds in models of aging and chronic CNS pathologies. Dr. Joseph will emphasize research on membrane lipid modifications in aging with a focus on increases in C2 ceramide and its implication in oxidative stress, neuroinflammation, and modification of MAPK signaling in hippocampal cell lines. He will further discuss how fruit derived polyphenols and fish derived polyunsaturated fatty acids provide multiple neuroprotective modes against oxidative and inflammatory stress. Dr. Sweeney will give evidence that anthocyanins from wild Atlantic blueberries interfere with nitric oxide signaling in brain neurons undergoing simulated stroke and oxidative stress. Dr. van Praag will present research showing that the flavanol epicatechin improves memory function, enhances brain blood flow and may reduce inflammation in the nervous system. Dr. Kuhn will emphasize research on a Mg2+-dependent neutral sphingomyelinase, a key activity in the progression of CNS inflammation, and the presence of a potent inhibitor in wild Alaskan blueberries.

Panel • Wednesday 4:30–6:30 PM • Wasatch

58. Old Toxins and New Tricks: Modeling Parkinson's Disease in Rodents, Flies and Worms

Michael Levine, Marjorie Ariano, David Krantz, Bernd Meurers, Richard Nass

The purpose of this panel is to evaluate markedly different models of Parkinson's disease (PD). Rodents have been used to model PD since the 1960s. Most models are based upon the variable depletion of nigrostriatal dopamine (DA) using a number of methods. Ariano will examine new critical findings that underlie altered pathophysiological and molecular mechanisms using a partial DA depletion model in the rat. Meurers first will discuss cell type specific gene array data from different areas in the basal ganglia to demonstrate the complexity of the cellular responses to chronic DA depletion in the rat. Then he will address the usefulness of toxin-induced models using low concentration rotenone to identify molecular defense mechanisms in DA neurons in response to environmental toxins. Krantz will describe how Drosophila melanogaster provides a powerful system to investigate the mechanisms by which

environmental and genetic insults can compromise the function of DA. He will discuss the molecular-genetic tools, cellular and behavioral assays that facilitate the investigation of DA cell death in the fly, and how the results of these studies may relate to PD. Nass has developed a novel pharmacogenetic model using the genetically tractable nematode C. elegans to dissect and characterize the molecular components involved in DA neuron degeneration. He will describe results from genetic screens that identify mediators and suppressors of DA neuron cell death and how these studies can facilitate the identification of novel genes and molecular pathways.

Workshop • Wednesday 4:30–6:30 PM • Superior A

59. Give Haptics A Hand

Gerald Loeb, Karen Moxon, Tansu Celikel, Gene Fridman, Francisco Valero-Cuevas

Haptics is usually associated with human hands, but it actually represents a broad range of cognitive tasks in which active movements are planned in order to acquire particular sensory information and must be considered when interpreting those data. Karen Moxon has been recording somatosensory neuronal activity from rats during both awake and anesthetized paradigms to understand the encoding of somatosensory information of active (haptic) touch as opposed to passive touch. Tansu Celikel has been applying advanced photonic techniques to get an overview of the cortical circuitry related to the rodent barrel (whisker) cortex and its function during discrimination tasks that involve whisking movements. The other discussants hope to apply these neurophysiological insights in biomimetic applications. Gene Fridman is putting cutaneous information back into the somatosensory cortex by microstimulation, eventually to provide tactile feedback for neural prostheses. Francisco Valero-Cuevas is studying how tactile information is used to stabilize grasp in humans with and without neurological and biomechanical deficits. Gerald Loeb has developed a tactile sensor array that provides biomimetic capabilities to finger tips and probes designed for prosthetic and telerobotic hands. Our workshop will consider what can be learned by comparing superficially different sensorimotor structures and problems in both biological and mechatronic entities. The overarching issue is the role of top-down processing in perception. Do we know what we are going to touch before we touch it? How does that information affect transduction, transmission and processing? How will the brain interpret extrinsic information inserted into these processes?

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

60. The Role of the Serine/Threonine Phosphate PP2A in Neuronal Signaling

Johannes Hell, Angus Nairn, Estelle Sontag, Mary Horne, Stefan Strack

Although neglected for the longest time, phosphatases are as critical as kinases for countless neuronal functions. This symposium will focus on different aspects of the phosphatase PP2A. PP2A is one of the main four serine/threonine phosphatases. It consists of a catalytic C and structural A subunit that associate with one of more than a dozen B subunits for specific targeting to selected substrates. Many mutations in PP2A subunits and inhibitors of PP2A are lethal. Dr. Angus Nairn will describe the regulation of cAMP and calcium-dependent DARPP-32 dephosphorylation by specific heterotrimeric forms of PP2A, which is critical for dopaminergic signaling in the brain. Dr. Estelle Sontag will talk about the regulation of PP2A methylation and its role in neurodegenerative disorders. Dr. Mary Horne will discuss the role of the unconventional cyclin G2, which associates with PP2A to control neuronal growth in the developing cerebellum. Dr. Stefan Strack will present on the role of PP2A in remodeling of mitochondria in neurons. Dysregulation of mitochondrial fission and fusion due to defects in the PP2A B subunit B beta is fatal for neuronal survival. This subunit is implicated in spinocerebellar ataxia 12 due to a poly-glutamine expansion in its primary sequence. This symposium thus touches on several key aspects of PP2A and will provide a coherent and up to date view of some of the critical issues surrounding PP2A.

Panel • Thursday 7:30–9:30 AM • Ballroom 1

61. Neurobiology of Dopamine Terminals: What Do Cannabinoid Receptors Have To Do with It?

Joseph Cheer, David Lovinger, Alexander Hoffman, Anatol Kreitzer, Eliot Gardner

Endogenous cannabinoid signaling is increasingly becoming recognized as an important negative feedback regulator of brain activity. Indeed, the principal central nervous system function of endogenous cannabinoids—compounds that bind to the same receptors as the main psychoactive component of marijuana—is as retrograde inhibitors of neurotransmitter release. Importantly, cannabinoid CB1 receptors are found in several

neural regions that are heavily innervated by dopamine inputs. Within this anatomical framework, CB1 receptor signaling can modulate the activity of dopaminergic pathways by influencing, directly or indirectly, dopamine neurotransmission through either postsynaptic or presynaptic mechanisms. This panel's objective is to discuss and highlight recent evidence suggestive of endogenous cannabinoid and dopamine interactions that may underlie psychotic disorders and addiction. First, David Lovinger will present electrophysiological data related to endogenous cannabinoid-dependent long-term depression in the striatum and its dynamic modulation by D2 receptors and cholinergic tone. Alex Hoffman will present voltammetric recordings of dopamine release obtained in CB1 receptor knockout mice to assess the function of other modulators of dopaminergic function (i.e., kappa opioids) in these animals. Anatol Kreitzer will present data on the role of postsynaptic D2 receptors in the regulation of endocannabinoid release and striatal long-term depression and their possible role in parkinsonian motor deficits.Finally, Eliot Gardner will discuss the interplay between glutamate and dopamine release in the nucleus accumbens in mediating the inhibitory action of cannabinoid receptor antagonists on the rewarding effects of cocaine.

Panel • Thursday 7:30–9:30 AM • Magpie

62. Protein Misfolding—A Common Theme in Neurodegenerative Diseases

Menelas Pangalos, Rakez Kayed, Daniel Otzen, Donald Lo, Peter Reinhart

Protein misfolding continues to be a common and exciting theme in neurodegenerative disease research, giving rise to both neuronal dysfunction and degeneration. As we increase our knowledge of the role of oligomeric, fibrillar, higher-order molecular misfolded proteins in neurodegenerative diseases, new approaches offer themselves for therapeutic intervention. Dr. Rakez Kayed will discuss advances in antibody and vaccine mediated approaches targeting toxic oligomers for the treatment of AD and PD. Dr. Daniel Otzen will discuss the earliest steps of alpha-synuclein aggregation and discuss the therapeutic potential of novel anti-aggregation approaches. Dr. Don Lo will present new work on the role of huntingtin protein aggregates in the pathophysiology of HD and Dr. Peter Reinhart will discuss work demonstrating that targeting the clearance of Abeta aggregates can modify both the disease progression and symptoms of AD. The session will be introduced and chaired by Dr. Menelas Pangalos.

Panel • Thursday 7:30–9:30 AM • Maybird

63. In Vivo Physiology in Genetic Models: Bridging the Gene/Behavior Gap

Joshua Gordon, Patricio O'Donnell, Malcolm Nason, Rui Costa

Increasingly, genes are being identified which predispose to neuropsychiatric illness. Understanding how these genes lead to disease requires systems neuroscience techniques in order to bridge the gap between molecular and behavioral studies. We will describe our recent efforts to characterize the effects of molecular alterations on brain activity in intact rodent models, with the common goal of understanding pathophysiological processes. Presenting data obtained from simultaneous hippocampal and prefrontal cortical recordings in behaving mice, Dr. Gordon will posit a role for communication between these structures in models of anxiety and schizophrenia. Dr. ODonnell will present data on recordings from prefrontal cortex, hippocampus and ventral striatum in normal rats and in developmental animal models of schizophrenia, suggesting a role for corticolimbic information processing in this disorder.. Dr. Role will present the results of neuronal recordings from the hippocampus and ventral striatum of neuregulin-deficient mice, supporting a role for this important schizophrenia predisposition gene in the maintenance of synaptic connectivity within the limbic system. Finally, Dr. Costa will discuss recent studies using multi-site neuronal recordings from cortex and striatum in behaving mice to investigate the molecular and circuit mechanisms underlying the learning of goal-directed actions and habitual behaviors. Together these presentations will convey the unique role in vivo neurophysiological methods can play in elucidating the pathophysiological processes underlying psychiatric illness, and highlight the benefits of combining molecular, neurophysiological and behavioral approaches.

Panel • Thursday 7:30–9:30 AM • Wasatch

64. Yin and Yang of Glial Cell Responses in Cerebrovascular Disorders

Jarowslaw Aronowski, Mark Goldberg, Gregory Del Zoppo, Bruce Ransom

There is increasing recognition that glial cells play active roles in brain homeostasis, development, and plasticity. Understanding the participation of glia in brain ischemia and intracerebral hemorrhage may help to identify new glial targets with therapeutic potential. Jaroslaw Aronowski will discuss the role microglia/macrophages may play after intra-

cerebral hemorrhage (ICH) in scavenger receptor-mediated oxidative stress, phagocytes and inflammation. Specifically, we postulate that pro-phagocytotic behavior of microglia could be achieved in the absence of oxidative stress and inflammation. We will demonstrate that specific pharmacologic approaches allow for switching microglia from pro-inflammatory to anti-inflammatory and pro-phagocytotic. We will also show that this strategy could represent a viable approach in combating inflammation, neuronal damage and intraparenchymal hematoma retention after ICH. Mark Goldberg will examine the interaction of oligodendrocytes and axons in ischemic white matter injury. Oligodendrocytes and their myelin are important for preservation of axonal conduction. On the other hand, oligodendrocytes are vulnerable to excessive activation of glial glutamate receptors, or excitotoxicity, and this appears to injure neighboring axons. In the developing brain, before myelin formation, excitotoxicity of oligodendroglial lineage cells does not contribute to axon injury. Does oligodendrocyte vulnerability also contribute to axon damage in cerebral palsy, trauma, or multiple sclerosis? Gregory del Zoppo will discuss the activation of microglia in the setting of focal ischemia and the interaction of these cells with other glial and vascular cell counterparts. The dependence of their reactivity to altered matrix environments in response to injury will be examined. Bruce Ransom will discuss the behavior of astrocytes during ischemia-like conditions in white matter. These cells alone have a carbohydrate store that can be used anaerobically to produce ATP. These cells, therefore, may continue to 'regulate' brain extracellular environment during ischemia. When this fails, however, it appears that astrocytes release glutamate by reverse exchange leading to excitotoxicity.

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

65. Your Brain on (Neuro)Steroids: A Myriad of Beneficial Functions in Animals and Human Beings

Leslie Morrow, Michael Rogawski, Roberta Brinton, Synthia Mellon

Neurosteroids are potent endogenous modulators of neurotransmitter-gated ion channels—particularly GABA-A and NMDA receptor channels that control inhibitory and excitatory neurotransmission. Synthesis of neurosteroids may be dysregulated in developmental, neurologic and psychiatric disease and altered by psychotropic agents including antidepressants and ethanol. Our panel will discuss several paradigms implicating abnormal neurosteroidogenesis in the etiology of disease, and will provide compelling evidence for effective neurosteroid treatment. Leslie

Morrow will present evidence the HPA axis regulation of neurosteroids in monkeys can predict subsequent alcohol drinking and that chronic drinking in monkeys and humans produces alterations in basal levels and HPA axis regulation of plasma neurosteroids. Mike Rogawski will discuss animal studies that implicate endogenous neurosteroids in the regulation of seizure susceptibility in perimenstrual catamenial epilepsy, stress and temporal lobe epilepsy, and will update us on the ongoing clinical trials with ganaxolone in the treatment of human infantile spasms and adult partial epilepsy. Roberta Brinton will discuss roles of neurosteroids in hippocampal neurogenesis, and the neurogenic potenial of allopregnanolone in the triple transgenic mouse model of Alzheimer's disease, suggesting that neurosteroids may maintain the regenerative ability of the brain thereby altering Alzheimer's pathology progression. Sindy Mellon will discuss the role of neurosteroids in childhood neurodegenerative diseases, particularly lysosomal storage diseases, where abnormal neurosteroidogenesis precedes neurodegeneration, and where neurosteroids have remarkable therapeutic efficacy. These presentations will provide a comprehensive discussion of the role of neurosteroids in seemingly disparate diseases, will show their clinical potential for intractable and fatal neurologic disorders, and may suggest potential new therapeutic approaches for other diseases.

Minicourse • Thursday 7:30–9:30 AM • Superior B

66. Generating Tools for the Study of Nervous System Function Using Adeno-Associated Viral Vectors: Design, Production and Applications

Corinna Burger, Edgardo Rodriguez

Viral vectors provide an attractive alternative to the use of transgenic animals in the study of nervous system function. In contrast to transgenic animals, viral vectors can be quickly produced and provide the means to control the temporal-spatial expression of transgenes in the nervous system. However, the lack of established, reproducible protocols has impeded the mainstream use of viral vectors in biological research. This minicourse is designed to take the "mistery" out of viral vector design and production. A general description of the different viral vectors available to the neuroscientist will be provided, with a focus on Adeno-Associated Virus (rAAV). Specific protocols for the production of rAAV will be presented. In addition, this course will provide information on how to design, test and construct siRNAs in the context of viral gene delivery. Since its initial description by Mello and colleagues, many have

exploited the use of RNA interference (RNAi) for the study of gene function. In this second part of the course, we will introduce the endogenous RNAi pathway with a focus on non-coding microRNAs and their role in neuronal function. Moreover we will discuss how one can manipulate this pathway in order to achieve gene specific silencing for functional studies or therapeutic applications in the nervous system. Finally, we will discuss new vector designs, protocols and methodology destined to improve both the efficacy and safety profile of RNAi delivery to the CNS. The course will include a syllabus and detailed protocols.

Panel • Thursday 4:30–6:30 PM • Ballroom 1

67. Motivation, Learning, or Reward: What Is Orexin's Role in Addiction?

Jim Fadel, Stephanie Borgland, Rachel Smith, Brian Baldo

The orexin (hypocretin) system has extensive connections with neuromodulatory and reward systems, putting it in a pivotal position for regulating arousal and reward. The panel will discuss functional roles that orexin may be playing during food and drug reward-based behaviors. Fadel will describe the functional significance of orexin innervation of the basal forebrain cholinergic system in the context of food reward and age-related deficits in stimulated cortical acetylcholine (ACh) release. These orexin-ACh interactions may represent an important link between the interoceptive correlates of motivated behavior and enhanced attentional processing of environmental cues related to physiological status. Borgland will present data which suggest that orexin signaling may be critically involved in motivation for highly salient rewards. The orexin receptor 1 antagonist SB-334867 (SB) significantly attenuates active lever presses, earned reinforcers and breakpoint for cocaine and high fat chocolate, but not food self-administration on a progressive ratio schedule. Smith will discuss the role of orexin in drug-cue associations in the self-administration paradigm. Pretreatment with SB significantly blocks cue-induced reinstatement of cocaine seeking, providing further evidence that orexin is critically involved in the learning and recall of drug-cue interactions. Baldo will discuss orexins role within a bi-directional pathway linking mediobasal hypothalamic energy-sensing systems with the forebrain. Orexin neurons are positioned to relay energy-balance signals to feeding circuits in the cortex and accumbens shell, and, conversely, appear to be functionally modulated by feeding-related accumbens shell manipulations. These presentations will provide anatomical and behavioral information supporting a role for orexin in food and drug seeking.

Panel • Thursday 4:30–6:30 PM • Magpie

68. Learning and Plasticity: What's Arc Got To Do with It?

John Guzowski, Kristen Keefe, David Rademacher, Jacqueline F. McGinty

Arc (activity-regulated cytoskeletal protein) is an effector immediate early gene that conveys signals between the nucleus and the synapse during longlasting synaptic plasticity. Newly synthesized Arc is rapidly transported into dendrites and accumulates at activated synapses where it regulates AMPA receptor trafficking after strong stimulation. This panel will discuss evidence that supports Arc's role in experience-dependent learning and memory. John Guzowski will discuss the evidence that arc transcription in hippocampal pyramidal neurons is driven by "place" field firing and co-requires theta rythmicity, but is also sensitive to the recent firing history of given neurons. These data support a role for Arc in hippocampal network plasticity, as well as metaplasticity to regulate capacity for synaptic modification in the behaving animal. Kristen Keefe will discuss the relationship between arc mRNA expression in striatopallidal and striatonigral neurons in the medial vs. lateral dorsal striatum and motor response learning. She also will provide evidence suggesting that the subcellular trafficking or stability of arc mRNA is different in striatonigral vs. striatopallidal neurons. David Rademacher will discuss the effect of amphetamine place conditioning on Arc-immunoreactivity and the distribution of Arc in dendritic and spinous structures and asymmetric synapses opposed to these structures. He will demonstrate that the induction of amphetamine place conditioning is associated with Arc trafficking in the basolateral amygdala. Jacqueline McGinty will discuss the significance of arc mRNA induction in cortico-striatal circuitry in abstinent rats re-exposed to the chamber in which they previously self administered cocaine. The presentations will elicit discussion about the functional significance of Arc in these different experience-dependent learning and memory paradigms.

Panel • Thursday 4:30–6:30 PM • Maybird

69. Neurodevelopmental Features of Schizophrenia: Genetic, Molecular, and Clinical Studies

Joel Kleinman, Paul Harrison, Barbara Lipska, Thomas Hyde, Eve Johnstone

Schizophrenia is a complex genetic disorder that usually presents in adolescence or early adulthood. This panel will focus on risk genes, their role in brain development and maturation and environmental factors associated with schizophrenia. Dr. Paul Harrison will review the neurodevelopmental hypothesis of schizophrenia focusing on susceptibility genes, including NRG1, COMT, and Olig2. He will discuss conceptual and practical issues that will affect the refinement of the hypothesis in the next few years. In order to better understand how risk genes and brain development contribute to the pathogenesis of schizophrenia, Dr. Barbara Lipska will present data on expression of selected susceptibility genes in normal human postmortem prefrontal cortex from gestational age 14-20 weeks (n=42) and from birth to >80 years (n=200). She will show that expression of Fez1, Ndel1 and Lis1, genes that interact with DISC1, increase dramatically over the second trimester of gestation, a period of extensive neural migration critical for cortical maturation. Dr. Thomas Hyde will discuss clinical parameters derived from the NIMH Sibling Study of Schizophrenia including neurological soft signs, enuresis, and handedness that precede the onset of schizophrenia and may reflect abnormal brain maturation. Dr. Eve Johnstone will review MRI and cognitive factors in the Edinburgh High Risk Study cohort and the interface of these results with genetic factors in subjects at familial high risk of developing schizophrenia. She will focus on COMT and NRG1 risk alleles that are associated with cognitive function, neuroimaging findings and psychosis.

Panel • Thursday 4:30–6:30 PM • Wasatch

70. Neuromodulation of Synaptic Transmission and Neuronal Excitability in the Medial Prefrontal Cortex (mPFC)

Mark Yeckel, Donald Cooper, Evelyn Lambe, LiLian Yuan

The prefrontal cortex (PFC) is essential for working memory and other cognitive functions. Its operations are highly dependent on many factors. In this session, four new investigators, from three different countries,

will present fresh ideas and perspectives on the regulation of activity of rodent medial PFC neurons by novel long-distance intracellular signaling, by neuromodulators, and by convergent inputs from multiple neural regions. Yeckel will describe the properties of intracellular Ca2+ waves, and how these waves contribute to the regulation of mPFC pyramidal cell activity. This type of regulation might be particularly important during the delay period of working memory tasks. Related to Ca waves^{2+}, Dr. Cooper's work demonstrates that activation of mGluR also results in delayed depolarization (dADP) that is modulated by the dopamine D1 receptor PKA pathway. This type of regulation of mPFC activity might be particularly important during the delay period of working memory tasks and is subject to long-term modulation of cocaine treatment. Lambe will discuss a striking developmental modulation of currents carried by nicotinic acetylcholine receptors in layer VI, the major source of corticothalamic projections. Corticothalamic cells are a subset of layer VI neurons that modulate thalamic activity and are thought to play a critical role in gating attention. Lastly, Yuan will present evidence supporting the identification of an extracortical, axonal bundle that encapsulates the contribution of afferents from ventral hippocampus. This pathway exhibits different synaptic properties from intracortical pathways, providing the necessary groundwork for the future characterization of input-specific neuromodulation in mPFC. These studies, examining different aspects of regulatory control over mPFC neurons, provide cellular mechanisms that may take place in vivo.

Panel • Thursday 4:30–6:30 PM • Superior A

71. Shared Functional Genetic Loci and Neurobiologies of Pain/Stress and Emotion

Jon-Kar Zubieta, Luda Diatchenko, Mitchell Max, David Goldman

Stress is a powerful risk factor in psychiatric disease, and reciprocally, mood is a modifier of pain. Limbic circuitry mediates both the affective interpretation of pain and strength of responses to emotional stimuli. This panel presents new discoveries elucidating roles for functional genetic loci in interindividual variation to placebo response in pain/stress, and brings together evidence for a common role of functional genetic variants in pain perception and emotional responses to other stimuli. Jon-Kar Zubieta finds large interindividual variation in placebo responses during pain anticipation and experimental pain, including PET-detected opioid neurotransmission in limbic regions including amygdala. Functional Neuropeptide Y diplotypes and the MAO-A VNTR account for one-third of the variance in neurochemical and psychophy-

sical responses to placebo. Luda Diatchenko shows that COMT regulates experimental pain perception as well as risk to develop chronic facial pain. Her data reveal epistatic interaction of synonymous COMT variants to alter the folding and the translatability of COMT mRNA. This finding strengthens COMT linkage to pain threshold, and may clarify effects of COMT in other behaviors. Mitchell Max reports a massive increase in biopterin synthesis and a large increase in mRNA of the biosynthetic enzyme GTP cyclohydrolase (GCH1) in ipsilateral dorsal root ganglion in the rat neurotomy model, and accompanying development of phantom limb pain. A specific inhibitor of GCH1 sharply reduces the experimental pain. In humans, a functional GCH1 haplotype is linked both to chronic leg pain following lumbar disc surgery and coherently predicts experimental pain in controls. David Goldman returns to the functional NPY haplotype discussed by Zubieta. With the help of in vitro constructs, the responsible locus in the promoter is identified. The functional NPY diplotype is linked to in vivo mRNA and peptide levels, trait anxiety, fMRI responses to emotional challenge and brain opioid responses (assessed vis PET) following the Zubieta Pain/stress challenge. Functional genetic variants are likely to alter the nature of these responses. Unique Data: Zubieta: 1) NPY and MAOA account for variance in PET-accessed variance in placebo responses. Diatchenko: 2) COMT SNPs epistatically alter mRNA structure and translatability. 3) High expression COMT haplotypes link to low pain threshold. Max: 4) Neurotomy induces a massive increase in DRG biopterin and GCH1 mRNA. 5) Pain is blocked by a specific GCH1 inhibitor. 6) Functional human GCH1 haplotype is linked to chronic clinical pain and experimental pain. Goldman: 7) A functional NPY haplotype alters in vivo NPY mRNA and peptide levels. 8) Identification of a functional NPY promoter SNP. 9) Linkage of reduction-of-function NPY haplotype to anxiety, amygdale emotional fMRI and amygdala opioid response to experimental pain.

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

72. Bugs and Your Brain: Consequences and Cures

Jean Harry, Fulton Crews, James Joseph, Nigel Greig, Susanna Rosi

Endotoxins, including lipopolysaccharide (LPS), are bacterial agents that induce systemic and CNS cytokine and inflammatory enzymes causing behavioral alterations and neurodegeneration, particularly sickness behavior, anxiety, and cognitive impairments. The aged brain appears particularly vulnerable to endotoxins. Covering several animal models, this session will examine the negative effects of systemic and

central endotoxin exposure as well as possible therapeutic interventions. J. Harry will chair and provide insight. F. T. Crews will describe how systemic endotoxins induce systemic and brain cytokines and oxidative enzymes, such as NADPHoxidase, COX2 and iNOS. Studies show long-term induction in brain following transient systemic responses. J. Joseph will discuss how age and diet alters endotoxins and oxidative stress. N. Greig will describe novel agents designed to minimize neuroinflammatory response to endotoxins. Using a model of chronic neuroinflammation induced by ventricular infusion of LPS, S. Rosi will describe how these novel agents can restore normal neuron-glia communication disrupted by endotoxin.

Workshop• Thursday 8:30–10:00 PM • Ballroom 1

73. U.S. Patent Reform: Is It Good/Bad for Scientists/Companies/Economy?

Phuong Pham, James Fox, Joseph Belanoff

The passage of the Stevenson-Wydler Act of 1980 which was expanded by the Federal Technology Transfer (TT) Act in 1986 and was further extended in 1995 and 2000 establishing incentives for investigators, expediting Cooperative Research and Development Agreements' negotiation, and allowing licensing of preexisting inventions. Since then researchers have been actively working with corporate partners who have been successful in commercializing research into profitable products. Over the years, there have been hundreds of thousands of licensing agreements executed on federal and university based technologies. For example, the NIH licenses generate product sales over $3 billion annually. Sometimes, commercialization and TT are best accomplished without patent protection. At times, technologies or know-how may be most appropriately transferred to the private sector through publication. For some technologies, patenting and licensing are costly, unnecessary, and could hinder dissemination and application of the technology. However, other technologies that have significant time and cost associated with their development, such as those with medical diagnostic and therapeutics or other high-tech resource intensive technologies may require patent protection for corporate product development. It is in these cases, that confidentiality, record keeping, and having a clear developmental strategy are crucial. Recent Supreme Court rulings, legislative proposals on patent reform and USPTO rule changes have combined to create what amounts to a perfect storm for scientists whose goal is to license yet protect their innovations. This workshop is designed to give an overview of TT, its recent changes and associated benefits/drawbacks for researchers derived from these changes.

Panel • Thursday 8:30–10:00 PM • Magpie

74. Distinguishing the Immature from the Mature Brain: Response to Drugs and Injury

Christopher Turner, Slobodan Todorovic, Vesna Jevtovic-Todorovic

Widespread, age-dependent, apoptotic injury is observed in the immature but not the mature brain in rodents and primates after exposure to a diversity of agents that include ethanol, MK801, ketamine, isoflurane and nitrous oxide. Injury is associated with activation of the pro-apoptotic enzyme caspase-3, followed later by DNA damage and nuclear condensation. In the rodent brain, such apoptotic injury peaks at postnatal day 7 (P7) and diminishes rapidly thereafter. We examine the question of why the environment of the P7 brain is so conducive to apoptotic injury compared to the adult brain. Dr Christopher Turner will begin with a brief summary of the findings from many labs regarding neonatal sensitivity to the above agents. He will then describe in greater detail the neurotoxic effects of the NMDA receptor antagonist MK801 in P7 animals. An age-dependent inability to adjust to loss of calcium in MK801-sensitive neurons may explain at least some of damage observed. Next, Dr Slobodan Todorovic will describe new findings in his lab that neonatal exposure to anesthetics leads to lasting changes in synaptic transmission in the thalamus. Finally, Dr Vesna Jevtovic-Todorovic will explain how exposure to a combination of agents can promote far greater injury compared to that found after single agent exposure and will finish the session by exploring the clinical implications of these presentations. Given that many of these agents are currently used as anesthetics in neonatology, or that similar agents are used as drugs of abuse during pregnancy, the clinical importance of the question we ask seems very clear.

Panel • Thursday 8:30–10:00 PM • Maybird

75. Your Aging Brain: The Monkey on Your Back

Mary Ann Ottinger, Peter Rapp, Steven Kohama, Donald Ingram, Don Gash

Emerging research continues to support the value of the rhesus monkey as a model of brain aging. Remarkable parallels exist between humans and rhesus monkeys on age-related changes in brain structure and function, neuroendocrine and neuropeptide production, neurotransmitter action, and behavioral performance. This panel will provide an overview of current research from several laboratories utilizing this valuable long-lived species. M.A. Ottinger will chair and provide insight about the

value of the models. P. Rapp will review the current status of research on the neuropsychological consequences of aging in monkeys, and emerging data on interventions that modulate neurocognitive outcomes. S. Kohama will discuss steroid effects on the brain, covering topics from gene expression to imaging to behavior. D. Ingram will review data on brain and behavioral aging from a longitudinal study of rhesus monkeys evaluating the effects of a low calorie diet. D. Gash will focus on studies of age-related changes in mitochondrial function in the nigrostriatal dopamine system of rhesus monkeys and their relationship to behavioral dysfunction.

Panel • Thursday 8:30–10:00 PM • Wasatch

76. Translational Research in Stimulant Dependence

Thomas Newton, Ron See, Edythe London

Translational research is designed to forge bidirectional links between preclinical and clinical research so that each level can inform the other, thus facilitating mechanistically informed treatment development. This intent is more often honored in the breech, however. This panel is intended to illustrate successes and pitfalls encountered in translational research in methamphetamine (MA) dependence. Three research programs will be addressed. Bupropion has been shown to reduce subjective effects of MA and has been shown to help some MA dependent patients reduce MA use, though there are minimal supportive preclinical data (Newton). By contrast, aripiprazole is a partial D2R agonist which blocks some effects of amphetamine in rodent and human preclinical models but which recently was found not to beneficially alter effects of MA in dependent volunteers (See and Newton). Modafinil is a cognitive enhancing medication hypothesized to improve inhibitory control over drug-taking behavior, though preclinical or human self-administration or efficacy data are still lacking (London).

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

77. Human Embryonic Stem Cells, from Pluripotency to Neuroregeneration

Catherine Schwartz, Martin Pera, Mahendra Rao, Xiamin Zeng

The use of human embryonic stem (ES) cells as a possible cell source generates great enthusiasm for potential treatment of neurodegenerative disorders. However, the promise of human ES cells relies on the ability

to expand pluripotent stem cells without compromise and to precisely direct stem cells along a desired lineage. Successful translation towards neurodegenerative disease treatment will require a better understanding of the mechanisms controlling human ES cell self-renewal, proliferation, neural lineage commitment, and neuronal sub-type specification. In this panel we will discuss the generation of neural and neuronal committed cells derived from pluripotent stem cells and their potential application to neurodegenerative disorders. Catherine Schwartz will provide an overview of pluripotent stem cells and the current methods of deriving populations of neural stem cells and sub-type specific neurons. Martin Pera will discuss recent advancements in the maintenance of embryonic stem cell pluripotency and the mechanisms responsible for commitment towards the neural lineage. He will focus on recent data concerning immunotranscriptional profiling of human ES cells at very early stages of differentiation and their relevance in neural differentiation. Mahendra Rao will discuss transcriptional regulation and genomic expression profiles of human ES cells and human ES cell derived neural stem cells. He will discuss the challenges pertaining to defining and deriving appropriate neural cell types for cell replacement therapy. Xianmin Zeng will discuss the generation and use of reporter human ES cell lines to examine dopaminergic neuron development in-vitro. She will also discuss the application of reporter cell lines to control and monitor dopaminergic differentiation and their potential application towards transplantation paradigms in Parkinson's diseases models. Overall, these presentations will provide insight into the mechanisms controlling neural differentiation of stem cells and its significance to neuroregenerative medicine.

Panel • Thursday 8:30–10:00 PM • Superior B

78. Skin Biopsies for Diagnosis of Polyneuropathy; Beyond Neurite Counts

William Kennedy , Anne Louise Oaklander, Anne Bertelsen, George Wilcox

Among polyneuropathies of known etiology, diabetic neuropathy is most common. Although the role of the immune system in somatic pain is well accepted, its role in neuropathic pain has been largely ignored until recently. The myelinated component of diabetic neuropathy, which dominated neurology for decades, has recently been supplanted by quantification of epidermal nerve fibers (ENFs) in skin biopsies. Recent clinical trials, however, including those examining rhNGF for diabetic neuropathy and enzyme replacement for Fabry disease, have failed to show that otherwise effective treatment increased neurite counts in skin

biopsies. Perhaps, late-stage neurite loss is an irreversible sign of neuropathy and other, earlier immune markers exist. This panel will explore possibilities for those early markers. Dr. Kennedy will describe alternative diagnostic techniques, such as immunohistochemical characterization of skin blister and colorectal biopsies, relate findings to somatic and autonomic neuropathies, and discuss the utility of such techniques for identifying the mechanisms of neuropathic pain. Dr. Oaklander will discuss changes seen in distal-leg skin biopsies from patients with polyneuropathy symptoms who have elevated neurite counts, which are statistically as abnormal as the low counts currently used to define small-fiber polyneuropathy. Dr. Bertelsen will put epidermal and dermal nerve fibers in context with immune cells and explore how immunocytes might contribute to neuropathic pain. Dr. Wilcox will introduce and moderate the session, encouraging active participation of the audience.

Panel • Friday 7:30–9:30 AM • Ballroom 1

79. Synaptic Plasticity: The Short and Long of It

William Catterall, Ling-Gang Wu, Alexandra Few, Roger Nicoll, Rob Malenka

Modification of the strength of synaptic transmission based on activity is a fundamental mechanism underlying learning and memory in the brain and many aspects of physiological regulation in peripheral tissues. Calcium ions entering neurons during electrical activity initiate intracellular regulatory processes that modify the function of neurotransmitter receptors and ion channels, which are responsible for the initial changes in synaptic strength. Slower processes are also engaged that change localization of receptors and ion channels, regulate gene expression, and alter protein processing. This symposium will focus on the temporal continuum of synaptic plasticity from short-term facilitation and depression measured in milliseconds to long-term potentiation that lasts hours and days. Catterall will give a brief introduction to the topic. Wu will describe mechanisms underlying short-term depression, including depletion of the readily releasable pool, presynaptic calcium channel inactivation, and action potential failure, at the large nerve terminal of the calyx of Held. Few will present her work showing that synaptic facilitation and depression at a model synapse transfected with wild-type and mutant Cav2.1 channels are caused by facilitation and inactivation of presynaptic P/Q-type calcium currents by calmodulin-like calcium sensor proteins. Nicoll will introduce long-term potentiation

and present his work on the role of TARPs in regulating the function of postsynaptic glutamate receptors during long-term potentiation in the hippocampus. Malenka will describe long-term depression processes at synapses in the striatum that are involved in novel aspects of learning, memory, motor control, and addiction.

Panel • Friday 7:30–9:30 AM • Magpie

80. Exercise Enhanced Neuroplasticity in Parkinson's Disesae and Its Animal Models

Michael Jakowee, Giselle Petzinger, Charles Meshul, Richard Smeyne, Beth Fisher

Anecdotal evidence indicates that patients with Parkinson's disease who engage in intensive exercise show symptomatic benefit. Epidemiological reports suggest exercise may in fact provide neuroprotection. Studies in animals are beginning to provide insights into the underlying mechanisms. This panel will review recent findings generated by these investigators on changes that take place in the CNS in both animal models and in patients with PD. Dr. Petzinger will discuss findings from the MPTP-lesioned mouse model subjected to intensive exercise showing that return of motor behavior correlates with enhanced striatal dopamine release indicated by electrophysiological analysis and altered glutamate receptor expression and function. Dr. Meshul will discuss studies in the 6-OHDA lesioned rat model showing changes in dopamine handling and altered glutamatergic neurotransmission. Dr. Smeyne will discuss how angiogenesis is influenced by exercise in rodent models and this may provide a mechanism for neurotoxicant protection. Dr. Fisher will present data from patients with PD undergoing treadmill exercise showing altered cortical excitability using transcranial magnetic stimulation as well as altered biokinematic parameters. Both Drs. Petzinger and Fisher will present studies in rodent models and patients with PD as to how PET-imaging is being used to document CNS changes. This presentation is designed to highlight new insights into how intensive exercise influences dopaminergic function in the basal ganglia and how non-dopaminergic neurotransmitter systems participate in behavioral recovery. These novel molecular mechanisms may provide a novel therapeutic target for the treatment of PD and neurodegenerative disorders and in fact may alter disease progression in patients.

Panel • Friday 7:30–9:30 AM • Maybird

81. New Ideas about Synaptic Integration in the Retina

Stewart Bloomfield, Joshua Singer, Jeffrey Diamond, Robert Miller

The vertebrate retina has served for many years as a model system for studying synaptic interactions in the CNS. The retina offers several advances over other CNS loci in that it is a relatively simple and accessible portion of the brain that can be isolated, yet still stimulated physiologically with light. This panel will detail recent advances in our understanding of how cellular conductances modulate the responses of individual retinal neurons and the impact on the integration and propagation of visual signals. Stewart Bloomfield will discuss how light modifies the conductance of gap junctions in the retina and their role in encoding visual signals sent to the brain. He will talk about how single gap junctions can perform the dual function of relaying and synchronizing visual information. Josh Singer will discuss how synaptic conductances interact with intrinsic ion conductances in AII amacrine cells to affect transmission of rod-mediated signals. Jeff Diamond will talk about excitatory synaptic inputs to ganglion cells, NMDA receptor activation, and differences between the ON and OFF retinal pathways. He will focus on the contribution of NR2B receptors in these pathways and its modulation by network activation of glycine binding sites on NMDA receptors. Bob Miller will discuss the functional role of D-serine in retina, which is believed to be an essential coagonist of glutamate at NMDA receptors throughout the CNS. He will discuss how endogenous D-serine limits NMDA-gated synaptic currents in retinal ganglion cells.

Panel • Friday 7:30–9:30 AM • Wasatch

82. ADHD: Rare and Common Gene Variants in Risk and Treatment Response

Harriet de Wit, Randy Blakely, Aurelio Galli, Kwang-Soo Kim

Attention-Deficit Hyperactivity Disorder (ADHD) is a common disorder of childhood featuring hyperactive/impulsive and inattentive traits. Recent studies by the panel members target genes that inactivate catecholamines and that are targets for psychostimulant medications to identify determinants of disease risk and treatment response. The session will be chaired by Dr. Randy D. Blakely, Ph.D. Director of the Center for Molecular Neuroscience at Vanderbilt. Speaker 1: Harriet de Wit, University of Chicago, will discuss her studies of genetic deter-

minants of methylphenidate and amphetamine response. Speaker 2: Randy D. Blakely, Ph.D., Vanderbilt University School of Medicine will discuss his recent efforts to apply high-throughput screening methods to uncover functional variants in norepinephrine and dopamine transporter proteins in ADHD probands. Speaker 3: Aurelio Gali, Ph.D., Vanderbilt University School of Medicine will discuss his patch-clamp and amperometry studies that reveal striking properties of ADHD-associated variants in the dopamine transporter. Speaker 4: Kwang-Soo Kim, Ph.D., McLean Hopital, Harvard, will describe his labs discovery of common norepinephrine transporter promoter variants, their impact of transporter gene transcrption and evidence of association and transmission in ADHD.

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

83. What Are the Roles of Trace Amine-Associated Receptor 1 in Primates?

Jerry Frankenheim, Theresa Branchek, David Grandy, Thomas Scanlan, Gregory Miller

Trace amine-associated receptor 1 (TAAR1) is a recently discovered, cloned, G protein-coupled receptor found in primate brain regions associated with monoaminergic systems. TAAR1 has a broad spectrum of agonists, including endogenous monoamines, amphetamines, trace amines (octopamine, tyramine, etc), and thyronamines (endogenous derivatives of thyroid hormone). This panel will focus on the putative roles, in primates, of this unusual receptor, and on how TAAR1 functions. Theresa Branchek will describe the discovery of the receptor, its potential importance based on trace amines in neuropsychiatric disorders, and possible roles of TAAR1 in these disorders. David Grandy will focus on TAAR1 species divergence, TAAR1 pharmacology and physiology, and the development of novel therapeutics that target TAAR1, including potential anti-methamphetamine medications. Thomas Scanlan will discuss the chemistry and biological activity of 3-iodothyronamine, a newly discovered thyroid hormone metabolite and potent agonist of TAAR1, with a focus on its role in complementing thyroid hormone action. Gregory Miller will discuss TAAR1 localization in the monoamine system and the role of TAAR1 in modulating monoamine transporter kinetics; TAAR1 as a receptor for dopamine, norepinephrine, and serotonin; the bi-directional regulation of monoamine transporters by TAAR1 and monoamine autoreceptors in synaptosomes; mechanisms by which TAAR1 mediates methamphetamine effects; and polymorphisms in the TAAR1 locus in primates and humans.

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

84. Functional Organization of Axons

Bettina Winckler, Matthew Rasband, Edward Cooper, Elior Peles

The generation, propagation, and modulation of action potentials in axons depends on the high density clustering of ion channels at specific subcellular domains. For example, voltage-gated Na+ and K+ channels are clustered in high densities at axon initial segments and nodes of Ranvier in myelinated axons. Furthermore, the establishment of these ion channel clusters requires cellular and molecular mechanisms to facilitate the development of polarized membrane domains in neurons. This panel will bring together four experts who have elucidated some of the neurobiological mechanisms that regulate neuronal polarity and the subcellular clustering of ion channels in axons. A necessary pre-requisite for ion channel clustering in axons is the appropriate delivery of membrane proteins to axons. Dr. Bettina Winckler will speak on the mechanisms that underlie targeting of proteins to axons and dendrites and will focus on NgCAM as model protein. Dr. Rasband will speak on the intrinsic neuronal mechanisms, emphasizing cytoskeletal and scaffolding proteins, that regulate molecular assembly of the axon initial segment, the site where action potentials are initiated. Dr. Ed Cooper will speak on the molecular mechanisms underlying recruitment and localization of KCNQ2/3 K+ channels to nodes of Ranvier and axon initial segments. Finally, Dr. Elior Peles will speak on the neuron-glia interactions that regulate the clustering of Na+ channels at nodes of Ranvie in myelinated axons.

Panel • Friday 4:30–6:30 PM • Ballroom 1

85. Impact of the Serotonin Transporter Genotype on Cognition and Affect in Mice, Monkeys, and Humans

Charles Bradberry, Andrew Holmes, Elizabeth Murray, Hank Jedema, David Goldman

Common genetic variants of the serotonin transporter linked polymorphic region (5HTTLPR) that alter transcriptional efficiency in vitro have repeatedly been implicated in affective and addictive disorders. However, impact of genetic variations in 5-HTT on emotional/cognitive functionality dependent on interactions between prefrontal cortex and basolateral amygdala is unknown. The following panel will present novel data exploring this area:

Andrew Holmes will present studies of how knockout of the SERT gene in mice alters cognitive flexibility via various measures of operant learning. The strength of this presentation lies in the unambiguous alteration of SERT function. Though the clinically significant allelic variants alter transcriptional efficiency in vitro, their effects in-vivo are unclear.

Betsy Murray will show that the monkey 5-HTTLPR orthologs (equivalent to the human) impact cognition in Rhesus Macaques, using behavioral tasks to assess cognitive flexibility, reward processing, and emotion. Specifically, she will demonstrate that monkeys homozygous for the Short allele show significantly reduced cognitive flexibility as measured by object discrimination reversal learning and instrumental extinction, as well as heightened socio-emotional reactivity.

Hank Jedema will present data from recent work with Rhesus Macaques demonstrating 5-HTTLPR linked differences in learning, response inhibition, and cognitive flexibility. He will also show high resolution PET imaging data of 5HTT in the same animals suggesting that the associations of 5HTTLPR with cognitive tasks are likely not a result of 5HTT differences in adulthood.

Panel • Friday 4:30–6:30 PM • Magpie

86. Beyond Reinforcement: Neurobehavioral "Systems" that Promote Addiction and Eating Disorders

Jeffrey Grimm, Hans Crombag, Sara Ward, Mary Olmstead

Preclinical research on addiction and eating disorders has focused largely on understanding the primary reinforcing properties of food or drugs. It is increasingly clear, however, that both disorders involve disruptions in many behavioral processes, and that these may have distinct pharmacological underpinnings. Such processes could work synergistically, or even competitively, to increase the susceptibility to pathological eating or drug use. This panel will present research from animal studies that focus on cue conditioning, motivation, and impulsivity as determinants of operant responding for food or drugs, and identify neuropharmacological mechanisms associated with each. Grimm will describe how time-dependent increases in responding for a sucrose-paired cue ("incubation of craving") are affected by dopamine and opiate antagonists, and by contextual habituation. Crombag will illustrate how Pavlovian cues exert dissociable effects on food-directed behaviors and that these effects are mediated by selective molecular events including phosphorylation of the GluR1 receptor. Ward will discuss motivational processes by

describing studies using the progressive ratio schedule: these reveal the importance of GABA, serotonin, and opioid systems in the motivation to self-administer cocaine and of cannabinoid receptors in the motivation to self-administer sweet and sweet/fat solutions. Olmstead will reveal a role for the opioid system in impulse control with evidence that deletion of mu opioid receptors decreases impulsive responding for a sucrose reward. This panel provides a framework for understanding how different behavioral and pharmacological processes contribute to the development of addiction and eating disorders. This "systems" approach may lead to more effective treatment strategies for both disorders.

Panel • Friday 4:30–6:30 PM • Maybird

87. How Does the Adolescent Brain Become an Adult when Dr. Dopamine and Her Limbic Colleagues Are Not Around?

Janet Finlay, Gregorio Galiñanes, Andrew Chambers, Kuei Yuan Tseng

Understanding the influence of mesocorticolimbic structures on development of cortico-subcortical interactions is an important step in unveiling the neural mechanisms underlying acquisition of mature cognitive abilities and cognitive abnormalities in psychiatric illnesses such as schizophrenia and attention deficit hyperactivity disorder (ADHD). First, Janet Finlay will summarize how an early partial loss of mesoprefrontal dopamine terminals sustained during infancy can result in persistent alterations in behavior and neurochemical activity of subcortical dopamine neurons in juvenile and adult rodents, despite the fact that residual cortical dopamine terminals appear to compensate for loss of neighboring nerve terminals. Using in vivo electrophysiological recordings, Gregorio Galiñanes will show how neonatal lesions of the nigrostriatal dopamine system influences the corticostriatal function during the peri-adolescent transition to adulthood and how these changes could be linked to ADHD. Next, Andy Chambers will present evidence that neonatal disruption of the hippocampus combined with differential environmental experiences through adolescence, represents a robust model-paradigm for exploring brain processes that underlie adolescent neurodevelopment and its contribution to adult-age psychiatric and addiction-related syndromes. Finally, Kuei Tseng will provide evidence of several synaptic, cellular, and subcellular mechanisms by

which mesocortical dopamine could regulate prefrontal cortex plasticity and shape its functional outcome during the transition to adulthood. We will conclude by proposing a common mechanism that couples the role of the mesocorticolimbic monoaminergic systems in the regulation of mature cortico-subcortical functioning and its link to different developmentally-regulated psychiatric phenotypes.

Panel • Friday 4:30–6:30 PM • Wasatch

88. Factors Affecting Impact of Early Stage Brain Damage

Bill Greenough, Donald Stein, Timothy Schallert, Michelle LaPlaca, David Hovda

Basic neuroscience and clinical ramifications are rapidly converging in the area of recovery from brain damage. This panel updates several leading areas, all of which stress importance of intervention soon after injury. Don Stein will address therapeutic effects of steroid hormone treatment and its time-efficacy dependence. Tim Schallert will highlight new fine-motor assessment methods and research indicating that physical training targeting nigrostriatal dopamine dependent functional deficits may promote neural protection or brain repair and enhance behavioral outcome, whereas motor impoverishment can be pro-degenerative, in rat models of early stages of Parkinson's disease. Michelle LaPlaca will discuss a novel neuropsychological assessment tool: Display Enhanced Testing for Cognitive Impairment and Traumatic Brain Injury (DETECT), a novel device developed to measure subtle changes in cognitive impairment. DETECT provides an additional objective assessment for early detection and treatment and can identify patients with MCI and possibly other cognitive impairment, in which subtle deficits were previously difficult to assess in a shortened, objective manner. David A. Hovda will discuss traumatically-induced developmental disability, in which mild traumatic brain injury early in life in the rat triggers multiple neurochemical and neurometabolic cascades in cells that are not bimechanically and irreversibility injured, rendering them temporarily dysfunctional and unresponsive to demands for plasticity for up to 2 weeks. The primary mechanisms appear to be related to a fundamental change in receptor subunit characteristics which prohibit appropriate synaptic activation preventing the normal plastic response.

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

89. Kainate Receptors: New Vistas for Cortical Function

Graham Collingridge, Karen Wilcox, Roland Jones, Mark Cunningham

The physiological function of kainate receptors (KARs) in the medial entorhinal cortex (mEC) is a matter of some conjecture. This is due, in part to a paucity of selective pharmacological tools currently available. Despite this fact, recent work has begun to shed light on the functional significance of this ionotropic glutamate receptor sub-type in the mEC. The aim of this symposium will be to present work from the presynaptic, post-synaptic and network level in order to form a coherent framework of the role of KARs in cortical function and dysfunction. Graham Collingridge will begin this panel session with an overview of the current status of selective KAR agonists and antagonists. Karen Wilcox will describe the relative contributions of postsynaptic KAR's to excitatory neurotransmission in a number of principal cell types in the superficial layers of the mEC. Roland Jones will follow this, describing recent work from his laboratory, detailing the role of presynaptic KAR's in the mEC. Finally, Mark Cunningham will talk about the role of KAR's in certain types of network oscillation activity in the mEC. In particular, he will show data illustrating the ability of KAR activation to contribute to mEC network dynamics. This panel presentation will discuss KARs in the context of learning, memory and epilepsy in a brain region known to be critically involved in the afore mentioned processes.

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

90. Skiing the Bowl: Post-Structural Insights into Glutamate Transporter Mechanism

Christof Grewer, Peter Larsson, Joseph Mindell, Richard Bridges

Glutamate transporters of the EAAT family are critical elements of the synaptic machinery, clearing released glutamate from the synapse to prepare for future signals. These transporters have been suggested to play roles in a range of diseases, in which glutamate homeostasis may be disrupted. Understanding the mechanisms of these transporters is of great importance; a recent xray crystal structure of a bacterial glutamate transporter homolog, GltPH, has sparked a revolution in understanding of this family. By revealing the basic molecular architecture of these proteins, the structure has provided a framework for understanding

existing functional data on the EAATs and has guided new experimental approaches. This session will focus on such insights. Christof Grewer will discuss his work using pre-steady state kinetics to probe EAAT function. Peter Larsson will present his studies using fluorescent indicators to probe conformational changes in EAATs. Joe Mindell will present his work establishing the bacterial aspartate transporter GltPH as a functional model for the EAAT chloride permeability. Finally, Rich Bridges will discuss the the structure activity relationships that may differentiate substrates from non-substrate inhibitors, and how they may be differentially interacting with the EAATs. Since the boundaries between these sets of molecules differ among EAAT subtypes they yield insight into subtype-specific substrate-transporter interactions.

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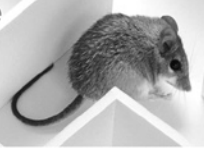

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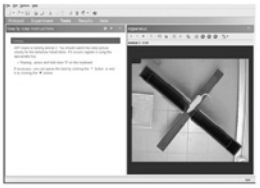

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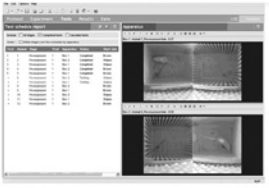

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Poster Abstracts

Poster Session 1

Sunday–Monday • Ballroom 2 & 3

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

P1. CP-809,101: A Potentially Novel Antipsychotic

Philip A. Iredale, Judith A. Siuciak, Douglas S. Chapin, Sheryl A. McCarthy, Victor Guanowsky, Janice Brown, Phoebe Chiang, Ravi Marala, Terrell Patterson, Patricia A. Seymour, Andrew Swick

CP-809,101 is a potent, functionally selective 5-HT2C agonist that displays approximately 100% efficacy in vitro. The aim of the present studies was to assess the efficacy of a selective 5-HT2C agonist in animal models predictive of antipsychotic-like efficacy and side-effect liability. Similar to currently available antipsychotic drugs, CP-809,101, dose-dependently inhibited conditioned avoidance responding (CAR, ED50 = 4.8 mg/kg, sc). The efficacy of CP-809,101 in CAR was completely antagonized by the concurrent administration of the 5-HT2C receptor antagonist, SB-224,282. CP-809,101 antagonized both PCP- and d-amphetamine-induced hyperactivity with ED50 values of 2.4 and 2.9 mg/kg (sc), respectively and also reversed an apomorphine induced-deficit in prepulse inhibition. At doses up to 56 mg/kg, CP-809,101 did not produce catalepsy. Thus, the present results demonstrate that the 5-HT2C agonist, CP-809,101, has a pharmacological profile similar to that of the atypical antipsychotics with low extrapyramidal symptom liability. CP-809,101 was inactive in two animal models of antidepressant-like activity, the forced swim test and learned helplessness. However, CP-809,101 was active in novel object recognition, an animal model of cognitive function. These data suggest that 5-HT2C agonists may be a novel approach in the treatment of psychosis as well as for the improvement of cognitive dysfunction associated with schizophrenia.

P2. Modulation of Dopamine-Dependent Protein Phosphorylation Provides a Novel Approach to Antipsychotic Drug Discovery

Gretchen L Snyder

ITI-007, a novel antipsychotic candidate with high potency and a reduced side effect profile, is currently in Phase 1 clinical trials. CNSProfileTM, a technology platform developed at ITI to monitor multi-site protein phosphorylation changes, revealed that antipsychotic drugs increase phosphorylation at S40, a regulatory site on tyrosine hydroxylase, proportional to their propensity to block D2 receptors and elicit extrapyramidal motor syndrome (EPS). Potent dopamine (DA) D2 receptor antagonists (haloperidol) elicit large increases in S40 phosphorylation; agents with low affinity for D2 receptors (clozapine) or partial D2 agonist properties (aripiprazole) elicit small changes in S40. ITI-007 elicits no change in S40 phosphorylation at behaviorally-effective doses, consistent with its pharmacological profile as a partial agonist at presynaptic D2 receptors, and indicating low liability for EPS. This was confirmed by measures of mouse striatal DA metabolism. Effects on striatal metabolism displayed an excellent correlation with S40 levels. Chronic haloperidol (21d) increased the major striatal DA metabolite, 3, 4-dihydroxyphenylacetic acid (DOPAC), relative to DA, by several-fold whereas aripiprazole elicited a significantly smaller (~2-fold) increase in DOPAC/DA. Notably, ITI-007 had no significant effect on DOPAC/DA at concentrations 10-fold the anticipated therapeutic dose. Thus, S40 phosphorylation, measured in CNSProfileTM, predicted adverse disruption of DA metabolism by antipsychotic medications. ITI-007 elicited minimal disruption of DA metabolism, consistent with a partial D2 agonist profile. (Supported in part by DAMD-17-03-2-0396 and R43 MH067488-01).

P3. Genetic Analysis of Whisker Barrels in SI in Recombinant Inbred Strains of Mice

Robert S. Waters, Taha A. Jan, Lu Lu, Cheng-Xiang Li, Robert W. Williams

Quantitative trait locus (QTL) mapping is an important tool for identifying potential candidate genes linked to complex traits. QTL mapping has been used to identify genes associated with cytoarchitecture, cell number, brain size, and brain volume. Previously, QTL mapping was utilized to examine variation of barrel field size in the somatosensory cortex in a limited number of recombinant inbred (RI) strains of mice. In order to further elucidate the underlying natural variation in mouse primary somatosensory cortex, we measured the size of the posterior

medial barrel subfield (PMBSF), associated with the representation of the large mystacial whiskers, in an expanded sample set that included 42 BXD RI strains, two parental strains (C57BL/6J and DBA/2J), and one F1 strain (B6D2F1). Cytochrome oxidase labeling was used to visualize barrels within the PMBSF. We observed a 33% difference between the largest and smallest BXD RI strains with continuous variation in-between. Using QTL linkage analysis from WebQTL, we generated linkage maps of raw total PMBSF and adjusted total PMBSF areas. After removing the effects of brain weight, we detected a suggestive QTL (likelihood ratio statistic [LRS]: 14.20) on the proximal arm of chromosome 4. Candidate genes under the suggestive QTL peak for PMBSF area were selected based on the number of single nucleotide polymorphisms (SNPs) present and the biological relevance of each gene. Among the candidate genes are Car8 and Rab2. The present study is an important step towards identifying genes underlying the size and possible development of cortical structures.

P4. Rapid Structural Plasticity of Astrocytes during Osmotic and Ischemic Stress in Cortical Brain Slices

Sergei A. Kirov, W. C. Risher, R. D. Andrew

The development of two-photon laser scanning microscopy (2PLSM) and of transgenic mouse strains with intrinsic fluorescent neurons and glia enables real-time imaging of these cells during the physiological and pathological conditions. Using 2PLSM we showed that pyramidal somata and dendrites steadfastly maintain their volume during osmotic stress, as do cerebellar axon terminals (Andrew et al., 2007). Here we use similar techniques to monitor changes in astrocytic volume to 20 min of overhydration (-40 mOsm) or dehydration (+40 or +80 mOsm) in cortical slices. Astrocytes reversibly swelled during overhydration and shrank during dehydration. These same astrocytes also rapidly swell upon exposure to ischemic (O2/glucose deprivation (OGD), 10 min) conditions. Adjacent pyramidal neurons also swell as water enters through open Na+ (and possibly other) channels. We then imaged these slices during recovery from OGD. Within 20 min, astrocytic volume recovered by 80-100%. Such recovery was not detected in adjacent pyramidal neurons which remained swollen with beaded dendrites post-OGD. Therefore in contrast to pyramidal neurons where functional aquaporins have not been reported, adjacent astrocytes are clearly volume responsive to acute osmotic stress. Simulated ischemia induces an immediate and dramatic swelling of astrocytes upon onset of anoxic depolarization. Astrocytes then display significant recovery from OGD, possibly the

result of water loss via functional aquaporins. In contrast, adjacent pyramidal neurons may stay swollen because of the low water permeability of their plasma membrane. Supported by the NIH NS057113 (SAK) and the HSFO T-4478 (RDA) and the CIHR MOP-69044 (RDA).

P5. Buprenorphine/Naloxone Treatment for Opioid Dependent Adolescents/Young Adults

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The usual treatment for opioid addicted adolescents/young adults is detoxification and counseling. Buprenorphine may be useful compared to methadone as it produces less physical dependence, has a higher margin of safety, and can be administered in primary care. This study was done at 6 programs in the NIDA Clinical Trials Network; subjects were 14–21 and opioid dependent. Excluded were those with serious medical or psychiatric disorders, pregnant, unable to provide benzodiazepine negative urine, or recently overdosed on sedatives. Subjects were randomized to 12-weeks of buprenorphine/naloxone (Bup/Nal) with a taper during weeks 9–12, or a 7–14 day bup/nal detoxification (Detox), each with individual and group counseling. Primary outcome was opioid positive urine tests at weeks 4, 8 and 12. Results: 229 subjects consented and 152 were randomized. Average age was 19; 27 were under 18; 42% female, 25% Hispanic, 2% African-American, 58% Caucasian; average years addicted was 2. Primary drug was heroin (55%), prescription opiates (35%), and polydrug (10%). 19% were hepatitis C+ at baseline and 4 became positive by week 12. Bup/Nal had fewer opioid positive urines than Detox. ($p<.0001$) and better retention. Need for additional treatment occurred in both groups following dose taper. Headaches occurred in 20–23%; other AEs were reported in less than 10%. Bup/Nal was safe and resulted in significantly fewer opioid positive urines and better retention than Detox. Many subjects needed additional treatment following dose taper suggesting that longer-term use of bup/nal should be studied in these patients.

P6. Promiscuous Pharmacology Complicates Distinguishing Connexin Hemichannels from Volume Activated Anion Channels in Astrocytes

Zucheng Ye, Bruce R. Ransom

The study of ion channels has relied heavily on the use of pharmacological blocking agents, however, many of them have non-specific effects or cross-reactivities that limit their usefulness and/or complicate the

interpretation of experimental results. Such promiscuity or "cross talk" may particularly compromise the interpretation of results when the affected mechanisms/pathways serve parallel functions. Swelling activated anion channels and connexin hemichannels can both mediate the release of small molecules like glutamate and taurine. We have found that certain blockers presumed "specific" for each channel type actually block both channels indiscriminately. Prior work has shown that some anion channel blockers can inhibit some types of connexin hemichannels. We have expanded this evaluation to a broader range of anion channel blockers and have also tested classic gap junction/hemichannel blockers for their ability to block swelling-activated channels. Astrocyte hemichannels (mainly composed of Cx43) were opened with reduced divalent cation solution (RDCS) and detected by glutamate and taurine efflux. Swelling-activated anion channels were opened using hypotonic solution and detected by glutamate and taurine efflux. The classical anion channel blockers NPPB, IAA-94 and tamoxifen blocked RDCS-induced glutamate/taurine release, and also blocked RDCS-induced lucifer yellow loading (lucifer yellow permeates hemichannels but not swelling activated anion channels). While 18α-glycyrrhetinic acid (AGA) and heptanol had no effects on swelling-activated anion channels, carbenoxolone (CBX), the most widely used gap junction/hemichannel blocker, effectively blocked swelling induced glutamate/taurine release, and this effect did not depend on the presence of Cx43 (i.e., was present in astrocytes from Cx43 knock out animals).

P7. Inflammatory Mediators Produced by IFN-gamma Stimulated Murine Microglia Are Attenuated by Taurine Chloramine: Disruption of Signaling Pathways and Decreased Inflammatory Gene Expression

Michael R. Quinn, C. Wang, Y. Liu

Inflammation in the CNS contributes to the pathology of several neurological disorders, including autism, where activation of microglia is reported to be associated with increased production of IFN-gamma, NO via iNOS, TNF-alpha, IL-6 and MCP-1. Microglia are immunoresponsive to stimulation with IFN-gamma alone, i.e. unlike astrocytes, they do not require the presence of LPS or other extrinsically added factors. For these reasons, we examined the response of BV-2 cells, a murine derived microglial cell line, to IFN stimulation and investigated the effects of taurine chloramine (Tau-Cl). Tau-Cl is formed in vivo at the site of inflammation by interaction of taurine with HOCl, a product of halide-dependent myeloperoxidase. BV-2 cells stimulated with IFN-gamma

(100 U/ml) produced NO and PGE2 via iNOS and COX-2 gene expression, respectively. Tau-Cl dose-dependently inhibited iNOS and COX-2 protein and gene expression. Production of IL-6, MCP-1 and RANTES was also dose-dependently inhibited by Tau-Cl. Accumulation of TNF-alpha in the conditioned media of activated BV-2 cells was essential for production of NF-kB regulated inflammatory mediators, including iNOS. Tau-Cl attenuated TNF-alpha secretion thereby inhibiting its autocrine effects. In addition, Tau-Cl disrupted IFN-gamma stimulated JAK/Stat and p38 MAP kinase signaling pathways. Results suggest that Tau-Cl has potential as a modulator of microglial inflammatory responses. (Supported by New York State OMRDD and NIH NS40721).

P8. Evidence for the Involvement of Ephrins and Ephs in the Guidance of the Peripheral Somatosensory System

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

Peripheral processes of trigeminal ganglion cells display target-directed growth resulting in precise topographic innervation of the vibrissal pad. Several guidance molecules have been implicated in the development and maintenance of topographic connections within the somatosensory system including netrins, sematophorins, neurotrophins, and ephrins/Ephs. Our laboratory has shown that ephrins and Ephs may play a role in the guidance of thalamocortical fibers into S-I cortex. However, a role for ephrins and Ephs in peripheral somatosensory organization has yet to be identified. Using immunohistochemistry, we have identified differential expression patterns of multiple ephrin ligands and Eph receptors within the peripheral innervation territory of the trigeminal primary afferent axons. At embryonic day 15 (E15), we have detected the presence of ephrin-A2 and ephrin-A3 in the growing trigeminal nerve fibers. Furthermore, ephrin-A2 and EphA4 are prominent in the follicles of the vibrissal pad. In the trigeminal ganglion, immunoreactivity for ephrin-A2, ephrin-A3, and EphA7 was present at E15. A similar pattern in the vibrissal pads was detected at E17 and postnatal day 0 (P0). However, by P4 the ephrin and Eph expression was diminished in the trigeminal nerve fibers within the vibrissal pad and was absent within the trigeminal ganglia. Taken together, these results identify the presence of several ephrins and Ephs in the developing peripheral somatosensory system, the expression of which is differentially localized around the vibrissal follicles and is temporally regulated. This expression may indicate a role for ephrin-Eph interactions in establishing correct topographic connections within the peripheral somatosensory system.

P9. Abused Inhalants May Interfere with Learning by Disrupting Hippocampal Inhibitory Circuit Function

M. Bruce MacIver

Little is known about the intoxicating effects produced by abused inhalants on synaptic circuits in the CNS. The present study investigated GABA-mediated inhibitory synapses as possible drug targets for the inhalant, toluene. Whole cell patch clamp recordings from rat hippocampal CA1 neurons in brain slices were used to monitor cell excitability and synaptic responses. Toluene had no significant effect on resting membrane potential, resistance, action potential discharge threshold, or current evoked discharge activity of CA1 neurons (Wilcoxon test for at least five experiments each). At intoxicating concentrations of toluene, a significant increase in Schaffer-collateral evoked EPSP/IPSP combined synaptic responses was evident ($p < 0.005$). Similarly, monosynaptic inhibitory postsynaptic current (IPSC) amplitudes were significantly increased by toluene (14.8 ± 3.2 % above control; $p < 0.01$; $n = 10$). Spontaneous IPSC frequency increased in the presence toluene although mixed effects on amplitude were evident—either no change, or often an increase in amplitude was seen. Miniature IPSCs, recorded in the presence of TTX to block action potentials, also exhibited an increased frequency (218 ± 16 %; $p < 0.001$), and GABA-A-Slow IPSCs were more strongly effected than GABA-A-Fast responses. Effects at GABA nerve terminals appear to play a role in the intoxicating actions of abused inhalants, and selective effects on different subtypes of GABA-A synapse nerve terminals were evident.

P10. Interactions of the Dopamine D2 Receptor with the Calcium-Binding Protein S100B

Kim Neve, Yong Liu

S100B is a calcium-binding protein that participates in both extracellular and intracellular regulatory activities in the mammalian brain. Using a bacterial two-hybrid assay, we have identified a novel interaction between S100B and the third cytoplasmic loop of the dopamine D2 receptor (D2-IC3). The binding of S100B to D2-IC3 was confirmed using a polyHis pull-down assay. In addition, the binding of heterologous S100B to full-length D2 receptor in HEK293 cells, and of endogenous S100B to endogenous D2 receptor in the rat neostriatum, was demonstrated by co-immunoprecipitation. Sequence analysis suggests the presence of a putative S100B binding motif at the N-terminus of

D2-IC3. Although S100B is thought of as a glial protein, immunoreactivity for S100B was detected in microtubule-associated protein-2 (MAP2) expressing cells in neostriatal neuronal cultures. Expression of S100B in HEK293 cells that also stably express the D2 receptor significantly increased D2 receptor stimulation of extracellular signal-regulated kinases (ERKs), while causing little change in NGF-stimulated activation of ERKs. Taken together, these fundings suggest that binding of S100B to the D2 dopamine receptor enhances D2 receptor activation of ERKs. (MH045372 and VA Merit Review)

P11. Neuroprotective Effect of VPS41, a Protein Involved in Lysosomal Trafficking, in Mammalian Cellular Models of Parkinson's Disease

David G. Standaert, Q. Ruan, G. A. Caldwell, K. A. Caldwell

VPS41 is a protein which emerged as a therapeutic candidate for Parkinson's disease (PD) from a recent high-throughput RNAi screen in C. elegans. VPS41 has metal ion binding, microtubule binding, RING finger, and AP3 interaction domains, and in yeast is involved in lysozomal trafficking. To validate VPS41 as a target for PD therapy, we examined its protective effect in mammalian cellular models of PD. For that purpose, cDNA clones of human VPS41 (both isoforms) have been subcloned into the mammalian expression vector pcDNA 6/myc-His. cDNA constructs have been verified by automated sequencing and expressed in HEK 293 cells. These constructs lead to expression of tagged proteins of appropriate size. Stably cell lines have been established in SHSY5Y neuroblastoma cells after transfection with VPS41 constructs as well as vector control and subsequent subcloning. In these stably transfected lines, immunocytochemical studies were performed using antibodies to the myc tag. These demonstrated that both isoforms of VPS41 are predominantly cytoplasmic proteins, and partially co-localize with the endoplasmic reticulum marker protein PDI. Studies of the neuroprotective properties of VPS41 were conducted in these stably transfected lines, using as both the broad-spectrum kinase inhibitor staurosporine as well as the PD-related neurotoxin, rotenone. We found that the presence of the VPS41 in our cell lines reduces the sensitivity of these lines to both toxins. These data suggest that VPS41 does indeed have neuroprotective properties in mammalian cells as well as in C. elegans, and that it is a promising target for the development of neuroprotective therapies. Supported by a Michael J. Fox Foundation Target Validation 2007 award.

P12. Role of Neuronal Pentraxin 1 in the Intrinsic Program of Apoptotic Neuronal Death

Ramon Trullas, Marta Enguita, Maria Alba Abad

In previous studies we have shown that Neuronal Pentraxin 1 (NP1) is part of the intrinsic program of apoptotic neuronal death and that overexpression of NP1 contributes to the neuronal damage evoked by reduction of neuronal activity. We have now investigated the mechanisms by which NP1 induces apoptotic neurotoxicity. Cerebellar granule cell cultures when switched from a depolarizing to a non-depolarizing extracellular concentration of potassium undergo apoptosis that requires macromolecular synthesis-dependent BAX translocation, cytochrome c release and caspase activation. Indeed, potassium deprivation induced apoptosis in cerebellar granule cells from wild type (Bax +/+) or heterozygous (Bax +/–) mice, but not in cells from Bax deficient mice (Bax –/–). In contrast, potassium deprivation induced a marked increase in NP1 expression that was similar in wild type, heterozygous and Bax deficient mice. Lentiviral mediated transgene overexpression of NP1 produced apoptosis in cerebellar granule cells from wild type but not in cells from Bax deficient mice. On the other hand, transgene overexpression of NP1 potentiated apoptotic cell death, cytochrome c release and cleavage of caspase 3 evoked by low potassium. Moreover, transgene overexpression of NP1 reduced the levels of PSD95. These results place NP1 upstream of BAX in the apoptosis pathway and indicate that the mechanism by which NP1 contributes to apoptotic neurotoxicity is associated with reduction of synaptic activity. Supported by FIS-PI040376 from Ministerio de Sanidad y Consumo and SAF2005-01167 from Ministerio Educación y Ciencia of Spain.

P13. Novel Roles for Aquaporin 1 in Spinal Cord Injury

Olivera Nesic, Julieann Lee

The role of water channel aquaporin 1 (AQP-1) in uninjured or injured spinal cords is unknown. AQP-1 is weakly expressed in neurons and astrocytes (novel finding) and ependymal cells, but most abundantly in small diameter sensory fibers of the dorsal horn. Rat contusion spinal cord injury (SCI) induced persistent and significant 4 to 8 fold increases in AQP-1 levels persisting up to 11 months post-contusion, not only at the site of injury (T10), but also in cervical and lumbar segments, a novel finding. Given that the anti-oxidant melatonin significantly decreased SCI-induced AQP-1 increases, we propose that chronic hypoxic conditions contribute to persistent AQP-1 upregulation after SCI.

Interestingly; AQP-1 levels were not affected by long-lasting extracellular hypertonicity that significantly increased astrocytic AQP-4, suggesting that the primary role of AQP-1 is not in regulating isotonicity in spinal cords.

Based on our results we propose novel roles for AQP-1 in injured spinal cord: (a) in neuronal swelling since AQP-1 was significantly increased in all surviving neurons after SCI, (b) in migration of astrocytes, since it was mostly expressed in scar-forming astrocytes surrounding the lesion site, and (c) in excessive axonal sprouting, since AQP-1 was co-localized with growth-associated protein 43, especially in the sensory fibers of the dorsal horn, a novel hypothesis. We have also shown that decreased AQP-1 in melatonin-treated SCI rats correlated with reduced AQP-1 immunolabeling in the dorsal horns, and with significantly decreased mechanical allodynia, further supporting a link between AQP-1, excessive sprouting of sensory fibers and pain after SCI.

P14. Structural MRI and Cognitive Brain Measures in Methamphetamine Dependence

Malcolm S. Reid, Hugh Knickerbocker, Jay Nierenberg

MRI studies in cocaine dependence suggest that chronic psychostimulant abuse is associated with changes in white matter integrity and striatal volume. However, methamphetamine produces more robust changes in dopamine systems than cocaine and has been reported to be associated with significant executive function and cognitive deficits. We tested 12 medically healthy, HIV-negative patients with methamphetamine dependence and 12 age matched healthy controls. All experimental group subjects were primary methamphetamine abusers (avg yrs: 4.9+3.3, avg days since last use 3.5+5.0), though the majority had a history of using used other drugs of abuse. MRI scans included eight-direction Diffusion Tensor Imaging (DTI), T2-weighted spin echo and FLAIR (Fluid Attenuated Inversion Recovery) and T1-weighted 3D volumetric scan. T1 weighted images were used for volume determinations and in intersubject registrations of the DTI data for voxelwise analyses. FLAIR images were used to evaluate the presence of white matter lesions. Fractional anisotropy (FA), a measure of white matter integrity, was analyzed using voxelwise t tests with false discovery rate correction of the voxel t-statistic. Computerized cognitive tests using the Cogtest® battery were used to evaluate attention, response inhibition, facial emotion recognition, auditory-verbal working memory, spatial working memory, set shift and tapping speed. Combined volume of caudate and nucleus accumbens was similar across groups and no gross white matter damage was noted based on the presence of white matter

hyperintensities. However, methamphetamine patients showed significantly lower FA in the white matter of the corpus callosum and superior longitudinal fasciculi bilaterally as well as in the left superior frontal and fusiform gyri and the right posterior cingulate gyrus. Methamphetamine patients also showed significantly higher FA in the left ventral tegmental area and mediodorsal thalamus and in the right subcallosal fasciculus. Methamphetamine patients showed performance deficits in specific cognitive areas; attention, set shift, spatial and verbal memory, and finger tapping speed, but did not show deficits in response inhibition and facial emotion recognition. Lower voxelwise FA in methamphetamine users in the corpus callosum and fasciculi paralleled findings derived from an ROI analysis in the same subjects as well as previous reports in active cocaine abusers. The absence of striatal volume deficits may be related to the lack of observed white matter hyperintensities due to cerebrovasculature damage. Correlations of cognitive deficits with changes in FA will be presented. Support: NIDA R21 DA017556 & NIDA R03 DA DA016220

P15. Reversible Silencing of the Glia-Specific Connexin-43 Produces Temporary Analgesia in a Rat Model of Orofacial Neuropathic Pain

Luc Jasmin, Jean-Philippe Vit, Peter T. Ohara, Aditi Bhargava

The disruption of gap junctions in sensory ganglia after nerve injury has been shown to produce analgesia. However, the specific connexins (the major constituents of gap junctions) which are involved in this antinociceptive effect are still unknown. Here, we present evidences that silencing connexin-43 (Cx43) accounts for this analgesic effect. After chronic constriction injury of the infra-orbital nerve, a model of orofacial neuropathic pain, the expression of Cx43 increases specifically in satellite glial cells, the cells that surround the cell bodies of sensory neurons in the trigeminal ganglion. This increase in Cx43 expression correlates with the appearance of both spontaneous pain (increased non-stimulated eye closures) and evoked pain (facial allodynia to von Frey hair application and decreased tolerance to innocuous stimulation in an operant conflict paradigm) on the side of the injury. To examine the functional importance of Cx43, we used RNA interference (RNAi) in vivo, which we show to cause specific and reversible gene silencing. Cx43 double-stranded RNA was directly injected in the trigeminal ganglion and selectively and reversibly silenced Cx43. This treatment resulted in a decrease in both spontaneous and evoked pain arising from a chronic constriction injury of the infra-orbital nerve. The analgesic effect was short-lasting, which

corroborates with the high turn-over of Cx43. A survey of several neuronal (ATF3, substance-P, isolectin B4...) and glial (GFAP, glutamate transporter...) markers of injury and/or pain in the trigeminal ganglion and in the spinal trigeminal nucleus (where the axons of the trigeminal sensory neurons terminate) was performed to determine the mechanism underlying the analgesic effect of the Cx43 inhibition. Our results support a growing body of evidence indicating that peripheral and central glial cells play an important role in the development and maintenance of neuropathic pain. Moreover, our findings show that in vivo RNAi of glia-specific genes may be a powerful tool for the treatment of chronic pain.

P16. Effects of Noggin on Oligodendrocytic Lineage Elaboration in Human Fetal Spinal Cord Tissue Derived Neural Precursor Cells

Tailoi Chan-Ling, Michael W. Weible II

Generating a stable in vitro population of cells of the oligodendrocytic lineage from neural stem/precursor cells of human embryonic and fetal spinal cord persists as an additional barrier in the development of a cell based therapy to treat demyelinating disease. Further insights into the conditions needed for prolonged generation and functional incorporation of oligodendrocytes are needed. Significant species and regional specification of neural stem cells suggests that studies of human spinal cord (HSC) derived neural stem cells (NSC) offer the best opportunity for translational studies in human spinal cord injury. Nine complete human spinal cords from specimens aged 13-19 weeks gestation were dissociated to a single cell suspension and expended in neural basal media enriched with EGF and FGF. At 14 days in vitro (DIV) resultant neurospheres were fixed, cryosectioned and found to be positive for the markers: A2B5, GD3 and O4 but not O1; a marker expressed later in OL development. However, if neurospheres were allowed to develop they react positive to O1 antibodies, demonstrating that OL maturation occurs within neurospheres. Neurospheres were plated onto ECM coated glass, cultured between 1-21 DIV, fixed at specific time points and immunocharacterized. Emergent OL began expressing the O1 marker by 1 DIV, GalC by 3 DIV and MBP by 5 DIV. By 21 DIV markers O4 and O1 were down-regulated respectively. We have previously shown that BMP4 significantly reduces the proportion of emergent OL from neurospheres and here we demonstrate that noggin, a BMP4 antagonist, can significantly increase the number of emergent OL by blocking BMP4 autocrine loops in the developing neurosphere. Our data demonstrates that second-trimester HSC derived neurospheres retain the potential

to generate oligodendrocytes, that the normal temporal sequence of OL marker expression is maintained in vitro, and that noggin can increase OL elaboration ion human fetal spinal cord tissue derived NSC.

P17. A Role for Beta 1 Integrin in Retaining Neural Stem Cells in the Ventricular Zone

Justin D. Lathia, Karine Loulier, Mohammed R. Mughal, Sung-Chun Tang, Bruce Patton, Mahendra S. Rao, Tarik F. Haydar, Mark P. Mattson, Charles ffrench-Constant

Laminin, an extracellular matrix molecule, and its integrin receptors are key regulators of stem cell behavior. Their exact role in brain development and influence on neural stem cells (NSCs) remains unknown. The goal of this project was to establish the expression pattern of these molecules and devise methods to perturb their function in vivo. In the murine embryonic NSC compartment, the ventricular zone (VZ), there was high immunoreactivity of integrin beta 1 and several laminin chains. The bipolar morphology of NSCs does not allow for a genetic approach to disrupting integrin signaling only in the VZ. Thus, a spatial-temporal perturbation of integrin signaling was developed by injecting beta 1 integrin blocking antibodies into the ventricles of viable embryos in utero. In addition, a co-injection/electroporation method was developed to mark the cells on the ventricular wall at the time of disrupted integrin signaling to examine the possibility of NSC detachment. Analysis 18 hours post injection showed a random pattern of cells throughout the cortex and a subset of cells with a detached foot process. Based on these findings, we propose a new model in which beta 1 integrin is pivotal in keeping NSCs in the VZ and ensuring proper brain development.

P18. Analysis of ApoE-Mimetic Peptides as Novel Therapeutics for Treatment of Parkinson's Disease

Dale J. Christensen, Feng-Qiao Li, Jessica Oddo, Carol Colton, Michael P. Vitek

Parkinson's Disease (PD) progresses due to destruction of dopaminergic neurons in the substantia nigra that results in movement disorders due to a severe reduction in dopamine concentrations within the brain. There are no current treatments that reduce the neurodegeneration of dopaminergic neurons. Recently there have been a number of reports defining a role that inflammation and genetic factors play in the progressive loss of dopaminergic neurons in PD. Based on reports that implicate

the ε4 allele of apolipoprotein E (apoE) as playing a critical role in the age of onset for development of PD, apoE provides a convergence point for these factors. Our previous work demonstrated that an apoE-mimetic peptide, COG133, exhibits potent anti-inflammatory and neuroprotective effects. We now report that mixed mesencephalic neuron-glial cultures exposed to LPS showed a toxic effect while cultures exposed to LPS plus COG133 showed a protective effect as measured by protection against loss of 3H-dopamine uptake, nitric oxide production, and reduction in the number of tyrosine hydroxylase positive neurons. In addition to inflammatory-mediated neurotoxicity, it has been demonstrated that excitatory amino acids such as N-methyl-D-aspartate (NMDA) may also play a role in the progression of Parkinson's disease. COG133 demonstrates direct protective activity against NMDA neurotoxicity. Given the protective activities of COG133 using in vitro assays, this compound has been analyzed for protection against dopaminergic neuron loss in a unilateral 6-hydroxydopamine model of Parkinson's disease. Results from behavioral, biochemical and immunohistochemical analysis in animals treated with COG133 or controls will be discussed.

P19. Ethanol Withdrawal-Induced Motor Impairment in Genetically Distinct Mice

Scott D. Philibin, Andy J. Cameron, John C. Crabbe

Alcohol dependence produces various withdrawal signs in humans and animals. Multiple mouse phenotypes reflect contributing factors to this complex trait. Establishing novel withdrawal phenotypes would aid elucidation of underlying neurobiological mechanisms. Ethanol (EtOH) withdrawal was evaluated using accelerating rotarod (ARR) acquisition, a simple motor learning task. Dependence was induced via 72 hours chronic ethanol vapor inhalation versus air-exposed controls. Eight inbred strains were tested at 6, 8 and 12 hours after ethanol exposure. Withdrawal disrupted ARR performance and strains were differentially affected. Withdrawal Seizure-Prone (WSP) and -Resistant (WSR) lines were selectively bred for severe or mild EtOH withdrawal handling-induced convulsions. Withdrawn mice had shorter latencies to fall at 8 hours, but these genotypes did not differ in withdrawal impairment. An outbred stock of mice was tested at 8 hours after ethanol exposure; controls were air exposed, using a yoked-control procedure to equate ARR practice with the ethanol groups. Animals were subsequently tested at 24 hours or one week. Withdrawal disrupted ARR performance at 24 hours but not one week. Inbred strain data suggest a genetic component to withdrawal-induced disruption of ARR performance. Deficits in ARR performance were not genetically correlated with the selection response

in WSP and WSR lines. Finally, these effects of withdrawal are time dependent and suggest a performance versus a learning deficit. Supported by AA10760, AA07468, and the Dept of Veterans Affairs.

P20. Heme Metabolism in Alzheimer's Disease

B.E. Dwyer, M. A. Smith, S. Richardson, G. Perry, X. Zhu

We are investigating if changes in cerebral heme metabolism contribute to Alzheimer's disease (AD) pathogenesis and progression. Heme (heme-b) is an essential cell metabolite, an intracellular regulatory molecule, and the prosthetic group of most hemoproteins including b-type respiratory cytochromes and the cytochrome P450 enzymes. It is also the precursor of heme-a, the prosthetic group of cytochrome c oxidase (respiratory complex IV). Heme biosynthesis requires eight enzymes. δ-Aminolevulinic acid (ALA) synthase, the first and rate-limiting enzyme in heme biosynthesis, is a mitochondrial enzyme. ALA dehydratase (ALAD) and porphobilinogen deaminase (PBGD) catalyze the second and third steps in heme biosynthesis, which occur in the cytoplasm. Here, we used RT-PCR to quantify expression of ALA synthase, ALAD and PBGD mRNAs in AD and control brain samples. In this initial series, relative expression of ALA synthase mRNA was reduced about 90% in AD brain (N=6) compared to control (N=5) (p=0.046), relative expression of ALAD mRNA was unchanged, and relative expression of PBGD mRNA was reduced about 60% in AD brain (N=10) compared to control (N=16) (p=0.015). The cause and consequences of these changes, and whether they occur early in disease progression, are under investigation. Supported by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs (BED) and the National Institutes of Health and the Alzheimer's Association.

P21. Amyloid Beta Induced Changes in Receptor Trafficking

W. D. Hirst, K. E. Kubek, J. Golembieski, R. G. Staal, M. N. Pangalos, P. H. Reinhart, S. P. Braithwaite

Alzheimer's disease is a chronic neurodegenerative disorder that is characterized by elevated levels, and deposition of, amyloid beta. Numerous studies have implicated the 42 amino acid amyloid beta peptide (Ab1-42) as key to underlying the disease. However transgenic mouse models expressing high levels, or mutant forms of amyloid precursor protein, leading to elevated Ab1-42, exhibit cognitive deficits prior to deposition of amyloid plaques and without neurodegenerative pathology. These

deficits in cognition may therefore be the result of synaptic dysfunction rather than neuronal death. We have explored whether Ab1-42 modulates key mechanisms in synaptic function by assessing changes in receptor trafficking at the synaptic membrane in acutely dissected hippocampal slices from adult rats. Biotinylation experiments have demonstrated that Ab1-42 selectively mediates endocytosis of subtypes of NMDA and AMPA receptors, but not GABA-A receptors, from the neuronal surface. Treatment with 1 uM Ab1-42 for one hour reduces surface expressed NMDA and AMPA receptors by 50%. We have also assessed the effects of pharmacological manipulations on trafficking of receptors to understand the relative contribution of Ab1-42 to induce receptor changes at the synapse. These studies demonstrate that the synapse is a dynamically regulated system that is influenced by multiple external influences. The receptor changes induced by Ab1-42 may underlie some of the symptoms of Alzheimer's disease.

P22. Modulating Microglial Activity and Neuroprotection

A. I. Faden, K. R. Byrnes, B. S. Stoica

Microglial associated inflammatory responses are implicated in acute and chronic neurodegeneration. Using microarrays, we found upregulation of numerous microglial inflammatory factors after spinal cord injury (SCI); increased expression of certain genes and associated proteins persisted for months. Similar gene and protein expression changes are found in activated microglial cultures, and appear to contribute to neuronal cell death in vitro. We now show that metabotropic glutamate receptor 5 (mGluR5), normally found in neurons and able to inhibit caspase dependent neuronal apoptosis, is highly expressed in microglial cultures after lipopolysaccharide (LPS) stimulation. Pre-treatment with the mGluR5 agonist CHPG or apocynin, an inhibitor of microglial factor p22phox, strongly inhibited LPS-induced microglial activation as reflected by decreased proliferation, nitric oxide production, and TNFα secretion. Co-culture of LPS-activated microglia with neurons caused neurotoxicity; pre-treatment of microglia with CHPG or apocynin prior to LPS blocked neuronal cell death. In parallel studies, CHPG or vehicle were infused intrathecally after moderate impact SCI in rats. CHPG treatment markedly reduced microglial associated inflammatory factors, including ED1 and p22phox, and chronic behavioral function was significantly improved. In this same model, apocynin reduced lesion volume at 28 days post-injury. Collectively, these studies indicate that mGluR5 and p22phox represent potential targets for attenuating microglial-related inflammation and associated neurotoxicity.

P23. Gender Differences in the Time Course of Voluntary Alcohol Intake in Adolescent Mice

Sophie Tambour, John C. Crabbe

Background: Female rodents tend to drink more alcohol than do males. This gender difference could partially be explained by biological factors including differences in circulating hormones, metabolic rates and/or sexually dimorphic mechanisms in the brain. As the peripubertal period is a critical developmental transition associated with dramatic hormonal changes, the present study examines the time course of alcohol intake in male and female mice during adolescence and the adolescent-to-adult transition. Methods: From early adolescence [postnatal day (P) 25-28] until adulthood [P 74-77], 14 female and 14 male WSC-1 mice were single-housed and given free and continuous access to two bottles, one containing water and one containing alcohol (6% v/v). Alcohol and water consumption were recorded daily at the same time of the dark phase of the circadian cycle. Results: Sex differences in ethanol intake were not seen in very young animals [~ 4 weeks] but emerged during the peripubertal period [~ 6 weeks], when females began to show higher alcohol intake. This increase in ethanol consumption by females, possibly due to hormonal changes associated with the pubertal period, persisted until adulthood. Conclusion: Together, these results show that male and female mice differ in the development of voluntary drinking behavior. Future studies will consider the effects of limited access exposure to alcohol solutions early during development to determine whether similar gender-specific dimorphisms are seen in binge-like drinking. Supported by AA010760, AA013519, the Dept of Veterans Affairs and the Belgian National Funds for Scientific Research (FNRS).

P24. The Cannabinoid Agonist CP-55940 Injected into the 4th Cerebroventricle Antagonizes Cfos Induced by Intraperitoneal Cholecystokinin

G.L. Edwards, D. R. Gaddam, K. G. Freeman

The cannabinoid agonist CP-55940 is reported to increase intake of highly palatable foods when injected into the fourth cerebroventricle (Physiol. Behav. 80: 611, 2004). It is possible that enhanced intake induced by cannabinoid agonists works by attenuating visceral signals from the gut. We have examined the ability of CP-55940 to attenuate activation of cFos by intraperitoneal cholecystokinin (CCK). It is well recognized the CCK induces cFos immunoreactivity in neurons of the caudal nucleus of the solitary tract (NTS) and area postrema (AP). We

found that CCK induced a significant increase in cFos-immunoreactive neurons in the NTS and AP. The number of cFos-immunoreactive neurons was decreased significantly by prior application of the cannabinoid agonist CP-55940. This reduction in cFos-immunoreactive neurons by CP-55940 was blocked by the CB1 receptor antagonist SR141716. Moreover, treatment with cannabinoid antagonist alone does not appear to significantly elevate cFos in the NTS. Our observations suggest that cannabinoids may act on vagal afferents terminating in the NTS to blunt inhibitory signals from the gut, thereby, resulting in elevated food intake. (Supported by Dept. of Physiol. & Pharm., Univ. of Georgia).

P25. Neurotrophins Protect Cortical Cultures against Hydrogen Peroxide Toxicity

Frank A. Welsh, Sharrol Bachas, Hiromi Muramatsu, Marc Dichter, Katalin Kariko

Neurotrophins have been shown to protect cells in the CNS against a variety of noxious stimuli; however, the neuroprotective mechanisms have not been fully elucidated. Recent studies indicate that neurotrophins are anti-inflammatory, a property which may contribute to their protective actions. The objective of the present study was to develop an in vitro model with which to investigate the anti-inflammatory mechanisms of neurotrophins. Mixed cortical cultures were prepared from E19 embryonic rats and cultured for two weeks. The cultures were exposed to hydrogen peroxide (0.12 mM, 0.25 mM, or 0.50 mM) for 1-24 hr in the presence or absence of NGF (100 ng/ml) or BDNF (100 ng/ml). Cell injury was determined by measuring LDH release during the peroxide exposure. As expected, hydrogen peroxide caused a dose-dependent release of LDH from the cultured cells into the media. Either NGF or BDNF reduced the release of LDH by 40%-50% at the two lower concentrations of peroxide, but had no effect at 0.5 mM peroxide. The protective effect of neurotrophins was observed at all concentrations of peroxide tested when the cultures were exposed to NGF or BDNF for 24 hr prior to and during peroxide treatment. However, preconditioning the cultures with neurotrophins by itself did not protect the cultures from peroxide. Preliminary results indicate that NGF induces the expression of inhibitors of cytokine-signaling. Thus, the protective effects of neurotrophins may be explained, in part, by the suppression of the inflammatory response to peroxide exposure.

P26. Effects of Sex and Saccharin Preference on Behavioral Inhibition and Cocaine Self-Administration

J. J. Anker, M. E. Carroll

The purpose of the present study was to examine the influence of sex and saccharin preference on behavioral inhibition and cocaine self-administration (S-A). In this study a Go/No-go (GNG) procedure was used to examine cocaine S-A and prepotent responding in male and female rats selectively bred for high (HiS) and low (LoS) saccharin intake. The GNG procedure consisted of three signaled 45 min periods in which rats had access to iv infusions of cocaine (Go components) separated by two 15 min No-go periods. During each No-go component a green stimulus light was illuminated and responses on the drug paired lever ceased to produce iv infusions of cocaine. Rats were initially trained to S-A 0.4 mg/kg cocaine under an FR1 schedule of reinforcement during daily GNG sessions. Once responding stabilized, the schedule was changed to FR3 for 2 days and subsequently to an FR5. GNG responding and drug intake were then assessed under an FR5 schedule of reinforcement for each of two randomly selected doses of cocaine: 0.2 and 0.4 mg/kg. HiS female rats infused more cocaine than HiS males and LoS females under all conditions. Under the FR1 and 3 schedules the HiS female group responded significantly more during the No-Go periods than all other groups. In addition, HiS female rats made significantly more No-go responses proceeding self-administration of 0.2 and 0.8 mg/kg cocaine than His male and LoS female rats. The present results suggests that sex and phenotype differences are present in both cocaine elicited prepotent responding, as measured during periods in which drug was not available, and cocaine intake.

P27. Internal and External Shifting in and Operant Task in 6-OHDA Lesioned Rats

Arjan Blokland, Rob Hameleers, Eva Wölbert,Yasin Temel

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is generally determined by motor disturbances such as slowness of movement, difficulty in initiating movement, rigidity and tremor. However, PD is also associated with cognitive deficits. These are characterized by difficulties in cognitive set-shifting, i.e. the ability to flexibly adapt behaviour in response to environmental changes. However, studies indicate that PD patients are more impaired in internal set shifting as opposed to set shifting on basis of external cues. In the present study we developed an operant task in which rats had to

switch in responding to a lever (left to right or visa versa) as determined by the computer (internal switch) or had to switch on basis of a light cue. Switching performance was defined as the number of lever presses to the non-rewarded lever (perseverative responses). Wistar rats were first trained on this task before they received sham lesion or a striatal 6-OHDA lesions. Rats acquired the task and performed better on the external switch task. Lesioned animals made more perseverative responses than sham lesioned animals when they had to make an internal shift. On the other hand, no differences were found when a cue light indicated the rewarded lever. These data suggest that this operant task can be used to evaluate the neurobiology of cognitive set shifting deficits in a PD model.

P28. Acute Citalopram Potentiates Amygdala Reactivity

Kristin L. Bigos, Bruce G. Pollock, Howard J. Aizenstein, Patrick M. Fisher, Robert R. Bies, Ahmad R. Hariri

This study evaluated the acute effects of the selective serotonin reuptake inhibitor (SSRI), citalopram, on amygdala activity using functional MRI. Eight healthy men completed the double-blind balanced crossover study of citalopram (20 mg infused over 30 min) and normal saline. Amygdala reactivity in response to novel facial expressions was assessed on 3 successive scans, once before drug/placebo infusion, once early in the infusion, and once at the end of infusion. A cluster in the right amygdala had increased activation early in the citalopram infusion compared to the baseline. An even greater bilateral amygdala response to citalopram was found at the end of infusion, when the citalopram concentrations approach their maxima, compared to the baseline task. This pattern was confirmed by results of regressions analyses between scan-specific plasma citalopram concentrations and amygdala activation, which revealed a strong dose-dependent increase in amygdala reactivity over infusion. Our data provide unique direct evidence that acute pharmacologic 5-HT reuptake blockade potentiates the reactivity of the human amygdala to salient environmental stimuli. The current pattern of 5-HT-mediated amygdala reactivity may represent an important pathway through which SSRIs achieve an antidepressant effect. Intriguingly, our data may also reveal a mechanism contributing to clinical observations of extreme agitation, restlessness and suicidal ideation in some individuals during acute SSRI treatment. These efforts contribute to the identification of biological mechanisms and pathways that mediate response to SSRIs, which will be instrumental in the development of more effective 5-HT based therapeutic interventions.

Poster Session 2

Monday–Tuesday • Ballroom 2 & 3

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

P29. Age-Related Changes in Astrocyte Density, Morphology and Pax2 Expression in the Rat Retina: Imbalance between Cell Proliferation and Cell Death

Tailoi Chan-Ling, Hussein Mansour; Coral G. Chamberlain, Suzanne Hughes, Michael W. Weible II

Astrocytes are intimate partners with neurons in virtually every function of the central nervous system and are therefore likely to play a significant role in aging-related loss of neural function. The aim of this study was to identify changes that occur in astrocytes during physiological aging. Astrocytes in retinal wholemount preparations from Wistar rats aged from 3 (young adult) to 25 months (aged) were investigated qualitatively and quantitatively following immunofluorohistochemistry. Glial fibrillary acidic protein, S-100 and Pax2 were used to identify astrocytes and blood vessels were localized using Griffonia simplicifolia isolectin B4. Cell proliferation was assessed by bromodeoxyuridine incorporation and cell death by TUNEL-labelling and immunolocalization of apoptosis markers active caspase-3 and endonuclease G. Between 3 and 9 months of age there was a marked increase in the density and total number of parenchymal astrocytes in the retina, followed by a marked decrease between 9 and 12 months. Proliferation of astrocytes was detected at 3 months but not beyond this age. In contract, the proportion of astrocytes that were TUNEL+ and the relative expression of active caspase3 and endonuclease G increased with aging. Furthermore, astrocytes exhibited gliosis-like morphological changes and tended to lose reactivity for Pax2. A small population of Pax2+/GFAP- cells was present in both young adult and aged retinas. Since changes in the retina during aging reflect that reported in the brain, the aging-related changes in astrocytes reported here may have a significant impact on their ability to maintain homeostasis and support neuronal function in the CNS in old age.

P30. Sorting Nexin-25 is a Novel Interacting Partner for D1 and D2 Dopamine Receptors and Influences their Trafficking and Expression

D. R. Sibley, R. B. Free, L. A. Hazelwood, D. M. Cabrera

We have employed a co-immunoprecipitation assay for dopamine receptors (DARs) from transfected cell lines, coupled with mass spectrometry sequencing to identify interacting partners. Through these studies we have identified sorting nexin-25 (SNX25) as a DAR interacting protein. When SNX25 is over-expressed with either D1 or D2 DARs in HEK293 cells, the receptors demonstrate increased expression levels as determined by radioligand binding and cAMP assays. There were no effects of increasing SNX25 levels on basal or forskolin-stimulated cAMP levels in the cells. This increase in receptor number was accompanied by an alteration in cellular distribution of the receptors to small internal compartments as seen using confocal microscopy. Intact cell binding assays using the D2 DAR confirmed this change in surface localization. This altered receptor distribution to internal compartments was not a result of receptor degradation as these compartments were not found in lysosomes as determined with co-localization studies using a lysosomal marker. We further examined the influence of SNX25 on DARs by blocking the expression of endogenous SNX25 using a plasmid-based siRNA approach. These studies found that decreasing the amount of SNX25 results in a decrease in both D1 and D2 DAR expression. We also examined the influence of SNX25 over-expression on D1 DAR desensitization and found that SNX25 over-expression does not appear to effect D1 DAR down-regulation or desensitization. Overall, these data suggest that SNX25 regulates the intracellular trafficking of D1 and D2 DARs.

P31. Methamphetamine-Dependent Males Perform Better on Tasks Assessing Working and Episodic Memory than Matched Females

Brian J. Jackson, Richard De La Garza, II, Ari D. Kalechstein, Thomas F. Newton

A number of published studies have shown that methamphetamine (MA) use is associated with a range of neurocognitive impairments, including perturbations in attention, working memory, executive function, and episodic memory. To our knowledge, however, no published studies have investigated the differences in neurocognitive function between male and female MA users. To this end, we conducted a study of differences in neurocognitive functioning in 8 male and 8 female MA

users. We administered a battery of tasks probing attention/psychomotor speed, working memory, and verbal episodic memory to 16 participants, who were 32.8 ± 9.6 years of age with 12.9 ± 1.8 years of education. Participants had used MA for 8.5 ± 5.0 years, and 20.4 ± 7.1 days out of the last 30. Male and female participants in this study were matched for age, education, and verbal intelligence. Preliminary results indicate female MA users perform more poorly on tasks assessing working memory (accuracy = 77.3% ± 9.3 for males and 57.9% ± 20.5 for females on a 2-back task; $p < 0.03$) and verbal episodic memory (total words recalled = 25.3 ± 4.0 for males and 18.8 ± 6.4 for females; $p = 0.04$). Males also performed better on a choice reaction time task (93.5% ± 6.9 vs. 87.8% ± 7.9 for females; $p < 0.09$), however this difference was not significant. These findings warrant further investigation with a more comprehensive neurocognitive battery to assess a wider range of functional domains.

P32. Hippocampal Theta-Modulation by Inhalational (Non-)Anesthetics at Amnesic Concentrations

Misha Perouansky, Tim Ford, Mark Perkins, Robert A. Pearce

Inhalational anesthetics all impairment of hippocampus-dependent learning at one third and one half the concentration necessary for ?surgical' anesthesia (i.e. immobility). We hypothesized that anesthetics with different activity profiles on the molecular / cellular level may have common effects on hippocampal network activity believed to be important for mnemonic function.

With the approval of the IACUC, linear microwire array recording electrodes with four sites spaced 200 micrometer apart were implanted into the hippocampi of 21 adult male Sprague-Dawley rats. EEG signals from the CA1 electrodes were recorded from unrestrained rats under control conditions and in the presence of N2O (30 and 60%, n=11), halothane (0.23-0.94%; n=8), isoflurane (0.29-1.24%, n=9) or F6 (0.52-3.8%, n=7) while the animal's behavior was scored. Spectral analysis of data obtained from the electrode closest to the hippocampal fissure was performed using a MATLAB-based custom program separately for exploring and immobile behavioral states.

Irrespective of receptor-level tropism, all anesthetics dose-dependently slowed the frequency of hippocampal theta-oscillations during exploratory (type I) behavior. At comparable sub-anesthetic concentrations,

theta-peak frequency decreased by 6, 10 and 16% for halothane, N2O and isoflurane, respectively. The non-immobilizer F6 depressed the amplitude of theta-peak, without slowing it. During immobility, only halothane induced large amplitude, regular theta-oscillations that have been previously shown to be atropine sensitive(Bland 2003). Conclusions: Slowing of hippocampal theta-oscillations might represent a signature effect of anesthetic-induced impairment of explicit memory. The effect of anesthetics on gamma-oscillations and on theta-gamma coupling remains under exploration.

P33. Time Course of Oxidative Stress and Synaptic Proteins Following Traumatic Brain Injury

S. W. Scheff, M. A. Ansari, K. N. Roberts

An imbalance between oxidants and antioxidants has been postulated to lead to oxidative damage following traumatic brain injury (TBI). Oxidative neurodegeneration plays an important role in the morphological responses and behavioral sequelae following TBI. The present set of studies was designed to delineate the early temporal sequence of the imbalance in order to enhance the design of possible antioxidant therapy. Young adult rats were subjected to a unilateral moderate cortical contusion. At various survival times post injury (1, 3, 6, 12, 24, 72 and 96h) animals were assessed for changes in cortical enzymatic and non-enzymatic oxidative stress markers. Fresh tissue was prepared for biochemical analysis of several antioxidants (glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), and oxidants (TBARS). Synaptic markers (Synapsin-I, PSD-95, SAP-97, GAP-43) were analyzed by western blot with antibodies directed against them. All activity levels were compared to sham operated controls. Activity of antioxidant enzymes and GSH clearly demonstrate a significant time-dependent increase in oxidative stress. Changes in pre and post synaptic proteins (Synapsin-I and PSD-95) occur early while SAP-27 levels demonstrate a protracted reduction. These results indicate that depletion of antioxidant systems following trauma could adversely affect synaptic function and plasticity. Because of the observed differences in the time-course of various markers, it may be necessary to stager selective types of anti-oxidant therapy to target specific oxidative components. The initial therapeutic window following TBI appears to be relatively short since oxidative damage occurs as early as 3h.

P34. Recruitment of Excitatory Serotonergic Neurotransmission to Cardiac Vagal Neurons in the Nucleus Ambiguus Post Hypoxia and Hypercapnia

David Mendelowitz, Harriet Kamendi

Inhibitory GABAergic and glycinergic neurotransmission to cardioinhibitory cardiac vagal neurons (CVNs) increase during inspiratory activity and likely mediate respiratory sinus arrhythmia, while the frequency of excitatory postsynaptic currents (EPSCs) in CVNs are unaltered during the different phases of respiration. However, following hypoxia and hypercapnia (H/H) the parasympathetic activity to the heart increases and thus far, identification of the pathways and neurotransmitters that are responsible for exciting CVNs post H/H are unclear. This study identifies different excitatory pathways to CVNs recruited post H/H. Spontaneous and inspiratory related EPSCs were recorded in CVNs before, during and after 10 minutes of H/H, in an in-vitro slice preparation that retains rhythmic respiratory activity. Before and during H/H EPSCs in CVNs were completely blocked by CNQX and AP5, selective AMPA / kainate and NMDA receptor blockers, respectively. However, after H/H, there was a significant increase in EPSCs during each inspiratory burst. While some of the inspiratory related EPSCs were blocked by the broad purinergic receptor antagonist Pyridoxalphosphate-6-azophenyl-2, 4'-disulphonic acid (PPADS) and the specific 2,3-O-(2,4,6-Trinitrophenyl) adenosine 5-triphosphate monolithium trisodium salt (TNP-ATP) a P2X receptor blocker, most of the recruited excitatory neurotransmission to CVNs is serotonergic since odansetron, a selective 5HT3 antagonist, abolished the majority of the spontaneous and inspiratory related EPSCs evoked during recovery from H/H. The results from this study suggest that following episodes of H/H two non-glutamatergic excitatory pathways, purinergic and serotonergic, activating P2X and 5-HT3 receptors, respectively, are recruited to excite CVNs in the post H/H recovery period.

P35. Unrestricted Access to Stimulants of Abuse in the Past Is Associated with Increased Stimulant Use in the Present

C. Culbertson, M. Costello, R. De La Garza II, T. F. Newton

Laboratory animals given long-access to stimulants have been shown to self-administer greater amounts of drug in an escalating pattern compared to animals under-short access conditions. To our knowledge, this

phenomenon has not been systematically investigated in humans. We interviewed one-hundred and six (77 male; 29 female) methamphetamine (MA) and ninety-six (81 male; 15 Females) cocaine (Coc) users and asked if they had experienced discrete period(s) of unrestricted access (URA) to unlimited quantities of MA or Coc. Fifty-eight MA users and fifty-three Coc users reported experiencing URA in the past, but not in the present. MA and Coc using participants with a prior history of URA reported significantly more current MA/Coc use, as compared to users with no prior history of URA. Specifically, MA participants reported more days used in the past thirty days ($F_{1,103}=5.8$ $p=0.018$), more days of use per week ($F_{1,101}=20.0$ $p=0.0001$) and greater total use per week ($F_{1,101}=10.2$ $p=0.002$). Coc using participants reported greater use across all measures including more days used in the past thirty days ($F_{1,93}=6.1$ $p=0.015$), more days of use per week ($F_{1,92}=5.5$ $p=0.021$), greater use per day ($F_{1,94}=8.3$ $p=0.005$), higher total use per week ($F_{1,92}=8.3$ $p=0.005$), and more years of use ($F_{1,92}=12.1$ $p=0.001$). These results suggest that a discrete period of URA to stimulants in the past is associated with long-lasting increases in stimulant use in humans. Further research aimed at characterizing the hypothesized neurobiological changes that accompany URA is of great interest.

P36. Protein Kinase C Delta Regulates Ethanol Intoxication and Ethanol Enhancement of Tonic GABA Currents

Robert O. Messing, Doo-Sup Choi, Zhan-Heng Qi, Weizheng Wei, J. Kevin Deitchman, Viktor N. Kharazia, Heidi M. B. Lesscher, Werner Sieghart, Kevan Shokat, Istvan Mody

Moderate ethanol intoxication may result from increased tonic GABA-mediated inhibition in neurons, though not all laboratories find that ethanol enhances tonic GABA currents. Here we show that ethanol sensitivity of tonic GABA currents is regulated by protein kinase C (PKC) delta, which might explain this discrepancy. We found that PKC delta (–/–) mice showed less rotarod ataxia and ethanol-induced loss of righting when compared with wild type littermates. These results were not due to altered ethanol clearance. PKC delta (–/–) mice also showed less ataxia than wild type mice when treated with the GABA-A agonists pentobarbital, pregnanolone, and gaboxadol, but both genotypes were equally sensitive to benzodiazepines. This pattern of drug response suggested that PKC delta regulates GABA-A receptors containing delta subunits, since all of these drugs except benzodiazepines modulate delta subunit-containing GABA-A receptors. Indeed, whole cell voltage

clamp recordings demonstrated that in wild type thalamic and dentate gyrus granule cell neurons, tonic GABA currents, which are mediated by delta subunit-containing receptors, were increased by 20 mM ethanol, whereas currents in PKC delta (–/–) neurons were not. Similarly in L(tk-) cells expressing alpha4/beta3/delta GABA-A receptors, ethanol enhanced GABA currents in a PKC delta-dependent fashion. These findings indicate that PKC delta facilitates alcohol intoxication by enhancing the effect of ethanol at extrasynaptic GABA-A receptors that contain delta subunits and mediate tonic inhibition in neurons.

P37. Seeing Is Believing? Why You Should Not Image Pain in the Anesthetized Brain

Pamela E. Paulson, Thomas J. Morrow

We previously reported that formalin-induced pain consistently produces detectable, well-localized, bilateral increases in forebrain activation within multiple somatosensory and limbic structures. The present study investigated the effects of anesthesia with ketamine or isoflurane on forebrain processing during formalin-induced nociception. Accordingly, we measured regional cerebral blood flow to assess brain activation in unanesthetized and anesthetized male Sprague-Dawley (Charles River) rats thirty-five minutes after injection of dilute formalin (2.5%, 0.05 ml, s.c.) into the left hindfoot. We report that both ketamine and isoflurane anesthesia alone (no formalin stimulation) produce robust decreases in brain activation in multiple brain structures, including most cortical and thalamic regions. However, ketamine did produce robust increases in retrospleniel and hippocampal cortices while isoflurane resulted in significant increases in the hypothalamus, habenular complex and the periaqueductal grey. More importantly, the formalin-induced increases in activation within somatosensory and limbic regions normally reported in unanesthetized animals were inhibited by the administration of either ketamine or isoflurane. These data suggest that anesthesia disrupts the activation in regions normally involved in central nociceptive processing while inducing complex changes in brain areas implicated in executive and cognitive functions. These findings have significant implications for the interpretation of in-vivo imaging data from studies using fMRI and microPET in animal models of pain.

P38. Polysynaptic Inhibitory Network among Striatal Cholinergic Interneurons

Matthew Sullivan, Huanmian Chen, Hitoshi Morikawa

The striatum is the primary point of entry for extrinsic inputs into the basal ganglia circuit and is critical for sensorimotor learning and action selection. Local GABAergic and cholinergic circuits interact with rich glutamatergic and dopaminergic inputs to shape the output of the striatum. Medium spiny neurons are the primary neurons of the striatum, comprising approximately 95% of the neuronal population, and are the only neurons to project out of the striatum. Cholinergic and GABAergic interneurons make up the remainder of the striatal neuronal population, however, it is not entirely clear how cholinergic interneurons are incorporated into the striatal GABAergic network. Here we show that activation of single cholinergic interneurons elicits polysynaptic GABAergic transmission on to themselves and nearby cholinergic interneurons in brain slices. The polysynaptic inhibition is mediated by nicotinic cholinergic excitation of local GABAergic neurons and is shaped by tonic dopamine D1 and D2 receptor activity. Stimulation of cholinergic fibers utilizes this polysynaptic inhibitory mechanism to induce a pause in tonic firing of cholinergic interneurons, resembling the synchronized pause response triggered by behaviorally salient stimuli in awake animals. These results demonstrate a novel microcircuit where nicotinic receptor activation of GABAergic interneurons enables recurrent inhibition among striatal cholinergic interneurons.

P39. Microglia Processes Block the Spread of Damage in the Brain

D. J. Hines, R. M. Hines, S. J. Mulligan, B. A. Macvicar

Microglia cells have been recently discovered to constantly probe surrounding brain tissue with filopodia extensions and to rapidly extend processes to damaged regions possibly guided by the release of ATP. However the impact of microglia process extension on the brain's response to damage is unknown. This is in line with the longstanding and unresolved debate concerning the overall beneficial versus harmful effects of microglia activation. In this study we show using two photon laser scanning microscopy that microglia process extension is an important protective response that prevents the spread of damage into surrounding undamaged tissue. We first blocked microglia processes outgrowth by either inhibiting microglia Cl- channels or by selectively

ablating microglia, then we quantified lesion volume. Cl channel inhibitors, NPPB (100 uM), DIDs (100 uM), tamoxifen (100 uM) reversibly blocked process outgrowth whereas K channel blockers (TEA, 4-AP or Ba) had no effect. Normally lesion volume decreased after microglia processes reached and surrounded the lesion; however when microglia process outgrowth was blocked, lesion volume increased and damage spread into surrounding tissue disrupting dendrite morphology. We used retroactive immunostaining to determine that the microglia processes that rapidly grow to the lesion express a glutamate transporter, GLT-1. Blocking GLT-1 with dihydrokainate (DHK) did not prevent microglia processes from reaching the lesion but prevented the microglia processes from reducing lesion size. This therefore suggests that newly formed microglia processes take up glutamate which limits the spread of damage caused by glutamate that leaks out of disrupted neurons. This form of microglia activation is therefore beneficial and represents the front line of defense against damage in the brain.

P40. Beyond TRPA1—Peripheral Neural Correlates of the Formalin Test

Tatjana I. Kichko, F. Klemm, R. Giron, T. Hoffmann, G. Carli, Peter W. Reeh

The formalin test is the most widely used behavioral screening test for antinociceptive drugs in the pharmaceutical industries, although its pain induction mechanism has remained cryptical for 30 years. Now, formaldehyde has been discovered to specifically activate TRPA1, the broad-spectrum irritant-sensing cation channel expressed in capsaicin-sensitive CGRP-containing primary nociceptive neurons. We confirmed this specificity using isolated mouse skin and trachea preparations to measure H2CO-induced CGRP release as an index of nociceptor activation. However, at nominal concentrations beyond 3mM the formalin effects could not be inhibited by camphor (2mM), the established blocker of covalently binding TRPA1 agonists, and they occurred also in TRPA1 knockouts in a concentration-dependent way. The classical formalin test uses 300mM concentration. This concentration (or 100mM) applied (for 3 min) to receptive fields in the isolated rat skin-nerve preparation resulted in a prolonged burst of action potentials (for 1-7min) in all types (Abeta/delta and C) of recorded single-fibers, followed by complete irreversible desensitization. However, 6-20min later almost all nociceptive C- and Adelta- but no Abeta-fibers resumed firing in a second period of discharge activity lasting for 10 -40min. These results were essentially reproduced using wildtype and TRPA1 knockout mice; in both genotypes formalin 100mM induced biphasic discharge activity

and irreversible desensitization. In conclusion, neither inflammation nor spinal sensitization are essentially required to explain the biphasic pain behaviour of rodents in the classical formalin test, biphasic nociceptor activity may suffice, and this does not seem to depend on TRPA1.

P41. Intrastriatal BDNF Infusions Restore Opioid Peptide Gene Expression in BDNF+/– Mice

Alicia J. Saylor, Jacqueline F. McGinty

Brain-derived neurotrophic factor (BDNF) is synthesized and anterogradely transported to striatal medium spiny neurons (MSNs) from cortical and mesencephalic afferents; the striatum itself expresses a negligible amount of BDNF from intrinsic sources. The trkB-expressing MSNs comprise two distinct populations that express either of the opioid neuropeptides, dynorphin or enkephalin. Previously we have shown that preprodynophin (PPD) and preproenkephalin (PPE) mRNA expression is markedly less in the striatum of BDNF heterozygous (BDNF+/–) vs. wildtype mice (Saylor et al., 2006). Since exogenous BDNF infused into the striatum (Sauer et al., 1994) or substantia nigra (Arenas et al., 1996) increases the expression of the PPE and preprotachykinin in rats, we hypothesized that intrastriatal infusions of BDNF would restore the depletion of opioid peptide gene expression in BDNF+/– mice. Wildtype and BDNF+/– mice received bilateral microinjections of BDNF (0.75ug/side/PBS) or PBS into the dorsal striatum. Mice were sacrificed 24 hours later and semi-quantitative in situ hybridization histochemical analysis revealed that PPD, PPE and D3R mRNA were decreased in BDNF+/– mice as compared to wildtype controls. Further, intrastriatal BDNF infusion restored the gene expression of PPE and D3R in BDNF+/– mice to wildtype levels. BDNF infusion increased PPD mRNA from its relative baseline in both wildtype and BDNF+/– mice by 63% and 126%, respectively. These results indicate that BDNF is an important regulator of gene expression in postsynaptic striatal targets. Supported by RO1 DA03982, PO1 AG023630, F31 DA020238.

P42. Novel mGluR5 Antagonists as Potential In Vivo Probes

Amy Hauck Newman, Santosh S. Kulkarni, Mu-Fa Zou, Jianjng Cao, Alice Rodriguez, P. Jeffrey Conn

The noncompetitive mGluR5 antagonist, MPEP, has been reported to reduce locomotor activity and drug-seeking behaviors induced by cocaine and other abused substances, in mice. In addition, mGluR5s

have been implicated in anxiety, depression, pain, and mental retardation, although until recently most of these studies were based on using MPEP alone as the mGluR5 antagonist. Thus the discovery of additional structurally diverse and selective mGluR5 antagonists provides novel in vivo tools with which to study the role of these receptors in CNS disorders and may provide leads toward medication development. Based on the MPEP pharmacophore and homology modeling of the transmembrane region of the mGluR5, a simple ligand design, which varied the 'a' and 'b' ring systems linked by either the alkyne function of the parent molecule or an amide group was initiated. These novel analogues were synthesized using a parallel design strategy and palladium-catalyzed cross coupling reactions. MGluR5 binding and functional data were obtained that demonstrated 1) most structural variations to the amide template were not well tolerated but 2) several of the alkynes showed higher affinity than MPEP at mGluR5. Further, a comparison of SAR between the amides and alkynes suggest that these compounds may be accessing different binding domains and that the structurally inflexible diaryl alkynes are preferred. Finally, several compounds show drug-like physical properties (e.g. cLogP range = 2–5) that support their use for in vivo investigation into the role of mGluR5 in CNS disorders, including drug addiction.

P43. Coordinate Regulation of the GABA (A) Receptor Alpha1 Subunit by the CREB and BDNF Pathways

Ingrid V. Lund, Yinghui Hu, Shelley J. Russek, Amy R. Brooks-Kayall

Changes in $GABA_A$ receptor (GABAR) a1 subunit levels occur during development and in disorders including epilepsy, alcoholism and stress. GABAR a1 levels decrease in dentate gyrus after prolonged seizures (status epilepticus or SE) and may be a determinant of later epilepsy development. We now find that a1 expression after SE is regulated by the CREB pathway. Increases in phosphorylated CREB (pCREB) and induction of inducible cAMP early repressor (ICER) after SE lead to enhanced pCREB and ICER binding at the CRE site of the a1-subunit gene (GABRA1) and reduced a1- containing synaptic GABARs. CREB/ICER over-expression decreases GABRA1 promoter activity in primary hippocampal neurons, confirming the role of CREB/ICER in a1 gene regulation. We further determined that brain-derived neurotrophic factor (BDNF) plays a critical role in regulating CREB/ICER repression of a1. BDNF treatment increased pCREB/ICER levels and reduced levels of a1 in cultured neurons. BDNF expression in hippocampus increases after SE coincident with increases in ICER and decreases in a1. The

effect of BDNF on ICER appears to be mediated by the Jak/Stat pathway because addition of a selective Jak inhibitor blocked BDNF-induced increases in ICER in cultured neurons as well as SE-induced increases in ICER *in vivo*. These findings identify CREB and ICER as key transcriptional regulators that are signaled by BDNF and work in concert to repress GABAR-dependent synaptic inhibition after SE and possibly during other disease states associated with reduced GABAR-dependent synaptic inhibition.

P44. AMPA Receptor Trafficking after Withdrawal from Cocaine Administration: Role of Transmembrane AMPA Receptor Regulatory Proteins (Tarps)

C.R. Ferrario, J. M. Reimers, M. Milovanovic, K. A. Ford, J. Uejima, K. L. Conrad, M. Marinelli, M. E. Wolf

It has become increasingly accepted that addiction is due, at least in part, to the ability of addictive substances to engage glutamate-dependent mechanisms of learning and memory. For example, repeated exposure to cocaine followed by withdrawal results in increased surface expression of AMPA receptors (AMPARs) in the nucleus accumbens (NAc). The trafficking and function of AMPARs in the cortex, hippocampus, and cerebellum are regulated in part by a family of transmembrane AMPAR regulatory proteins (TARPs). TARPs are necessary for AMPAR membrane insertion and synaptic targeting. The latter may be facilitated by TARP phosphorylation. In addition, particular TARPs differently regulate AMPAR channel gating. For example, ?4 modulates AMPAR channel gating more potently than λ2, predicting increased currents when AMPARs are complexed with λ4. Thus, alterations in TARP expression can influence both trafficking and responsiveness of AMPARs. Our goal is to understand the contribution of TARP adaptations in the NAc to the increased AMPAR surface expression observed after withdrawal from repeated cocaine exposure. We have found that TARP surface expression in the NAc is increased after withdrawal from a sensitizing regimen of cocaine as well as after withdrawal from a cocaine self-administration regimen that produces enhanced drug craving. Studies are underway to determine whether TARP phosphorylation is also altered, and to evaluate possible cocaine-induced shifts in associations between particular TARPs and AMPAR subunits. In addition, we have begun to examine cocaine-induced alterations in AMPAR and TARP surface expression in the caudate putamen. Support: DA09621, DA015835, and DA00453 (MEW) and DA020654 (MM)

P45. Coupling of Neuronal Nitric Oxide Synthase Phosphorylation to the NMDA Receptor and Signaling Pathways

Gerald A. Rameau, David S. Tukey, Elsa D. Garcin-Hosfield, Roseann F. Titcombe, Latika Khatri, Elizabeth D. Getzoff, Edward B. Ziff

The release of neurotransmitters at synapses activates excitatory and modulatory receptors. N-methyl-D-aspartate receptor (NMDAR), an ionotropic excitatory receptor, regulates the production of nitric oxide (NO) by neuronal nitric oxide synthase (nNOS). Under normal conditions NO plays an important role in synaptic plasticity but under pathological conditions it can be lethal. However, various nNOS releasing neurons were found to be resistant to cell death in neurodegenerative diseases which suggests that controlled production of NO can have neuroprotective benefits. Thus, there are subtle differences by which NO is cytoprotective that may ultimately be useful in identifying new potential therapeutic targets. The objective of this study is to understand how NMDARs regulate the production of NO via phosphorylation, and consequent effects on levels of intracellular Ca2+ concentrations and induction of mechanism of cell survival and cell death. The findings that sequential phosphorylation of nNOS activates and inhibits the enzyme, is novel. Negative phosphorylation is inhibited after treatments with excitotoxic glutamate, which suggests the importance of phosphorylation of nNOS. The identification of biochemical signaling pathways by which nNOS phosphorylation is regulated present an opportunity for therapeutic interventions to control cell death associated with neurological diseases and stroke.

P46. Sherrington Was Right: Tail Withdrawal Responses in Rats Are Limited in Direction

C.L. Cleland, D. Weiss, J. B. Harrold, L. A. Burns, S. L. Clegg

In the early 1900s, Sherrington proposed that a stereotyped flexion response was elicited by noxious stimuli applied anywhere on the leg. In contrast, recent studies using EMG recordings have suggested the withdrawal response is directed away from stimulus location, resulting in the response direction being highly dependent on stimulus location. However, the complexity of limb biomechanics calls into question the validity of using EMG to predict movement direction. The goal of our research was to use movement and force measurements to distinguish between these two opposing hypotheses for the withdrawal of the rat tail in response to heat stimuli. Localized heat stimuli were applied to the tail with an infrared laser and responses in intact or spinalized rats

measured as movement (high-speed video) or isometric force (6 DOF force/torque transducer). In spinalized rats, our central finding was that regardless of stimulus location (8 locations distributed circumferential around the tail), stimulus intensity (1-3xT), number of simultaneously applied stimuli (one or two), or rostral-caudal location of the stimulus (5 locations), the response was directed in only two directions, +~14 degrees lateral to ventral. There were no dorsal or pure ventral responses. Responses in intact rats were similar except reversed in the dorsoventral direction. These results support Sherrington's observations and suggest the mammalian withdrawal response is designed to trade off "accuracy" for computational simplicity and presumably lower response latency.

P47. Bilateral Putamen Connectivity during Human Motor Task Execution

William R. Marchand, James N. Lee, John W. Thatcher, Lindsey Healy, Edward W. Hsu, Esther Rashkin, Jennifer Starr

The putamen serves as an input nucleus for the frontal-subcortical circuits, which consist of the cortex, basal ganglia and thalamus. These circuits are thought to be involved in motor, cognitive and emotional processing and function abnormally in multiple neuropsychiatric disorders. However, the function of these circuits in normal individuals is poorly characterized. We studied 34 normal subjects using functional magnetic resonance imaging at 3 T. All subjects were strongly right-handed. Subjects completed 3 motor activation paradigms. These were a self-paced and externally-paced button-pressing task and a complex button-pressing task. Group results showed bilateral activation of most basal ganglia structures and thalamus was seen for all contrasts at the 0.05 corrected level of significance and bilateral activation for many basal ganglia structures persisted at the 0.000001 level. Functional connectivity analyses based on the general linear model were completed for each contrast with the right and left putamen as separate seed regions. These analyses were thresholded at a significance level of 0.000001 corrected and revealed some bilateral functional connectivity for all contrasts and extensive bilateral cortical, subcortical and cerebellar connectivity with the putamen for the complex task. Historically, theories of frontal-subcortical circuit motor function have been based on the hypothesis that the circuit ipsilateral to the controlling motor cortex was primarily involved in motor execution. Our findings suggest that these circuits are activated bilaterally and further have extensive bilateral connectivity. If replicated, these findings may have significant implications for the understanding and treatment of disorders that involve the basal ganglia circuits.

P48. Isolation Rearing Enhances Prepulse Inhibition Deficits in a Rat Model of Schizophrenia

Carrie E. John, Gwendolyn C. Calhoon, Chuma G. Obineme, Patricio O'Donnell

Prepulse inhibition (PPI) of the acoustic startle response is a reduction in the magnitude of the startle reflex to loud sounds when they are preceded by acoustic stimuli of low-intensity at a specific time interval. This test is useful for measurements of the functioning of sensorimotor integration in both humans and animals. PPI deficits are one behavioral abnormality seen in schizophrenia patients as well as in several animal models of schizophrenia, including isolation rearing and the neonatal ventral hippocampal lesion (NVHL) models. In this study, we sought to determine if isolation rearing could exacerbate PPI deficits seen in NVHL rats. At postnatal day 7, pups received either an excitotoxic lesion of the ventral hippocampus or sham surgery. At weaning (postnatal day 24-27), rats were housed in either groups of 2-3 or singly. At adulthood, rats were tested for PPI measurements with 3 different prepulse levels (5, 10 and 15 dB above a background noise of 70 dB). We found that higher intensity prepulse resulted in greater prepulse inhibition, lesion animals showed deficits compared to sham controls and isolates showed deficits compared to group housed rats. There was a strong trend toward an interaction between lesion status and rearing condition, suggesting that environmental factors during a critical developmental stage (i.e. adolescence) can affect neural circuits disrupted by the neonatal lesion.

P49. Global Gene Expression Profiling of Rat Prefrontal Cortex after Chronic Oral Risperidone Treatment

Mark E. Bardgett, Brian Hoffman, Molly S. Griffith, Xiaohong Li, Nigel G. F. Cooper

While antipsychotic drugs antagonize several neurotransmitter receptors, this immediate biological effect does not fully explain their delayed therapeutic effect. As such, studies are needed to identify other molecular targets of chronic antipsychotic drug treatment. The present study used global gene expression profiling to determine the effects of chronic oral treatment with the atypical antipsychotic drug, risperidone, on gene expression in the rat medial prefrontal cortex. Adult male rats were provided with one of two doses of risperidone (1.25 or 5.0 mg/kg/day) or vehicle via their drinking water for 35 days. Locomotor activity was measured weekly, and tissue from the medial prefrontal cortex was coll-

ected on the last day of treatment. Total RNA from individual animals (n = 6-7 per group) was extracted and hybridized into an Agilent Rat Whole Genome array (60-mer). Risperidone decreased locomotor activity in a dose-dependent manner. The expression of 88 transcripts was significantly increased in the high dose group as compared to controls, while the expression of 134 transcripts was elevated in the low dose group as compared to controls. Many of the same transcripts were elevated in both treatment groups. Decreased expression of six and thirty-nine transcripts was found in respective comparisons of the high and low dose groups with controls. Notably, the transcript for the GABAB receptor-1 was elevated in the high dose group. The results suggest that global gene expression profiling may be useful in revealing novel mechanisms of action for existing antipsychotic drugs, and novel molecular targets for potential candidate compounds. Support Contributed By: P20RR16481, P20RR018733, P30ESO14443, & MH07678. Risperidone was provided by the National Institute of Mental Healths Chemical Synthesis and Drug Supply Program.

P50. Expression of the Cannabinoid Receptor CNR1 in Schizophrenia and across Life Span in Postmortem Human Prefrontal Cortex

R. C. Buerlein, T. M. Hyde, T. Ye, A. Joseph, L. Joseph, B. K. Lipska, J. E. Kleinman

Some studies support an association between the endocannabinoid system and schizophrenia. The use of cannabis in vulnerable individuals causes and/or exacerbates psychosis, and people with psychotic disorders use cannabis more frequently. We examined expression profiles of two cannabinoid receptors (CNR1 and CNR1a) during human life span in 218 postmortem prefrontal cortical samples (CBDB/NIMH and University of Maryland collections acquired using protocol 90M0142 and informed consents from next-of-kin), spanning human aging from gestational age 14-20 weeks (N=38) and from day 1 after birth to 78 years (N=180), each without history of neuropsychiatric illness, neurological disease or drug use, and tested whether changes in the expression of CNR1 and CNR1a mRNA are present in postmortem dorsolateral prefrontal cortex and hippocampus of patients with schizophrenia (N~30) as compared with normal controls (N~70). We measured CNR1 and CNR1a expression by quantitative real-time PCR using two assays: one assay recognized both CNR1 and CNR1a, while the second was specific to CNR1a. The expression of both transcripts (CNR1 and CNR1a together) as well as CNR1a alone increased significantly in the frontal cortex between gestational weeks 14 and 20 ($r>0.4$, $p<0.006$). Later in life, CNR1 and CNR1a

expression measured together and CNR1a measured alone, declined significantly with increasing age ($r<-0.5$, $p<0.002$). We did not find any significant differences in the expression of cannabinoid receptor mRNA between patients with schizophrenia and normal controls.

P51. Expression of Ephrin-A3 and Epha4 in Somatosensory Cortical and Thalamic Neurons in Neonatal Rats

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

During early development, ephrins have a recognized role in guidance and topographic ordering of thalamocortical axons (TCAs) from ventrobasal thalamus (VB) to primary somatosensory cortex (S-I). Well after target innervation and terminal patterning have occurred, constitutive regulation of ephrin expression continues and may serve to function in pattern maintenance or plasticity. Immunohistochemistry reveals expression of ephrin-A3 in a barrel-like manner within S-I from postnatal day (P) 6 to P14. EphA4, a receptor for ephrin-A3, is concurrently expressed in thalamus and in cortex in barreloid/barrel-like patterns. Development of ephrin-A3 patterned expression is dependent on the integrity of subcortical somatosensory pathways immediately following birth, but thereafter does not require the continued presence of TCAs. We base this on three findings: infraobital (IO) nerve transection on P0 eliminates patterned ephrin-A3, but neither IO nerve transection on P8 nor lesions of VB at P4 or P6 alters patterned expression. The VB lesions did, however, abolish patterned EphA4 in S-I, suggesting that TCAs are the likely source of these receptors. Confocal microscopy of S-I also shows that EphA4 co-localizes with a known marker for VB TCAs—the selective serotonin transporter. The precise cellular source of ephrin-A3 in S-I has yet to be identified, and the question of whether ephrin-A3 interacts with EphA4 to maintain TCA patterns as the terminals mature is still unanswered. Nevertheless, the data presently suggest that ephrin involvement in S-I is ongoing when TCAs and intracortical connections are growing into this area and when compartmentalization of barrels may still require molecular guidance.

P52. Wake-Enhancing Effects of Nicotine Are Mediated by α4β2 and α7 Subunit-Containing Nicotinic Acetylcholine Receptors (Nachrs) in Rats

M. Gasior, J. A. Gruner, V. Marcy, Y-G Lin, M. Williams, M. J. Marino

The specific subunit composition of nAChRs mediating wake-enhancing effects of nicotine has not been established. This study investigated the involvement of α4β2 and α7 subunit-containing nAChRs in the acute effects of nicotine on sleep/wake activity. Male Sprague-Dawley rats were chronically implanted with electrodes for monitoring time spent in wake, slow-wave sleep (SWS), and rapid-eye-movement sleep (REMS). Sleep/wake activity was recorded for 12 h in rats dosed at 1 PM (8 AM lights on/8 PM lights off) with nicotine (0.1, 0.3, 1.0 mg/kg s.c.), dihydro-β-erythroidine (DHβE, α4β2 antagonist, 1, 3, 10 mg/kg s.c.), or methyllycaconitine (MLA, α7 antagonist, 0.1, 1.0, 10 mg/kg i.p.) alone. Subsequently, the effects of selected doses of DHβE and MLA were evaluated on nicotine-induced waking. Nicotine dose-dependently increased wake activity by up to 48 min over 4 h post dosing at 1 mg/kg ($p < 0.05$, Dunnett's). At this dose, SWS and REMS were correspondingly decreased for 2 h post dosing. Onset latency for SWS but not REMS was increased at 0.3 and 1.0 mg/kg. Neither DHβE nor MLA alone up to 10 mg/kg altered sleep/wake activity ($p > 0.05$; ANOVA). DHβE (10 mg/kg) completely (100%) blocked the wake-enhancing effect of 1 mg/kg nicotine ($p < 0.01$ vs. nicotine, $p > 0.05$ vs. vehicle, Bonferroni) whereas MLA (10 mg/kg) produced a partial but non-significant block (58%; $p > 0.05$ vs. nicotine or vehicle, Bonferroni). These data demonstrate the involvement of both α4β2 and α7 subunit-containing nAChRs in the wake-enhancing effects of acute nicotine in rats. Relative roles of different nAChR subtypes on rebound hypersomnolence following nicotine-induced wake are being investigated. *Supported by Cephalon, Inc.*

P53. Orbitofrontal Cortex Does Not Signal Reward Prediction Errors (OFC VS VTA)

D. J. Calu, M. R. Roesch, G. Schoenbaum

Reward learning is thought to require animals to form expectations about what rewards are imminent and be able to detect when violations to those expectations have occurred. Recording studies suggest that orbitofrontal cortex (OFC) signals expectation of reward, while dopaminergic neurons (DA) of the midbrain signal reward prediction errors. However, recent neuroimaging studies suggest that OFC also signals violations of reward expectations. Here we apply the same prediction error

analysis to activity of neurons recorded in OFC and VTA in two groups of rats performing an identical task. Rats were trained to respond at two fluid wells for rewards. During training, time to and size of reward were independently manipulated. As a result, the rewards were systematically delivered or omitted unexpectedly. Most dopamine neurons show clear evidence of encoding of reward prediction errors. These same neurons go on to develop activity that signals the relative value of the cue. DA neurons showing positive prediction errors also demonstrate negative prediction error signaling. In contrast, a non-significant proportion of neurons in OFC show positive reward prediction error signaling (no more than expected by chance), and those that do, do not go on to develop cue-selective firing reflecting any measure of value. Additionally, OFC neurons showing positive prediction errors do not show corresponding negative prediction errors.

P54. Orbitofrontal Cortex Is Critical for Conditioned Reinforcement Mediated by Outcome-Specific Representations

Kathryn A. Burke, Danielle N. Miller, Theresa M. Franz, Geoffrey Schoenbaum

Neutral cues paired with reward through Pavlovian conditioning can come to evoke representations of the reward as well as feelings/general affect associated with that reward. These cues can even go on to support instrumental learning in the absence of reward, a process known as conditioned reinforcement (CRf). Previously, it has been shown that orbitofrontal cortex (OFC), a region important for using information about outcomes to guide behavior, is implicated in CRf (Pears et al., 2003). Here we show that OFC is critical in guiding responding for conditioned reinforcers only when these cues evoke a representation of the outcome. Using a transreinforcer blocking procedure (Rescorla, 1999), rats were trained to associate two light cues (A & B) with two different outcomes (A-O1, B-O2). Subsequently, in compound conditioning, A & B were paired with two auditory cues, X & Y, leading to either the same outcome (AX-O1) or a new outcome (BY-O1). This procedure created a partially blocked cue (Y), biased to evoke outcome representations, a fully blocked cue (X), and two fully conditioned cues (A/B). We found that OFC lesioned rats learned to respond normally for fully conditioned cues (A) but not for the partially blocked cue (Y). Further, probe tests demonstrated that OFC lesioned rats did not exhibit Pavlovian responding for Y. These data suggest that OFC is critical in using outcome representations to guide responding in CRf.

P55. What Affects Resting Glutamate Levels in Striatum and Prefrontal Cortex of Awake Rats and Mice?

Peter Huettl, Erin R. Hascup, Kevin N. Hascup, Francois Pomerleau, Kirk W. Johnson, Greg A. Gerhardt

Regulation of resting or basal glutamate (Glu) levels in the central nervous system involves a variety of complex processes and its modulation is still debated. We have developed a unique enzyme-based microelectrode array (MEA) to selectively measure resting Glu levels in the CNS of awake rats and mice. These MEAs used in conjunction with amperometry have sub-second (600 msec) time resolution and are virtually free from major electroactive CNS interferents such as DOPAC and ascorbate. Effects on resting Glu levels in the prefrontal cortex and striatum were investigated using local application of the following drugs: $mGluR_{2/3}$ agonist (LY379268) and antagonist (LY341495), sodium channel blocker tetrodotoxin (TTX), cystine-glutamate exchanger blocker (S)-4-carboxyphenylglycine (CPG), D,L-*threo*-β-hydroxyaspartate (THA), a transportable, competitive inhibitor for excitatory amino acid transporters (EAAT), ω-conotoxin, a Ca^{2+} channel blocker and an anesthetic (urethane). TTX and ω-conotoxin significantly ($p<0.05$) decreased resting Glu by 25% and 60%, respectively, while THA significantly ($p<0.05$) increased resting Glu by 60%. The $mGluR_{2/3}$ agonist and antagonist were seen to decrease or increase, respectively, resting Glu by ~15%. CPG was seen to decrease resting Glu levels by ~15% and urethane anesthesia decreased it by over 60%. Our results indicate that we can reliably measure either negative or positive modulation of neuronally-derived resting Glu levels on a second-by-second time scale in the brain of awake rodents.

P56. Impaired Mismatch Negativity in Phencyclidine-Rat Model of Schizophrenia

Andrea Balla, Megan Nattini, Daniel C. Javitt

Auditory event-related potentials (ERP) are disturbed in schizophrenia. Schizophrenic patients show a deficit in mismatch negativity (MMN) generation and in an interstimulus-interval-dependent P1 and N1 generation. Clinical and primates studies demonstrate similar dysfunctions in the auditory cortex after systemic or local infusion of N-methyl-D-aspartate (NMDA) antagonists, supporting glutamatergic and phencyclidine (PCP)/NMDA models of the disorder. This study evaluated the validity of the rat P1/N1 and MMN model and investigated the effect of chronically administered PCP and glycine (GLY) on ERPs. Method:

Duration and frequency deviant MMN and a repetitive auditory stimuli presented at 3 levels of ISI (1, 3 and 6 sec) were recorded in awake rats using surface electrodes. Electrodes were implanted above the left, right auditory cortex. ERP were recorded sequentially at baseline during 2 week PCP treatment (15 mg/kg/day) and during subsequent treatment with PCP and GLY (16 % GLY diet). Results: Rat showed P1 and N1 amplitude with increasing ISI, similar to what is observed in humans. Rats also showed activity resembling human MMN at duration but not frequency deviants. PCP inhibited P1 and N1 refractoriness at long 6 sec ISI and duration deviant MMN generation. These effects were partially reversed by GLY treatment. Conclusion: Rodent models may be useful for investigating the etiology of the neurophysiological disturbancies in schizophrenia and that ERP may be associated with impaired neurotransmission at NMDA-type glutamate receptors.

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Poster Session 3

Tuesday–Thursday • Ballroom 2 & 3

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

P57. Consolidation of Motor-Skill Memory in the Dorsal Striatum: Post-Trial Interference Reversed by Cocaine

I. Willuhn, H. Steiner

Drug-induced aberrations in procedural learning, mediated by the dorsal striatum, are thought to contribute to psychostimulant addiction. Our previous studies showed that cocaine alters procedural (skill) learning in a novel running-wheel paradigm and associated gene regulation in the striatum. Blockade of striatal D1 dopamine receptors during running-wheel training inhibits the acquisition of wheel-skill memory. Here, we investigated whether the striatum is also involved in the consolidation of this skill memory and how cocaine affects this process, by using post-trial drug infusion into the striatum. Rats were trained on a running wheel on two days (40 min/day), with or without cocaine (25 mg/kg, i.p.). Immediately after each training session, they received an intrastriatal infusion of lidocaine or vehicle, or a sham infusion. The ability to control the movement of the running wheel (wheel skill) was tested before and repeatedly after the training (up to 4 weeks). Sham-infused controls displayed a significantly improved wheel skill for at least 4 weeks. In contrast, post-trial infusion of lidocaine or vehicle into the striatum attenuated wheel-skill memory consolidation. This effect was more pronounced in animals that practiced less during the training. Cocaine administered before each training session prevented disruption of skill-memory consolidation by either post-trial manipulation. These findings demonstrate that the striatum is not only involved in the acquisition but also in the consolidation of motor-skill memory. Furthermore, our results suggest that cocaine "stabilizes" such motor-memory consolidation. Cocaine-induced stabilization of motor-memory consolidation may contribute to psychostimulant addiction.

P58. Neurons in the vSub Are Activated by Noxious Stimuli and Are Modulated by NE Afferents

Witold J. Lipski, Anthony A. 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 effect of noxious stimuli and locus coeruleus (LC) inputs on vSub neuron electrophysiological activity has 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 50% of vSub neurons tested (450% firing rate increase relative to baseline, N =11/22). The remaining vSub neurons exhibited no significant change in firing rate (N = 11/22) during footshock. Moreover, electrical train stimulation of the LC was found to activate neurons of the vSub (290% firing rate increase 60 s following LC train, N = 8). Single neuron responses were accompanied by high frequency LFP activity, indicating the presence of synchronized network activity. Preliminary results indicate that systemic application of alpha-2 NE receptor antagonist yohimbine or the beta NE antagonist propranolol each partially blocked the response to LC stimulation. 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 to that response.

P59. Differences in Receptor Expression and Dopamine Cell Activity during Adolescence May Predispose Adolescents to Drug Addiction

J. E. McCutcheon, S. B. Carr, K. L. Conrad, K. A. Ford, M. E. Wolf, M. Marinelli

Human studies suggest that adolescents differ from adults in their patterns of drug use and reactivity to drug exposure. However, it is unclear whether there is a biological underpinning to this. As the adolescent brain is still developing, including the dopamine system which is critical for drug addiction, there may be age-related differences in drug-induced behaviors in adolescence. As dopamine cell activity correlates with drug reactivity in several animal models, we decided to investigate differences in this parameter between adolescents and adults. Indeed, our results

show that, in anesthetized rats, dopamine cells in adolescents fired faster than in adults. We also noted that D2-mediated autoinhibition of these cells was lower in adolescents than in adults. To probe the underlying mechanisms further we used biochemistry to examine receptor expression in the ventral tegmental area. We found lower expression of the D2 receptor in adolescents compared with adults, suggesting reduced dopamine-induced autoinhibition during adolescence. Additionally, glutamate AMPA receptor subunits were expressed at a higher level in the VTA of adolescents, indicating more excitation in adolescents than in adults. To confirm that the observed differences in receptor expression could influence the firing of dopamine cells, we used immunohistochemistry to show that AMPA receptor subunits co-localize with tyrosine hydroxylase, a marker for dopamine cells. In summary, elevated dopamine cell activity observed in adolescents is due, at least in part, to a shift in the balance of inhibition and excitation in these cells. These findings may help to explain sociological findings on teenage drug use.

P60. Imaging Brain Activation: Looking "Through the Eyes" of Different Tracers

N. F. Cruz, K. K. Ball, G. A. Dienel

Unanticipated fluxes can be revealed by use of different tracers to evaluate steps of the same metabolic pathway, and several studies found that the magnitude of rates of glucose utilization (CMRglc) evoked by sensory stimulation of conscious rats is greatly underestimated in autoradiographic studies using [14C]glucose compared to [14C]deoxyglucose. We found that tonotopic activation bands are not adequately registered by either [1-14C]- or [6- 14C]glucose, consistent with rapid release of 14C-metabolites. Extracellular lactate level doubles during activation, suggesting that increased lactate formation may lead to greater release to blood or increased oxidation to 14CO2. If local lactate oxidation via pyruvate dehydrogenase matched its formation via glycolysis, the levels of [14C]lactate and 14CO2 in extracellular fluid (ECF) should be similar when [3,4-14C]glucose is microinfused into the inferior colliculus during acoustic stimulation. However, analysis of microdialysates of ECF revealed that the proportion of 14C recovered in acidic compounds (including lactate) greatly exceeded that of 14CO2 before, during, and after acoustic activation, suggesting that lactate release contributes more to underestimation of CMRglc than generation of 14CO2. Focal underestimates of CMRglc could also arise from rapid dispersal of 14C-metabolites, and widespread perivascular distribution of microinfused

fluorescent tracers, as well as spreading of label from [6-14C]glucose, support the likelihood of intracerebral movement of labeled metabolites. Taken together, the low accumulation of products of [1- or 6-14C]glucose in activated tissue and small amount of 14CO2 formed from [3,4-14C] glucose support the notion that lactate release from activated brain cells exceeds local lactate oxidation.

P61. Potential Role of NUDEL-Oligopeptidase Enzymatic Activity in PC12 Cells Differentiation Process

Juliano R. Guerreiro, Atsushi Kamiya, Nick Brandon, Maurício Machado, Joana D. Campeiro, Vitor Oliveira, Akira Sawa, Antonio C. M. Camargo, Mirian A. F. Hayashi

NUDEL-oligopeptidase, initially known as endooligopeptidase A (EOPA), is a cysteine peptidase isolated from the cytosol of rabbit brain. This enzyme can selectively hydrolyze oligopeptides of 7 to 13 amino acid residues, such as neurotensin and bradykinin. This enzyme was shown belong to a family of phosphorylated coiled-coil proteins that interact with microtubules-associated proteins (MAPs). Recently, these interactions were shown to be essential for brain development and cortical organization during embryogenesis. We have analyzed the structural organization of the human NUDEL-oligopeptidase gene showed the presence of putative binding sites for several known transcription factors, including Sp1, GATA-1, Nkx2, c-Myb, CP2, CdxA, and SRY were observed. Knowing the cell specificity expression of this oligopeptidase we examine the promoter activity of the 5' upstream region and serial deletion mutants of human NUDEL-oligopeptidase gene in PC12 cells induced to differentiation. Surprisingly, a clear upregulation of human promoter could be observed three days after induction of differentiation process, when neurite outgrowth is observed. The potential activator of the promoter activity was found to be located within positions [-514 to -245] upstream of the transcription initiation site. NUDEL-oligopeptidase enzymatic activity and protein expression in these cells are consistent with the observed promoter activity. Evaluation of neurite outgrowth of these PC12 cells induced to differentiation after transfection with enzymatically active wild-type and inactive mutant form of NUDEL-oligopeptidase, and full-length Disc1, allowed suggest that the NUDEL-oligopeptidase activity plays a crucial role for the differentiation process of PC12 to neurons. A functional role for this proteolytic activity in neuronal migration and axonal outgrowth is also being suggested.

P62. Does the Mesocorticolimbic Dopamine System Contribute to the Subthalamic Nucleus Hyperactivity in Parkinson's Disease?

Shannon R. Blume, Kuei Y. Tseng

It is our goal to establish an animal model of parkinsonism that accounts for a comparable age of disease onset mimicking both motor and cognitive deficits as seen in human Parkinson's Disease (PD). Here we use the chronic MPTP/probenecid mouse model to determine the relationship between nigrostriatal and mesocorticolimbic dopamine deficits, and parkinsonism induced akinesia and subthalamic nucleus (STN) hyperactivity. Chronic MPTP/probenecid treatment in 10 month old mice resulted in ~75% decline in tyrosine hydroxylase (TH+) neurons in the substantia nigra (SN). This deficit was positively correlated with the stepping test performance, a behavior measurement of akinesia in rodents. Mice exhibiting greater than 70% decline of SN TH+ cells showed significant impairments in their adjusting steps. These changes are accompanied with an increase in STN metabolic activity as revealed by cytochrome oxidase staining. However, the hyper STN state is not correlated with the degree of SN TH+ cell loss or stepping test deficits. Interestingly, the STN hyperactivity is positively correlated with the degree of TH+ cell loss in the VTA. These observations suggest that chronic deficits in the mesocorticolimbic dopamine system play an important role in the pathophysiology of STN hyperactivity in PD.

P63. Postnatal Maturation of Calcium Plateau Potentials in the Prefrontal Cortex during Adolescence: Role of L-Type Calcium Channel and Protein Kinase A Signaling

Lijun Heng, Xiuti Hu, Kuei Y. Tseng

The cellular mechanisms that contribute to convert an immature prefrontal cortex (PFC) into a mature network remain unknown. Evidence indicates this process could be associated to the interaction between a late maturation of intrinsic neuronal properties, combined with a delayed acquisition of adult levels of dopamine and glutamate receptors. Here we investigated how intrinsic calcium function in the PFC changes during the peri-pubertal/adolescent transition to adulthood. We conducted whole-cell patch clamp recordings in layer 5 pyramidal neurons from the medial PFC and compared the duration of a pharmacologically isolated somatic calcium plateau potential in brain slices from pre- (postnatal day, PD<35) and post-pubertal (PD 42-80) rats. We found

that the duration of calcium plateaus becomes significantly prolonged in the postpubertal PFC; only a small proportion of neurons recorded from prepubertal rats showed calcium plateau durations similar to that from the adult PFC. Furthermore, the L-type calcium channel antagonist nifedipine and the PKA inhibitor PKI[5-24] reverted the adult calcium plateau profile to the prepubertal range. Altogether, these data suggest that pyramidal neurons in the PFC gradually acquire the mature calcium response during the peri-pubertal/adolescent transition to adulthood. These changes are likely to be mediated by an enhancement of L-type calcium channel function and require postsynaptic PKA signaling.

P64. Transcriptional Profiling of Postmortem Anterior Prefrontal Cortex from Cocaine Users

E. Lehrmann, A. Deep-Soboslay, R. H. Lowe, T. M. Hyde, M. A. Huestis, J. E. Kleinman, W. J. Freed

Substance use changes brain function, which is reflected in gene expression changes. Microarray analysis was employed to examine postmortem anterior prefrontal cortex (aPFC) from cocaine users. Ten cases with confirmed ante-mortem cocaine use, by case history and/or cocaine positive hair testing and with cocaine-positive toxicology in brain, were selected. Each was individually compared to four brain pH, postmortem interval, smoking history, gender and age-matched control cases, and significantly regulated transcripts identified. Cases differed in the manner and cause of death, with acute trauma (stab/gunshot wounds, S/GSW) for seven and acute drug intoxication (AI) for three cases. Among transcripts with increased expression, 60% were shared for both groups, 6% were identified only in S/GSW cases, and 34% only in AI cases. In contrast, all transcripts with decreased expression in S/GSW cases (40%) were also identified in AI cases, while the remaining 60% were decreased only in AI cases. For all cases, there was a decreased expression of transcripts encoding calcium/calmodulin-related functions, with increased expression of transcripts functionally annotated to ER/Golgi function, clathrin-coated vesicle/trafficking and lipid metabolism, in particular cholesterol biosynthesis and transport. Quantitative PCR for individual transcripts (CALM2, SEMA3B and APOL2), each representing a functional classification, validated these findings. Changes in pathways effecting synaptic function and plasticity may therefore represent transcriptional correlates of changes in aPFC function in cocaine users.

P65. Glutamate Release in the Ventral Striatum Is Regulated by Both D1 and D2 Receptor Activity

Nigel S. Bamford, Dennis Dever

Dopamine modulation of excitatory glutamatergic afferents in the accumbens core is implicated in habit formation and drug dependence. We observed the effect of dopamine on glutamate release from corticoaccumbal terminals, using a combination of presynaptic optical imaging and post-synaptic whole-cell patch clamp experiments in sagittal sections prepared from C57Bl6 mice. Cortical terminals were loaded with the fluorescent endocytic tracer FM1-43 via bipolar stimulation over the prefrontal cortex and visualized using a multiphoton confocal microscope. Re-stimulation of the cortex produced exocytosis that was quantified by the release halftime (t1/2), defined as the time required for puncta to reach 50% luminescence. Corticoaccumbal release was slower in the presence of the dopamine-releaser amphetamine (t1/2=287 sec vs. 176 sec for controls;$p<0.001$). The D1 (t1/2=308 sec; SKF38393;10uM) and D2 (t1/2=254 sec; quinpirole;0.5uM) agonists also inhibited release ($p<0.001$) by depressing activity from terminals with the lowest probability of release. The inhibitory effect of amphetamine was seen at 20Hz cortical stimulation but not at 1Hz or 10Hz, and was reversed only following exposure to both D1 (SCH23390;10uM) and D2 receptor (sulpiride;10uM) antagonists (t1/2=193 sec;$p>0.5$). D1 actions were partially dependent on adenosine, as the adenosine antagonist DPCPX (500nM) reduced the inhibition caused by SKF38393 (t1/2=219 sec;$p<0.001$), but did not abolish it. Both D1 and D2 receptor agonists also inhibited low amplitude-high frequency spontaneous excitatory postsynaptic currents ($p<0.05$). Dopamine acts a low-pass filter, with filtering applied to less-active cortical inputs. Disruption of this neural integrator would likely disturb critical cortical-basal ganglionic networks resulting in disorders of thought and movement.

P66. Expression of Schizophrenia Susceptibility Genes in Human Cerebral Cortex across the Lifespan

Hetal Choxi, R. Buerlein, T. M. Hyde, T. Ye, C. Colantuoni, A. Elkahloun, D. R. Weinberger, J. E. Kleinman, B. K. Lipska

In order to better understand how risk genes and brain development contribute to the pathogenesis of schizophrenia we examined expression of selected susceptibility genes (in particular, DISC1 and genes in the

DISC1 pathway) in normal human prefrontal cortex in 240 postmortem brain samples (CBDB/NIMH and University of Maryland collections acquired using protocol 90M0142 and informed consents from next-of-kin), spanning human aging from gestational age 14-20 weeks (n=38) and from day 1 after birth to 78 years (n=180), each without history of neuropsychiatric illness, neurological disease or drug use. We used quantitative real-time PCR to measure expression of mRNA. Expression of three main isoforms of Citron (CIT) declined sharply from the 2nd trimester of gestation to ~10 years of age and then gradually increased. Other genes interacting with DISC1 and investigated in this study, Ndel1, PAFAH1B1 (LIS1) and FEZ1 showed upregulation early in life and a gradual decrease with ageing. We also found that DISC1 mRNA was expressed at stable levels during 2nd trimester of gestation. DISC1 expression was highest at early postnatal age (from birth to 1 year of age), and thereafter gradually declined with ageing. These studies identify genes important in early development of the human prefrontal cortex.

P67. Progression of Immune Activation in Ventral Horn and Ventral Nerve Roots in the Transgenic G93A-SOD1 Rat Model of Amyotrophic Lateral Sclerosis

B.T. Harris, D. J. Graber, C. H. Cogbill, K. Merkens, W. F. Hickey

Mechanisms leading to motor neuron loss in ALS remain unclear and there is no effective treatment to halt disease progression. Early immune activation has been well characterized in the transgenic models that over-express mutated human superoxide dismutase-1 (mhSOD1). Transgenic G93A mhSOD1 rats have been developed more recently and provide a valuable tool to compare with previous findings from the murine model to determine important factors in disease initiation and progression. To further understand the role of immune cell activation in the development of ALS, we examined various immune activation markers at time points prior to clinical manifestation, at symptom onset, and at end-stage of disease in G93A and age-matched wild-type rats using immunohistochemistry. In the ventral horn of G93A rats, focal elevations in CD11b expression were observed at 90 days and its distribution increased as the disease progressed. The phagocytic lysosome marker CD68 was not evidenced at 90 days, but there was moderate ?punctate' labeling at 105 days and its tissue distribution also increased over time. Few cells expressed MHC class II, CD11c, and CD86 at 90 days. While the numbers of MHC class II+ cells increased as disease progressed, CD11c+ and CD86+ cells increased at 105 days and then decreased at symptom onset. These results indicate that the immune

activation occurring prior to and during ALS symptom onset is distinct around motor neuron somas and its axons in the nerve roots. Dual-labeling of immune and neural markers is currently being assessed to determine the cell types expressing the immune markers and their spatial relationship to dying motor neurons.

P68. Ventral Striatal Neuronal Entrainment to Hippocampal Theta and Representation of Reward in the Awake Behaving Rat

John A. Wolf, Leif H. Finkel, Diego Contreras

The nucleus accumbens (NAcb) integrates inputs from the prefrontal cortex (PFC) and hippocampus (HC), as well as the amygdala and thalamus. Abnormal integration of inputs from the HC and PFC in the NAcb has been proposed as a possible factor in schizophrenia. In HC, cells entrain to theta oscillations (4-12Hz) at a phase modulated by the animal's location. Cells in the NAcb and the PFC have been demonstrated to entrain to these HC oscillations as well. To investigate the relationship between PFC inputs to the NAcb and HC theta in the awake animal, we chronically implanted male Long-Evans rats and examined the response properties of NAcb cells to afferent stimulation from the PFC. Animals were implanted with 8 movable tetrodes in the NAcb, a bipolar recording electrode in ventral hippocampal CA1, and a bipolar stimulating electrode in the PFC. Trains of stimuli were delivered to the PFC at an interstimulus interval of 2 seconds + a random value (<500msec) while the animal performed a T-maze task. Most recorded NAcb cells responded robustly to PFC stimulation. A subset of cells was sensitive to the phase of HC CA1 theta, with a phase-locked increase in response magnitude. A subset of these cells are also entrained to HC theta during non-stimulated runs. Ongoing analysis will determine whether subregions of the task lead to greater or less synchronization of spike output from the NAcb with HC theta. Results from experiments of ensemble activation by different flavored rewards in the T-Maze will also be presented.

P69. Investigating the Role of Oligodendroglia in Retrovirus-Induced Spongiform Neurodegeneration

William P. Lynch, Rochelle Cutrone, Ying Li, Wendy Macklin

Certain retroviruses, like prions, can induce progressive spongiform neurodegeneration in brainstem and spinal cord gray matter upon infection of the CNS. The molecular/cellular mechanisms by which

these neurovirulent retroviruses (NV) induce vacuolar changes in motor neurons are not known. Evidence to date indicates that the degenerating motor neurons are not infected. Instead, the primary CNS targets are the microglia, whose infection co-localizes with spongiform change. While microglial infection is prominent in regions of pathology, their infection does not induce detectable cellular changes, suggesting that microglia may simply act to disseminate virus to other CNS cells. Perineuronal oligodendroglia may constitute one such target given that they are observed to undergo vacuolation as disease progresses. However, prior immunohistochemical studies using traditional oligodendroglial markers have only rarely documented NV protein co-expression in such cells. Therefore, in this study we have re-examined the issue of oligodendroglial susceptibility to NV using mice where EGFP is expressed in both immature and mature oligodendroglia by virtue of the proteolipid protein(PLP) promoter. In these experiments neonatal IRW-PLP-EGFP mice were infected with either NV or NN (FrCasE and Fr57E, respectively) and assessed immunohistochemically for virus distribution and vacuolation in relation to GFP expression. Infection of GFPneg and GFPlo cells could be detected while GFPhi cells were not. The findings and their implications for neuropathogenesis will be discussed.

P70. Effects of MDMA on Neurogenesis and Conditioned Place Preference in Adolescent Rats

Ashley E. Sponaugle, Briony J. Catlow, Kimberly A. Badanich, Cheryl L. Kirstein, Juan Sanchez-Ramos

Adolescence is typically the period when drug abuse is initiated and is often defined by high risk taking, exploration, and sensation seeking. Drugs of abuse are believed to have a marked effect on neurogenesis in the adolescent brain. MDMA abuse in human adolescence is prevalent; moreover, abuse during this time period may impact normal development of the brain or potentiate the likelihood of subsequent drug use/abuse. The aim of the present study was to 1) evaluate the effects of MDMA in adolescent rats using the conditioned place preference (CPP) paradigm to measure MDMA-induced reward and 2) to measure effects of MDMA on neurogenesis in the adolescent hippocampus. Methods: MDMA CPP was measured in early adolescents [postnatal day (PND) 28-39] by training rats to associate 1.25, 2.5, 5.0 mg/kg/ip MDMA or saline with environmental cues. After drug cessation (24 hr or 2 weeks) Bromodeoxyuridine (BrdU) was injected followed by euthanasia. Unbiased counts of the number of BrdU, doublecortin and calretinin positive cells in the dentate gyrus were estimated. Data show MDMA-induced place conditioning effects at several doses. Ontogenetic differences in

MDMA-induced neurogenesis may mediate dose response effects in MDMA-induced place conditioning in adolescent rats.

P71. Gene Delivery to Sensory Neurons Following Direct Lumbar Puncture

Carolyn A. Fairbanks, Lucy Vulchanova, Lalitha Belur, Maureen Riedl, Kelley F. Kitto, R. Scott McIvor

The adeno-associated virus (AAV) serotype has been useful for gene transfer to neurons in brain.. Through application of a mannitol pre-treatment we have now achieved widespread spinal cord and dorsal root ganglion (DRG) transduction of the marker green fluorescent protein (GFP) following a direct lumbar puncture injection of an AAV serotype 5 (AAV5) in conscious rodents. The presence of GFP in DRG neurons is consistent with the following evidence for primary afferent origin of the majority of GFP-positive fibers in spinal cord: 1) GFP-positive axons were evident in dorsal roots, which bring the central processes of sensory neurons to the spinal cord, and in the dorsal columns, which contain processes of large-diameter sensory neurons projecting to brainstem; 2) dorsal rhizotomy, which severs the primary afferent input to spinal cord, abolishes the majority of GFP labeling in dorsal horn suggesting that a significant component of the the labeled dorsal horn fibers are of primary afferent origin 3) Some of the labeled neurons of the DRG also contain CGRP and SP which suggests that neurons of nociceptive origin are transduced with GFP by the AAV5 vector which is important for relevance to pain pathways. Efficient AAV5-mediated gene transfer to the spinal cord and DRG could offer substantial opportunities to 1) further study mechanisms underlying chronic pain and 2) develop novel gene-based therapies for the treatment and management of chronic pain using a non-invasive delivery route with established safety margins.

P72. Fast Desensitization of Synaptic GABA-A Receptors after Brief Hi-Frequency Firing as a Trigger for Seizures

David E. Naylor

The episodic and unpredictable occurrence of seizures in epileptics is an enigma. Recently, hi-frequency discharges or “fast ripples” are implicated with epilepsy. We find that GABA release evoked by hi-frequency stimulation of perforant path inputs in the hippocampal slice increases GABA-A tonic currents in dentate gyrus granule cells by 13.5 +/– 4.8 pA ($p<.05$). This non-desensitizing extrasynaptic tonic inhibitory current

is estimated to correlate with a 1-2 uM increase in the concentration of extracellular GABA. In addition, exposure of synaptic GABA-A receptors to micromolar levels (3 uM) of GABA rapidly desensitizes/downregulates receptors and diminishes the amplitude of miniature inhibitory postsynaptic currents (mIPSCs) from -51.3 +/– 15.2 pA to -28.8 +/– 6.7 ($p<.001$). Consequently, hi-frequency stimulated release of GABA, as might occur with ?fast ripples', could rapidly degrade synaptic inhibition. Math models that optimize the kinetic properties of GABA-A receptors through fits of IPSCs show that stimulation frequencies of 20, 40 and 160 Hz for 400 msec duration can reduce IPSC amplitudes by 39%, 57% and 75%, respectively. Furthermore, recovery from desensitization is slow and may be completely prevented by persistent intermittent discharges of frequencies as low as 0.5-2 Hz. These results suggest that very brief hi-frequency discharges can lead to sustained loss of synaptic inhibition, especially if low-frequency interictal discharges also are present. Since loss of synaptic inhibition > 30% increases seizure likelihood, evoked GABA release with rapid desensitization of postsynaptic GABA-A receptors may be important in the transition from interictal to ictal states.

P73. Involvement of the Ventral Tegmental Area and Nucleus Accumbens Septi in the Reinstatement of Cocaine Place Conditioning during Adolescence

Cheryl L. Kirstein, Kimberly A. Badanich

Psychostimulant-induced reinstatement of place preferences have been used to investigate underlying physiological mechanisms mediating drug-seeking behavior in adolescent and adult rodents; however, it is still unclear how psychostimulant exposure during adolescence affects neuronal communication in the mesolimbic DA pathway and whether these changes would elicit enhanced drug-seeking behavior later in adulthood. The aim of the present study was to investigate the effects of intra-ventral tegmental area (VTA) or intra-nucleus accumbens septi (NAcc) dopamine (DA) D2 receptor antagonist infusions on cocaine-induced reinstatement of cocaine place conditioning. Beginning on postnatal day (PND) 28, each rat was exposed to 7 different phases including 1) handling 2) baseline chamber test 3) acquisition of cocaine place conditioning (20 mg/kg/ip) 4) expression of cocaine place preference 5) maintenance and extinction of cocaine place preference 6) implantation of guide cannula into either the VTA or NAcc and 7) infusion of the D2 DA receptor antagonist sulpiride (100uM; PND 70). Data show the impact of locally infused D2 antagonist into the VTA or NAcc on the

reinstatement of cocaine place conditioning. These data suggest intrinsic compensatory mechanisms in the mesolimbic DA pathway mediate adolescent behavioral responsitivity to cocaine prime-induced reinstatement of cocaine place conditioning in adulthood.

P74. Putative Dopamine Responses during a Dopamine-Dependent Motor Behavior in a Rodent Model of Parkinson's Disease

Kristin K Anstrom, Timothy Schallert

Parkinson's disease (PD) is characterized by a host of motor symptoms including deficits in movement initiation. Despite the clear link between decreased dopaminergic (DA) neurotransmission and movement disorders, few studies have documented how DA neurons encode motor behaviors. The goals of the experiment were to: 1) identify phasic DA responses across vibrissae-elicited forelimb placing, a DA-dependent sensorimotor behavior and 2) to determine how unilateral 6-OHDA infusions affect DA firing rate and burst firing. Neural activity was recorded under homecage resting conditions and during placing trials where the experimenter moved the rat toward a table edge and brushed the whiskers against the table corner, eliciting a quick movement of the forelimb on to the table top. A total of 35 putative DA neurons were recorded in 11 rats. Average homecage firing rate prior to 6-OHDA infusions (n=14) was 4.30 ± 0.06 Hz and burst firing (% of spikes in bursts) was 20.29 ± 0.9. Both firing rate and burst firing were increased during placing. There was no significant difference in firing rate and burst firing during left vs. right placing trials. On post-infusion Day 14 (n=13), homecage firing rates and burst firing were increased (4.57 ± 0.09 Hz, 29.39 ±1.1). Placing trials further increased firing and burst indices. Firing rate and burst firing were higher during left/impaired limb placing trials even if there was no motor response. Timelocked, *phasic* DA responses were bilateral (evoked by both left and right trials), occurred after paw contact with table top and were inhibitory. Finally, if two or more putative DA neurons were recorded simultaneously, cross-correlational analysis showed that these neurons fired in a coordinated fashion. These results suggest that increases in rate and burst firing may compensate for decreased number of DA neurons. Furthermore, inhibitory phasic DA responses are not necessarily associated with aversive conditions and can coincide with increased burst firing. Clearly, to understand how DA firing patterns contribute to behavioral control or disease states, more experiments that allow delineation between behaviorally evoked responses and intrinsic DA firing patterns will be necessary.

P75. Interactive Dynamics between Frontal Cortex, Basal Ganglia, and Norepinephrine in High-Conflict Decisions and Response Inhibition

Michael Frank

The basal ganglia (BG) and frontal cortex interact intimately to facilitate adaptive motor commands while suppressing others. We use neural network simulations to investigate the interactive dynamics of this system during learning, action selection, and inhibitory control. Here we focus the role of the subthalamic nucleus (STN) within the overall BG system. Our model suggests that the STN provides a "Hold your Horses" signal that prevents premature responding during difficult decisions. This STN signal is dynamically modulated by the degree of decision conflict represented in dorsomedial frontal cortex, providing an adaptive mechanism for modulating decision thresholds. We tested model predictions in Parkinson's patients on and off STN deep brain stimulation. As predicted, DBS selectively interfered with the normal ability to slow down when faced with decision conflict—patients on DBS actually sped up under high conflict conditions. Recent extensions to this model explore how interactions with inferior frontal cortex and modulatory control by norepinephrine can recruit this same functional circuitry to support „outright response inhibition" to cancel an already planned motor response, in the context of a stop-signal task. Neuroimaging data corroborates model predictions regarding the roles of the STN and frontal areas in both conflict-induced slowing and response inhibition.

P76. A Demonstration and Interactive Explanation of the Inability To Perceive One's Own Eye Movements in a Mirror

Ralph Berger

The inability to see one's own eye voluntary movements in a mirror is rarely noticed, although originally reported more than a century ago. This phenomenon has been attributed to central neural suppression associated with saccadic eye movements. However, saccadic suppression cannot account for the inability to observe the altered position of ones eyes after they have fixated, first on one facial feature and then another. In contrast, passive motions produced by gently pushing the eyeball with a finger are easily observed. Gibsons (1966) concept of retinal "proprioception" is germane to these phenomena. Voluntary eye movements reveal successive peripheral aspects of the environment in the direction

of motion, which are accompanied by disappearance of contra-lateral aspects. Since ones eye movements are small relative to their induction of large changes in peripheral visual features, their own movement is imperceptible (c.f. the phenomena of "change blindness" in which large changes in a visual scene are usually unnoticed). An observer who focuses on one's eyes in the mirror clearly sees them move, since all other aspects of his visual field remain stable. Placing ones nose close to the mirror magnifies ones eyes, while the size of peripheral changes induced by eye movements are proportionally reduced. After looking in an extreme temporal direction and fixating on the peripheral visual boundary, one sees a "Triclops": the adjacent eye displaced laterally from its original "ghost" image and unaltered contra-lateral eye.

P77. Neuroregulation of Non-Exercise Activity Thermogenesis (NEAT) and Obesity Resistance

Catherine M. Kotz, Jennifer A. Teske, Charles J. Billington

High levels of spontaneous physical activity in lean people, and the non-exercise Activity thermogenesis (NEAT) derived from that activity, appears to protect them from obesity during caloric challenge while obesity in humans is characterized by dramatically reduced spontaneous physical activity. We have similarly demonstrated that obesity resistant rats have significantly greater spontaneous physical activity than obesity prone rats, and that spontaneous physical activity predicts body weight gain. Neural mediators of spontaneous physical activity and NEAT are beginning to be defined. Orexin is a lateral hypothalamic neuropeptide that is important to feeding behavior, maintenance of wakefulness and NEAT. Gene knockout of orexin in mice leads to reduced physical activity and obesity. We found that obesity resistant rats have elevated spontaneous physical activity as compared to obesity prone rats (prior to their obesity), enhanced sensitivity to orexin stimulation and robustly and significantly increased gene expression of the orexin receptors in orexin sensitive hypothalamic areas. Further, blockade of orexin receptors in these obesity resistant rats reduces their activity levels to that of obesity prone rats, and administration of orexin in obesity prone rats reduces body weight gain. We found that strain differences in orexin stimulation pathways for spontaneous physical activity and NEAT appear to track with the body weight phenotype, providing a potential mechanistic explanation for reduced activity and weight gain. Together, these studies suggest that orexin-mediated NEAT may be important to the obesity resistant phenotype.

P78. Repeated Ferret Odor Exposure Induces Same-Stressor Habituation and Novel-Stressor Sensitization of Neuronal Activity across Numerous Forebrain Regions in the Rat

Marc S. Weinberg, Aadra P. Bhatt, Milena Girotti, Cher V. Masini, Robert L. Spencer

Repeated exposure to a moderate stressor produces an attenuation of the HPA axis stress response (habituation) upon re-presentation of the same stressor; however, if a novel stressor is presented to the same rats, the HPA axis stress response may amplify (sensitization). The exact mechanism(s) of these phenomena are not well understood, and while neural correlates of habituation have been well documented, little is known with regard to neural correlates of HPA axis sensitization. Moreover, no studies have tested whether habituation and sensitization manifest in the same populations of neurons. This study tested whether repeated ferret odor (FO) exposure, a relatively intense psychological stressor for rats, leads to both same-stressor habituation and novel-stressor sensitization of neuronal activity, and whether this habituation and sensitization manifest in the same populations of neurons. Rats were presented with FO in their homecages thirty minutes a day for up to two weeks and subsequently challenged with FO or restraint. Our results (in situ hybridization) indicate that rats express widespread habituation of the c-fos gene throughout the brain in as few as three repeated presentations of FO, with little additional habituation apparent beyond this point. However, repeated exposure to FO leads to a linearly increasing sensitization of c-fos expression to restraint, manifest over many of the same brain regions expressing habituation, including primary sensory cortices and the prefrontal cortex. The shared spatial expression but separate temporal development of habituation and sensitization phenomena suggests two independently developed processes with opposing influences across overlapping brain systems.

P79. Does Mother Nature Always Know Best? Fetal Ethanol Experience and Olfactory Plasticity

S. L. Youngentob, P. F. Kent, J. C. Molina, N. E. Spear

Studies show extensive neurodevelopmental sequelae associated with prenatal exposure to ethanol in terms of the drugs toxic effects. Nevertheless, there are subtler, potentially just as detrimental long-term consequences. Clinical and epidemiological studies provide strong data for a correlation between prenatal exposure and the risk for ethanol

abuse in adolescent and young adults. In fact, gestational exposure in humans is considered, perhaps, the best predictor of later ethanol abuse during adolescence. Thus far, there is a paucity of evidence regarding the factors contributing to these long-term ingestive consequences. In this respect, there is extensive data demonstrating the general finding that olfactory experience influences olfactory function, that postnatal behaviors controlled by odor stimuli can be influenced by fetal odor experiences, and these early experiences can later modulate adult intake and preferences. Thus, we have begun testing the hypothesis that altered olfactory system responsiveness to ethanol odor, following fetal exposure, acts as a potential contributing risk factor for postnatal preference. To accomplish this, we have been applying behavioral and optical recording methods to test this hypothesis in both early postnatal and adult animals. Experimental rats were exposed *in utero* by administering ethanol to a pregnant dam in a liquid diet [6.7% (v/v) ethanol during gestational day 11–20, following weaning onto the diet between G6-G10] that served as the sole source of nutrition. The developing data from these studies provide evidence for a relationship between prenatal ethanol experience, postnatal odor-guided behavioral responsiveness to the drug and olfactory neural function.

P80. Initial Phase 2 Trial of a Nicotinic Agonist in Schizophrenia

Lynn L. Johnson, Ann Olincy, Josette G. Harris, William R. Kem, Robert W. Buchanan, Robert Freedman

Nicotinic acetylcholine receptors are possible therapeutic targets for schizophrenia, based on neurobiological and molecular evidence for deficiencies in expression of α7-nicotinic receptors. Patients' heavy smoking suggests attempted self-medication through this mechanism. 3-[(2,4-dimethoxy)benzylidene]anabaseine (DMXB-A) is a partial α7-nicotinic agonist and can be taken orally. A Phase 1 trial showed evidence for cognitive enhancement in schizophrenia. Thirty-one subjects with schizophrenia received DMXB-A at two different doses and placebo for periods of 4 weeks in a three-arm, two-site, double-blind, crossover Phase 2 trial. The MATRICS Consensus Cognitive Battery assessed cognitive effects, and the Scale for Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS) assessed clinical effects. Subjects continued their current antipsychotic drug during the trial and were non-smokers. There were no significant changes in the MATRICS cognitive measures compared to placebo over the three treatment arms, but the patients experienced significant improvement at the higher DMXB-A dose on SANS total score

and a trend towards improvement on BPRS total score. Improvement was most notable on the SANS Anhedonia and Alogia subscales. Examination of the first treatment arm showed effects of DMXB-A on the Attention-Vigilance and Working Memory MATRICS domains, compared to baseline. Five subjects developed mild tremor, and nearly half had mild nausea on DMXB-A. DMXB-A, a nicotinic agonist that activates α7-nicotinic receptors, improved clinical ratings of negative symptoms that are generally resistant to treatment with dopamine antagonist antipsychotic drugs. The clinical utility of this treatment is not yet determined.

P81. Insertion of GluR1 Is Required for the Synaptic Plasticity Evoked by Addictive Drugs in the VTA

Bénédicte Balland, Lionel Dahan, Manuel Mameli, Rafael Luján, Rolf Sprengel, Günther Schütz, Rainer Spanagel, Christian Lüscher

Excitatory synapses onto dopaminergic neurons of the ventral tegmental area (VTA) undergo long-term plasticity following an *in-vivo* exposure to an addictive drug. The single exposure to cocaine drives the insertion of GluR2-lacking AMPARs (Bellone & Lüscher, Nat. Neurosci. 2006), which are subsequently removed by mGluR-LTD (Mameli et al., Science, 2007). Here we show that the insertion of GluR2-lacking receptors is common for representative members of all classes of addictive drugs (Ungless and Lüscher, PLoS Med, 2006). When slices were prepared 24h after the exposure to morphine, nicotine and cocaine, AMPAR-mediated postsynaptic currents showed significant rectification. When the same slices were then prepared for EM analysis, immunogold labeling for GluR2 was significantly reduced at the membrane. In line with the requirement for the insertion of GluR1, we found that the cocaine-evoked plasticity was abolished by the selective deletion of GluR1 in dopamine neurons of the midbrain ($GluR1^{DATCre}$). Conversely in $GluR2^{DATCre}$ mice, where AMPAR-EPSCs were already strongly rectifying at baseline, cocaine still led to a potentiation of synaptic transmission (increased AMPA/NMDA ratio). Finally, in $NR1^{DATCre}$ mice NMDA-EPSCs were absent and no potentiation was observed. However, at baseline the frequency of spontaneous AMPAR-EPSCs was significantly increased, suggesting that the absence of cocaine-evoked plasticity may be due to the occlusion of the expression of the plasticity. Taken together, our findings indicate that the insertion of GluR1 is essential for the early adaptive changes induced by addictive drugs at excitatory synapses onto dopamine neurons of the VTA.

P82. Olfactory Marker Protein Is a Novel Modulator of Ca2+ Efflux in Olfactory Sensory Neurons

P. F. Kent, S. L. Youngentob, F. L. Margolis

Ca^{2+} participates in essentially all eukaryotic signaling cascades. In olfactory sensory neurons (OSNs) Ca^{2+} entry following odorant stimulation is the first step in signal transduction. Odorant signal transduction occurs in the cilia of OSNs where they are initiated by odorant molecules interacting with olfactory receptors. The subsequent activation of G-protein coupled adenylylate cyclase results in elevated intracellular cAMP leading to opening CNG cation channels and Ca^{2+} entry. The Ca^{2+}current is amplified by a Ca^{2+}- activated chloride channel. As the rise in intracellular Ca^{+2} is critical to the transduction process, there are also mechanisms that return Ca^{+2} to pre-stimulus levels. OMP (Olfactory Marker Protein) is a 19kDa protein that is phylogentically conserved and highly restricted to mature OSNs. Based on recent data, it has been hypothesized that OMP is a novel modulator of Ca^{2+} efflux, playing a key role returning intracellular Ca^{+2} to pre-stimulus levels, thereby preparing the OSN to respond to the next stimulus. We used optical recording methods and a voltage-sensitive dye to study the consequence of varying external Ca^{2+} concentration on the odorant responses of OMP-KO and WT mice. Relative to WT mice, odorant responses recorded from the olfactory epithelium (OE) of KO animals were unaffected by the changes in external Ca^{2+}. Whereas increasing or decreasing external calcium relative to normal levels had the effect of respectively increasing and decreasing the magnitude and timing of the OE's response in WT mice, no such effects were observed in OMP-KOs. OMP-KO animals maintained their typical response defects.

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